RAQUEL HERNANDES MARQUES

SAÚDE ORAL EM PACIENTES PORTADORES DE DOENÇA DE PARKINSON

SANTOS

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Projeto apresentado ao Programa de Stricto Sensu de Saúde e Meio Ambiente da Universidade Metropolitana de Santos, para Defesa de Mestrado Profissional.

ORIENTADOR: *PROF. DR. FÁBIO CÉSAR PROSDÓCIMI*

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BANCA EXAMINADORA E ATA DE DEFESA DA DISSERTAÇÃO DE MESTRADO PROFISSIONAL

A sessão pública de defesa da dissertação de mestrado profissional intitulada de SAÚDE ORAL EM PACIENTES PORTADORES DE DOENÇA DE PARKINSON, da discente RAQUEL HERNANDES MARQUES, orientada pelo Prof. Dr. FÁBIO CÉSAR PROSDÓCIMI, foi realizada na data abaixo informada, por meio de videoconferência, via sistema da plataforma Zoom, do Programa de Stricto Sensu da Universidade Metropolitana de Santos, tendo o candidato cumprido, previamente, todas as exigências regimentais do Programa de Stricto Sensu de Saúde e Meio Ambiente, de acordo com a secretaria de pós-graduação da instituição. Realizada a apresentação da dissertação e arguição do pública do candidato, os membros da banca em reunião fechada deliberam e emitiram parecer abaixo.

Banca examinadora:	**Resultado:**	**Assinatura**
Prof. Dr. Fábio César Prosdócimi	( ) Aprovado ( ) Reprovado	
Profa. Dra. Paula Andrea de Santis Bastos	( ) Aprovado ( ) Reprovado	
Prof. Dr. Cyro Eduardo de Carvalho Ottoni	( ) Aprovado ( ) Reprovado	

Homologação do resultado pelo presidente da banca examinadora:

( ) Aprovado ( ) Reprovado

Prof. Dr. FÁBIO CÉSAR PROSDÓCIMI

Presidente da banca examinadora

DATA DA DEFESA: 19/01/2021

PROGRAMA DE STRICTO SENSU EM SAÚDE E MEIO AMBIENTE DA UNIVERSIDADE METROPOLITANA DE SANTOS

FICHA DE CLASSIFICAÇÃO DA DISSERTAÇÃO E DO PRODUTO

Título da dissertação: SAÚDE ORAL EM PACIENTES PORTADORES DE DOENÇA DE PARKINSON

Linha de Pesquisa: Saúde

Projeto de Pesquisa do Orientador: Prof. Dr. Fábio César Prosdócimi

Produto(s) gerado(s):

1 – Vídeo-Aula sobre a Dissertação;

2 – Revisão de Literatura da Saúde Oral no atendimento ao paciente portador de Doença de Parkinson.

Classificação da Produto

Critério	**Justificar**
Inserção social e econômico:	Possibilidade ampla de inserção profissional em âmbito privado e público
Impacto – realizado:	Produto direcionado a uma melhor abordagem profissional frente ao paciente portador da Doença de Parkinson
Impacto – potencial:	Proporcionar atendimento adequado aos pacientes portadores de Doença de Parkinson
Aplicabilidade - Abrangência realizada :	Ampla aplicabilidade profissional frente ao paciente portador da Doença de Parkinson
Aplicabilidade - Abrangência potencial:	Aplicabilidade na Odontologia, de modo amplo, local, regional, nacional e internacional
Aplicabilidade – Replicabilidade:	Replicável aos profissionais da Odontologia
Inovação:	Médio teor de inovação
Complexidade:	Médio teor de complexidade

PROGRAMA DE STRICTO SENSU EM SAÚDE E MEIO AMBIENTE DA UNIVERSIDADE METROPOLITANA DE SANTOS

TRANSFERÊNCIA DE CONHECIMENTO

Ao avaliar os artigos científicos sobre procedimentos odontológicos em pacientes portadores da Doença de Parkinson, verificou-se que o tema, cada vez mais frequente devido ao envelhecimento da população, é pouco abordado durante a Graduação. Desse modo, o atendimento ao paciente portador da Doença de Parkinson torna-se restrito à poucos profissionais treinados, deixando uma lacuna de atendimento especializado aos pacientes portadores da Doença de Parkinson.

Após ampla pesquisa frente aos artigos mais relevantes, uma reflexão (além da disponibilização dos artigos) e discussão cientifica sobre o tema, o assunto, no que se refere ao atendimento multiprofissional e, em específico, o atendimento odontológico, é colocado na pauta de conhecimento diário dos profissionais de saúde, em especial o profissional da Odontologia.

DEDICATÓRIA

Dedico a minha Dissertação de Mestrado para Minha Querida Vania Lucia, sempre participativa e pelo companheirismo, aos Meus Pais pela vida, pelo amor e incentivo, e a Todos aqueles que fizeram o meu sonho tornar-se realidade, me proporcionando forças para que eu não desistisse indo atrás do que eu buscava para minha vida. Obrigada por tudo! Muitos obstáculos foram impostos durante esses últimos anos, mas graças a vocês eu não fraquejei!

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E, a todos, que direta ou indiretamente fizeram parte da minha formação, o meu muito obrigada.

SUMÁRIO

LISTA DE SÍMBOLOS, SIGLAS E ABREVIATURAS

BMS: Síndrome da boca ardente

CD: Cirurgião-dentista

CPI: Índice Periodontal Comunitário

DA: Doença de Alzheimer

DIP: Doença inflamatória periodontal

DM: Diabete melito

DMFT: Dentes cariados, ausentes e restaurados

DP: Doença de Parkinson

DTM: disfunção temporomandibular

G: Grupo

GABA: Ácido gama-aminobutírico

GOHAI: Índice Geral de Avaliação de Saúde oral

n: Número de participantes

OHRQoL: Qualidade de vida relacionada à saúde oral

PAL: Perda de inserção periodontal

RCT: ensaio clínico randomizado

RDC/TMD: Critérios de diagnóstico de pesquisa para doenças temporomandibulares

SNC: Sistema Nervoso Central

SO: Saúde oral

VPI: índice de placa visível

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RESUMO

A saúde oral do paciente com doença de Parkinson, compromete a higiene, tornando-a inadequada. Há significativa dificuldade na prevenção, cada vez mais evidente, justamente pelo avanço dos sintomas. A doença de Parkinson é uma doença neurodegenerativa, progressiva e incurável, cuja etiologia, ainda não é totalmente esclarecida. Vários sinais e sintomas desta doença comprometem a habilidade motora, em diferentes estágios, de ordem cognitiva e comportamental, necessitando um acompanhamento clínico contínuo, abrangendo uma extensa gama de profissionais que incluem desde neurologistas até fisioterapeutas, entre outros profissionais da saúde. O manejo odontológico pelo cirurgião-dentista, um auxílio aprimorado, compondo a equipe multiprofissional composta por neurologistas, geriatras, terapeutas ocupacionais, fisioterapeutas, enfermeiros, psicólogos e demais profissionais da área da saúde. O presente trabalho, vem esboçar por meio de revisão de literatura, a importância de uma prevenção oral em pacientes acometidos da doença de Parkinson. As estratégias de busca utilizadas modularam as referências selecionadas. Poucos estudos associaram saúde oral e doença de Parkinson, mesmo com aumento da longevidade da população e processo de desenvolvimento do envelhecimento saudável. Cada estudo se ateve a uma forma particular de direcionamento, que envolve a saúde oral e os sintomas da doença Parkinson.

PALAVRAS-CHAVE: Doença de Parkinson; atendimento odontológico; saúde oral.

ABSTRACT

The oral health of patients with Parkinson's disease compromises hygiene, making it inadequate. There is significant difficulty in prevention, which is increasingly evident, precisely because of the progression of symptoms. Parkinson's disease is a neurodegenerative, progressive and incurable disease, the etiology of which is not yet fully understood. Various signs and symptoms of this disease compromise the motor ability, at different stages, of a cognitive and behavioral order, requiring continuous clinical follow-up, covering a wide range of professionals including neurologists to physical therapists, among other health professionals. Dental management by the dental surgeon, an improved aid, composing the multiprofessional team composed of neurologists, geriatricians, occupational therapists, physiotherapists, nurses, psychologists and other health professionals. The present work outlines, through a literature review, the importance of oral prevention in patients with Parkinson's disease. The search strategies used modulated the selected references. Few studies have associated oral health and Parkinson's disease, even with increased population longevity and the development process of healthy aging. Each study adhered to a particular form of targeting, which involves oral health and the symptoms of Parkinson's disease.

KEYWORDS: Parkinson's disease; dental care; oral health.

1. INTRODUÇÃO

A Doença de Parkinson (DP) é a segunda doença neurodegenerativa mais frequente, atrás somente da Doença de Alzheimer (DA). É caracterizada por sintomas motores, autonômicos, cognitivos e comportamentais. Pacientes com DP conviverão com essa condição, se "conduzida a termo" desde o início até a morte, passando por uma variedade de tratamentos farmacológicos e/ou não farmacológicos. Os fatores cardinais da DP incluem o tremor de repouso, rigidez, acinesia e instabilidade postural. Os sintomas da DP podem ser expostos como não-motores, incluindo alterações psicológicas, cognitivas e distúrbios do sono e motoras (rigidez no movimento, lentidão dos movimentos, tremores) [1,2].

O tratamento inicial se concentra nos aspectos motores da doença, quando então os sintomas cognitivos e comportamentais podem aumentar a condução da clínica, enquanto a disfunção autonômica sobreposta torna o manejo da DP particularmente desafiador. A saúde oral (SO) é parte de um complexo que envolve, entre outros, fatores de controle de infecções e transformação de alimentos, em sua fase inicial, em nutrientes essenciais para a vida. Além disso, a SO envolve não apenas os aspectos estéticos e funcionais, mas ainda faz parte de um complexo aspecto relativo à qualidade de vida[2].

Fatores sistêmicos, como alterações cardiovasculares, diabete melito (DM), gestação, alterações sanguíneas podem ser fatores de comorbidade associadas à DP. A xerostomia observada em pacientes com DP contribui para uma piora da SO, uma vez que as propriedades como solução-tampão da saliva estarão reduzidas. Pacientes portadores da DP podem apresentar dificuldades, em diferentes níveis, do controle da higiene oral, derivado do menor controle voluntário dos movimentos dos membros, em especial dos membros superiores e das mãos, dificultando ou até mesmo incapacitando-o quanto à uma correta higiene oral. Distúrbios motores orais estão presentes em aproximadamente 50% dos pacientes[3]. Desse menor controle, doenças periodontais, cáries dentais e halitose, entre outros desconfortos, podem ser observados em pacientes portadores da DP. Frente aos sintomas incapacitantes, a SO pode se tornar um aspecto secundário na vida dos pacientes.

Cuidadores de pacientes com DP deverão estar atentos, entre tantos aspectos, às condições da SO do seu paciente[4]. A orientação do correto uso da escova dental, fio dental, enxaguatórios orais torna-se, com o decorrer da progressão da DP, cada vez mais necessária por parte do cuidador e

uma composição multiprofissional, incluindo neurologistas, clínicos gerais, terapeutas ocupacionais, fisioterapeutas, enfermeiros, psicólogos, geriatras, cirurgiões-dentistas e demais profissionais apresenta importância elevada na condução do acompanhamento do paciente portador de DP[5]. Com isso, a atuação do cirurgião-dentista (CD) deverá ser orientada de modo a observar os diferentes aspectos individuais e buscar a melhor conduta clínica frente ao paciente portador de DP [6].

2. REVISÃO DE LITERATURA

2.1. SAÚDE ORAL

A SO é fundamental para o correto funcionamento do nosso organismo e está intimamente relacionada com a saúde geral. Na cavidade oral podemos diagnosticar indícios de várias doenças sistêmicas que afetam o organismo, e que aí podem ter a sua primeira manifestação. A relação entre a saúde oral e a saúde geral compreende-se quando assumimos que a boca é a porta de entrada dos alimentos e a função mastigatória eficiente tem capacidade de processar os alimentos e cumprir a primeira etapa da sua digestão fundamental para a saúde do organismo no seu conjunto. Quando algo na cavidade oral não está bem, desenvolvem-se situações que podem refletir sistemicamente[6].

Com o avanço da tecnologia, notou-se um grande avanço nas técnicas preventivas e corretivas acerca do tratamento odontológico, resultando, diretamente, em um menor número de indivíduos edêntulos e, portanto, em um maior número de idosos com seus dentes até idades muito avançadas[7]. Desse modo, problemas dentais em indivíduos idosos também apresentaram aumento em relação a décadas passadas e assim, a carie dental e as disfunções periodontais, protéticas e tantas outras foram observadas com maior frequência[8].

Por outro lado, pacientes idosos recorreram a tratamentos mais sofisticados, como implantes dentários, enxertos com biomaterial, próteses mais sofisticadas, implanto-suportadas ou mesmo removíveis. Desse modo, necessitam de um controle profissional mais efetivo e programado, necessitando de atendimento tanto preventivo quanto corretivo. Assim, uma maior complexidade da condição da saúde oral, associada a um maior potencial de doenças sistêmicas e utilização de medicamentos diversos, tornam o paciente idoso mais vulnerável aos problemas relativos à saúde oral, quando comparado a um paciente jovem; principalmente àquele com disfunções cognitivas, onde, então, a higiene oral pode ser negligenciada ou reduzida, acarretando em uma maior incidência de complicações orais[9,10,11,12].

Problemas cardiovasculares, diabete, doenças do sistema imunológico podem ter repercussões na saúde oral e serem significativas. Com relação ao risco cardiovascular, pode ocorrer, quando de uma infecção oral, observarmos um processo inflamatório que pode lesionar as artérias, chegando mesmo a atingir a corrente sanguínea. No caso da diabete melito, uma infecção oral pode elevar os níveis glicêmicos e fazer com que a diabete melito apresente um

controle adverso. Confirmou-se também que os adultos com diabete melito não compensada apresentar um risco três vezes maior de instalação da doença periodontal.[10,11]

Sabe-se que a gengivite pode criar complicações durante a gestação, aumentando, por exemplo, o risco de partos prematuros e bebês com baixo peso. Cientistas analisaram o papel de uma bactéria, a *Porphyromonas gingivalis*, no desenvolvimento da Doença de Alzheimer (DA). Encontrada na boca, a bactéria se prolifera por causa da má higiene e pode causar periodontite, doença que afeta tecidos ao redor dos dentes. A pesquisa identificou enzimas ligadas a essa bactéria em cérebros de pacientes mortos que tiveram DA, e também localizou material genético ligado à *Porphyromonais gingivalis* em pacientes vivos[11,12].

Problemas mastigatórios, dores na boca ou a perda de dentes podem originar distúrbios alimentares e um descontrole na alimentação. Tudo isso tem influência na mastigação, uma vez que o alimento não é devidamente triturado, obrigando a um mau funcionamento do estômago e provocando, por consequência, problemas digestivos. Além disso, deixa-se de consumir alimentos difíceis de triturar, mas que são necessários para o organismo, o que pode gerar uma alimentação desequilibrada[13].

Algumas doenças neurológicas podem repercutir e apresentar relação com a cavidade oral. Distúrbios motores e cognitivos tornam-se cada vez mais severos, sendo previsível que a saúde oral seja diretamente afetada, visto que o paciente passa a apresentar maiores dificuldades motoras na realização de cuidados diários de higiene oral. Entre as implicações orais mais comuns estão a disfagia (dificuldade em deglutir), xerostomia (sensação de boca seca), sensação de ardor oral, doença periodontal e aumento da incidência de lesões de cárie[13].

Explicando de forma mais detalhada sobre estas principais manifestações, vale destacar que a deglutição no paciente parkinsoniano se modifica com o avanço da doença, caracterizando-se assim um quadro de disfagia[14,15].

A lentidão dos movimentos, a fraqueza da musculatura oral e o comprometimento da coordenação das ações orais, dificultam a ingestão de alimentos, o que afeta diretamente o estado nutricional do paciente. Além disso, a dificuldade em deglutir, acompanhada da manutenção da cabeça sempre inclinada para baixo, leva o paciente a salivar excessivamente e a acumular saliva nas comissuras labiais, propiciando quadros infecciosos frequentes de queilite (inflamação) angular. Já a xerostomia, caracterizada pela sensação de boca seca, é considerada a manifestação oral algo frequente nos pacientes com problemas neurológicos que pode ser consequente da diminuição ou interrupção da função das glândulas salivares. A xerostomia nestes pacientes é um

estimulador da cárie dental e doença periodontal, visto que a saliva auxilia tanto na lubrificação e na limpeza dos tecidos orais e estruturas dentárias, como também na neutralização dos ácidos e remineralização do esmalte[16,17].

Porém a maior incidência da cárie (sobretudo a cárie radicular) e da doença periodontal nos pacientes com problemas neurológicos está relacionada às dificuldades motoras e o comprometimento da destreza manual que dificultam a realização dos cuidados de higiene oral com frequência e qualidade[18].

Alguns estudos ressaltam a importância de uma equipe multiprofissional de cuidadores no atendimento adequado ao paciente portador de DP, entretanto não incluem o cirurgião-dentista. É essencial muitas vezes a colaboração de cuidadores nesta tarefa na realização de procedimentos preventivos e manutenção de uma boa higiene oral, por meio da instrução de técnicas de escovação, uso de fio dental e limpeza das próteses removíveis, além de consultas periódicas ao consultório odontológico sendo realizadas por profissionais altamente especializados e treinados para as diversas fases (ou estágios) da doença[19,20].

2.2. DOENÇA DE PARKINSON

Sabe-se que a Doença de Parkinson (DP) foi descrita em um ensaio por James Parkinson em 1817 como uma paralisia de tremor ("*shaking palsy*") e que Charcot, baseado em características clínicas[21,22].

A DP é a segunda doença neurodegenerativa mais comum, atrás somente da DA [1,2]. Apresenta uma neurodegeneração progressiva, lenta, o que explica a sua maior observação com o aumento da expectativa de vida da população[22,23]. Estima-se a presença de 6,1 milhões de pessoas com diagnóstico de DP em 2016, valor, em 1990, estimado em 2,5 milhões[24]. A DP afeta aproximadamente 2% da população mundial, com incidência estimada em aproximadamente 20/100.000 pessoas e prevalência de 150/100.000[19]. Os homens apresentam a doença 1,5 mais vezes que as mulheres e alguns estudos citam uma maior incidência da DP na população rural[20]. A DP é observada, anatomicamente, em diversas áreas do Sistema Nervoso Central (SNC), mas notoriamente observada na *substantia nigra pars compacta*, composta por neurônios dopaminérgicos. A dopamina é um neurotransmissor notadamente responsável pela coordenação muscular voluntária e sua ausência ou redução pode determinar alterações motoras lentas e progressivas com o passar dos anos[24, 25].

A DP apresenta modificações neurológicas no encéfalo, onde observa-se a formação de estruturas proteicas esféricas anormais denominadas corpos de Lewy e estruturas fusiformes, em parte, ramificações dos neuritos dos neurônios envolvidos, determinando áreas e avançando topograficamente pelo SNC[26, 27]. A degeneração dopaminérgica nigroestriatal é descrita como a primeira neurodegeneração motora da DP, mas células nervosas glutamatérgicas, colinérgicas, GABAérgicas, triptaminérgicas, noradrenérgicas e adrenérgicas também apresentam alterações em seu citoesqueleto[22].

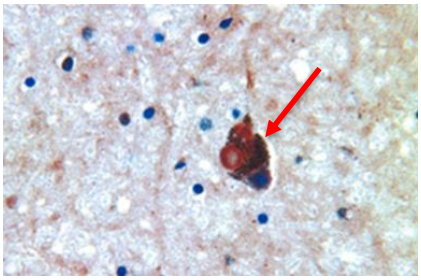

Fig. 01 – **Corpo de Lewy, seta vermelha** (coloração de sinucleina, 200X). Sveinbjornsdottir S. The Clinical Sumptons of Parkinson's Disease. J Neurochem, 2016;139(S1):318-24.

Os fatores cardinais da DP incluem o tremor de repouso, rigidez, acinesia e instabilidade postural[23] (tremor, rigidity, akinesia and postural instability, TRAP) utilizado em diversas classificações. Os sintomas da DP podem ser expostos como não-motores, incluindo alterações psicológicas, cognitivas e distúrbios do sono) e motoras (rigidez no movimento, lentidão dos movimentos, tremores)[30].

Fig. 02 – **Fatores cardinais da DP.** Souza CFM et al. A Doença de Parkinson e o processo de envelhecimento motor: uma revisão de literatura. Rev Neurosci 2011;19(4):718-23.

Os fatores de risco da DP podem ser genéticos ou não-genéticos, sendo a mutação genética descrita como um fator de desenvolvimento da DP[25]. Fatores outros, como nutricionais (antioxidantes, ácidos graxos) estão sendo pesquisados. Acerca da neuropatologia, a perda neuronal e gliose dos neurônios nigroestriatais compõe o padrão ouro do diagnóstico da DP. Braak[26] propôs uma sequência lógica do desenvolvimento da DP (figura 03):

Estágios 1 e 2: as lesões se apresentam no núcleo olfatório anterior, no núcleo motor dorsal dos nervos IX e X (glossofaríngeo e vago, respectivamente), nos núcleos da rafe e na formação reticular,

Estágios 3 e 4: a lesão está circunscrita ao tronco encefálico e ao mesocórtex temporal anterolateral, onde a "*substantia nigra"* é a principal estrutura afetada e,

Estágios 5 e 6: envolvimento agudo do encéfalo na maioria das áreas neocorticais.

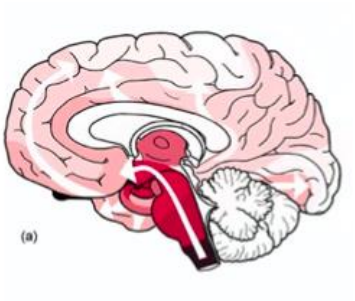

Fig. 03 – Estágios da DP. Estágios 1-2. Vista medial de corte sagital do encéfalo, hemisfério direito. Apontadas pela seta branca, núcleo olfatório anterior, no núcleo motor dorsal dos nervos IX e X (glossofaríngeo e vago, respectivamente), nos núcleos da rafe e na formação reticular. Braak H. Staging of brain pathology related to sporadic Parkinson's Disease. Parkinson's Disease, 2003;24(1):197-211.

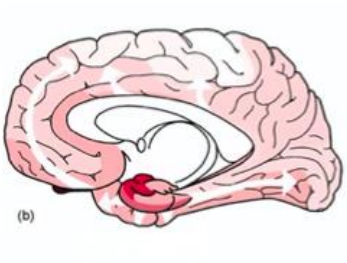

Fig. 04 - Estágios da DP. Estágios 3-4. Vista medial de corte sagital do encéfalo, tronco encefálico parcialmente removido, hemisfério direito. Apontadas pela seta branca, lesão no mesocórtex temporal anterolateral, onde a *substantia nigra* é a principal estrutura afetada. Braak H. Staging of brain pathology related to sporadic Parkinson's Disease. Parkinson's Disease, 2003;24(1):197-211.

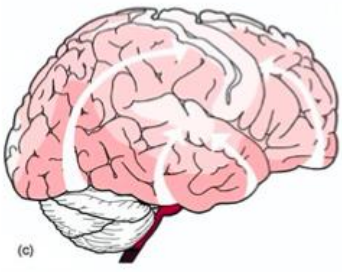

Fig. 05 – Estágios da DP. Estágios 5-6. Vista lateral do encéfalo, hemisfério direito, apontada pela seta branca, áreas neocorticais. Braak H. Staging of brain pathology related to sporadic

Parkinson's Disease. Parkinson's Disease, 2003;24(1):197-211. Braak H. Staging of brain pathology related to sporadic Parkinson's Disease. Parkinson's Disease, 2003;24(1):197-211.

A etiologia da DP não é ainda bem entendida, entretanto modelos experimentais de DP, utilizando-se pesquisas neurológicas, estudos genéticos (sabe-se que 10 *loci* distintos responsáveis pela expressão da DP) e análises epidemiológicas tentar elucidar tais questões[31, 32, 33, 34, 35].

O padrão neuronal diferencial de perda celular com projeções dopaminérgicas nigroestriatais em associação com a alfa-sinucleina contendo corpos de Lewy é bastante aceita e relacionada a distúrbios motores, apesar de outros neurotransmissores estarem associados à distúrbios não-motores derivados da DP. Entretanto, apresentam impacto tanto em distúrbios motores e não-motores da DP, onde comorbidades estão relacionadas à polimedicação, podendo resultar em efeitos adversos de interações medicamentosas ou confundir a prescrição para o controle da DP[36]. O papel dos corpos de Lewy são amplamente pesquisados, mas com descrições atuais apontando para um papel de liberação de príons determinando a neurodegeneração[37,38]. Desse modo, a DP é reconhecida como um espectro de alterações alfa-sinucleina e tau-proteína que diminuem ou alteram a olfação, gustação, visão, função cardiovascular, sono, salivação, atividade de glândulas sebáceas, humor, cognição e função digestória[38]. Na maioria dos casos é observado um início em apenas um dos lados, onde a parte contralateral desenvolverá os sinais com o passar de poucos anos. A bradicinesia determina diminuição das expressões faciais (hipomimia) e diminuição da amplitude de movimentos das mãos. A progressão dos tremores é gradual, podendo afetar os membros superiores, membros inferiores, pés, lábios e cabeça. Para muitos portadores de DP, os tremores são fatores estressantes de exposição pública, causando ansiedade e depressão. Portadores de DP apresentam dificuldades de se comunicar com os demais indivíduos, com alterações vocais, de fala, compreensão e, em alguns indivíduos a progressão da DP é rápida[39].

Os cuidadores, em geral familiares, normalmente atuam na residência do portador de DP, realizando as tarefas diárias, minimizando ou gerenciando as atividades do paciente, sendo decisivos nas decisões no final da vida[38,39]. Um tratamento multidisciplinar é indicado devido às diversas necessidades do paciente, incluindo neurologistas, clínicos gerais, especialistas em atendimento individual, gerontologistas, enfermeiros, fisioterapeutas, psicólogos, farmacêuticos, entre outros[40,41].

Fig. 06 – **Equipe multiprofissional.** INCNEFRO, Instituto Nefrológico de Campinas, site: incnefro.com.br/blog/54 – a-importancia-da-equipe-multiprofissional-na-saude.html

Distúrbios motores orais são comuns, observado em mais de 50% dos pacientes, com problemas em deglutição e salivação excessiva[37].

Desse modo, um estudo sobre a interação Saúde Oral – DP se faz necessária.

2.3. SAÚDE ORAL E A DOENÇA DE PARKINSON

Uma vez que a DP pode interferir com movimentos manuais curtos da mão[38] (fig. 05), o ato de escovar os dentes é diretamente prejudicado e, assim, SO de pacientes que apresentam a DP é afetada[42]. As alterações motoras, somada à fatores não-motores, como demência ou apatia, e ainda alternâncias do controle motor das mãos influenciam negativamente a higiene e a qualidade da saúde oral dos pacientes portadores de DP. Pacientes, portadores de DP tem mais cáries, maior número de dentes perdidos e biofilme além de uma saúde periodontal de pior qualidade[43].

Fig. 07 – **Movimentos manuais curtos da mão.** Centro de Informação Farmacêutica. CIF. Cifph.wordpress.com/2015/04/11/119.

A SO representa um bem-estar, não é somente ter bons dentes. A avaliação clínica do paciente, em especial dos idosos, normalmente é superestimada devido à menor percepção da SO. A SO apresenta medidas multidimensionais a respeito da percepção individual subjetiva, refletindo um bem-estar psicológico, social e funcional, induzindo à uma maior busca por tratamento com especialistas[44,45,46]. Pacientes portadores de DP reportaram incômodo com a SO, com o uso de próteses totais e com a mastigação[44, 45]. Inabilidade física e desconforto psicológico foram ainda descritos por portadores de DP[44]. Um índice de dentes presentes, cariados, perdidos e restaurados, além do fluxo salivar, índice de biofilme e condições clínicas de próteses dentárias resultaram em uma observação onde pacientes portadores de DP foram comparados à um grupo controle sem a presença de DP; sendo relatado uma pequena piora da SO em pacientes portadores de DP [45] em alguns resultados e ainda uma grande piora da SO devido, provavelmente, à uma maior perda de dentes[46]. Os pacientes portadores de DP indicaram ter uma pior auto-percepção acerca de sua SO.

Quando comparados à um grupo controle, pacientes portadores de DP apresentaram menor número de dentes piora da saúde periodontal[42,46], relatou um aumento da presença de restos alimentares, biofilme e piora do quadro geral da SO em pacientes com estágios mais avançados da DP[47], enquanto Muller descreve que em pacientes jovens e internados, portadores de DP, nota-se piora do índice de presença de biofilme quando comparados ao grupo controle[20].

Doenças Orais, incluindo alterações periodontais, cáries dentais, problemas endodônticos, mal posicionamento dental, dores dentais e orais, etc, não determinam somente problemas locais, mas ainda podem provocar condições sistêmicas adversas, como aterosclerose, DM, DA e artrite reumatoide[48], pneumonia e piora nutricional [49].

Sabe-se ainda que a idade é um fator dominante de risco, onde uma correlação evidente foi demonstrada e estudos demonstraram que, aos 60 anos aproximadamente 1% da população é afetada e, a partir dos 80 anos, a prevalência atinge 3% dos indivíduos. Desse modo, a idade representa um significante fator de risco para o desenvolvimento da DP. Observando-se o fato de que uma piora do quadro geral devido à DP conduz à uma piora da SO, devem ser considerados os diferentes estágios da DP e sua adaptação individual e em um planejamento da atuação dos cuidadores e/ou equipe multiprofissional[50,51].

Pacientes portadores de DP apresentam tanto uma higiene oral pior quanto uma maior predisposição à cáries dentais e doenças periodontais, e ainda verificada uma menor utilização de escovas elétricas e fio/fita dental quando comparadas à média da população, demonstrando uma pior habilidade manual na manutenção da higiene e saúde oral, sendo o uso de enxaguatórios orais contendo fluoretos altamente recomendado[52].

Pradeep[53] demonstrou que a SO em pacientes portadores da DP é pior quando comparada à população geral em termos de saúde periodontal e aumento do sulco gengival. 45 pacientes portadores de DP foram subdivididos em 5 subgrupos de acordo com a escala de Hoehn e Yahr (tabela 02) e foram comparados ao grupo controle, sem a presença de DP. Em ambos os grupos, com escovação dental diária pelo menos uma vez, notou-se um aumento da profundidade do sulco gengival e presença de biofilme, piorando com o estágio mais avançado na escala Hoehn e Yahr, corroborando estudos prévios[54].

Tabela 01 – Escala Hoehn e Yahr. Ng JS. Palliative care for Parkinson's disease. Ann Palliat Med 2018;7(3):296-303.

Estágio	**Descrição**
1	Envolvimento unilateral com mínima ou nenhuma alteração funcional
2	Envolvimento bilateral ou da linha média sem prejuízo do equilíbrio
3	Doença bilateral: deficiência leve a moderada com reflexos posturais prejudicados; fisicamente independente
4	Doença gravemente incapacitante; ainda capaz de andar ou ficar de pé sem ajuda
5	Confinamento à cama ou cadeira de rodas, a menos que seja ajudado

Orientações sobre a reabilitação protética em pacientes portadores da DP edêntulos e com grande perda de dentes consideram a xerostomia, fraqueza muscular e a estabilidade das próteses, fixas, removíveis e mesmo implanto-suportadas, observando uma melhora na qualidade de vida e bem-estar dos pacientes, recomendando aos pacientes anotarem suas impressões sobre sua qualidade de vida após a instalação das próteses uma hora antes da medicação (levodopa), recuperando a dimensão vertical e técnica de manipulação bilateral, onde os dentes protéticos apresentaram cúspides menos evidentes, reduzindo interferências em movimentações involuntárias da boca, com decréscimo de bruxismo (quando presente), onde uma oclusão lingualizada aumenta a estabilidade das próteses parciais removíveis[55].

Recursos educacionais estão sendo criados e desenvolvidos com o intuito de orientar sobre a SO dos pacientes portadores de DP e estão disponíveis online no site da Associação Americana da Doença de Parkinson. Através da interação entre profissionais da Odontologia e médicos de atenção primária, neurologistas, fisioterapeutas espera-se uma melhor e mais abrangente adoção de conduta clínica individual no que se refere ao paciente portador de DP. [55]

3. OBJETIVO

O objetivo do presente estudo foi revisar diferentes aspectos da saúde oral em pacientes portadores de DP por meio de revisão da literatura.

4. MÉTODOS

Ensaios clínicos e estudos observacionais avaliando diferentes aspectos da saúde oral em pacientes com DP foram incluídos nesta revisão, envolvendo a associação entre diferentes aspectos da DP e doenças da cavidade oral. Relatos de caso, revisões, diretrizes e estudos experimentais foram excluídos.

Uma pesquisa abrangente foi realizada nos seguintes bancos de dados eletrônicos: MEDLINE (via Pubmed), Embase (via Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL), América Latina e Caribe Literatura em Ciências da Saúde (LILACS) (via Biblioteca Virtual em Saúde - BVS) e Bibliografia Brasileira de Odontologia (BBO) (via BVS), sem restrições de idioma ou data.

Também, analisou-se busca manual as listas de referência de estudos relevantes para identificar qualquer estudo elegível potencial. As estratégias de pesquisa completas são apresentadas no arquivo anexo 01. Não houve restrições de idioma ou data.

5. RESULTADOS

As estratégias de busca recuperaram um total de 121 referências. Após a remoção de 17 duplicatas, 104 foram selecionados por título e resumo e 41 referências potencialmente elegíveis foram analisadas no texto completo. Vinte e dois estudos não atenderam aos critérios de inclusão e foram excluídos (revisões e relatos de caso). Assim, 17 estudos (relatados em 19 artigos) foram incluídos nesta revisão. A Figura 08 mostra o processo de seleção dos estudos e a tabela 02 mostra as características dos trabalhos selecionados.

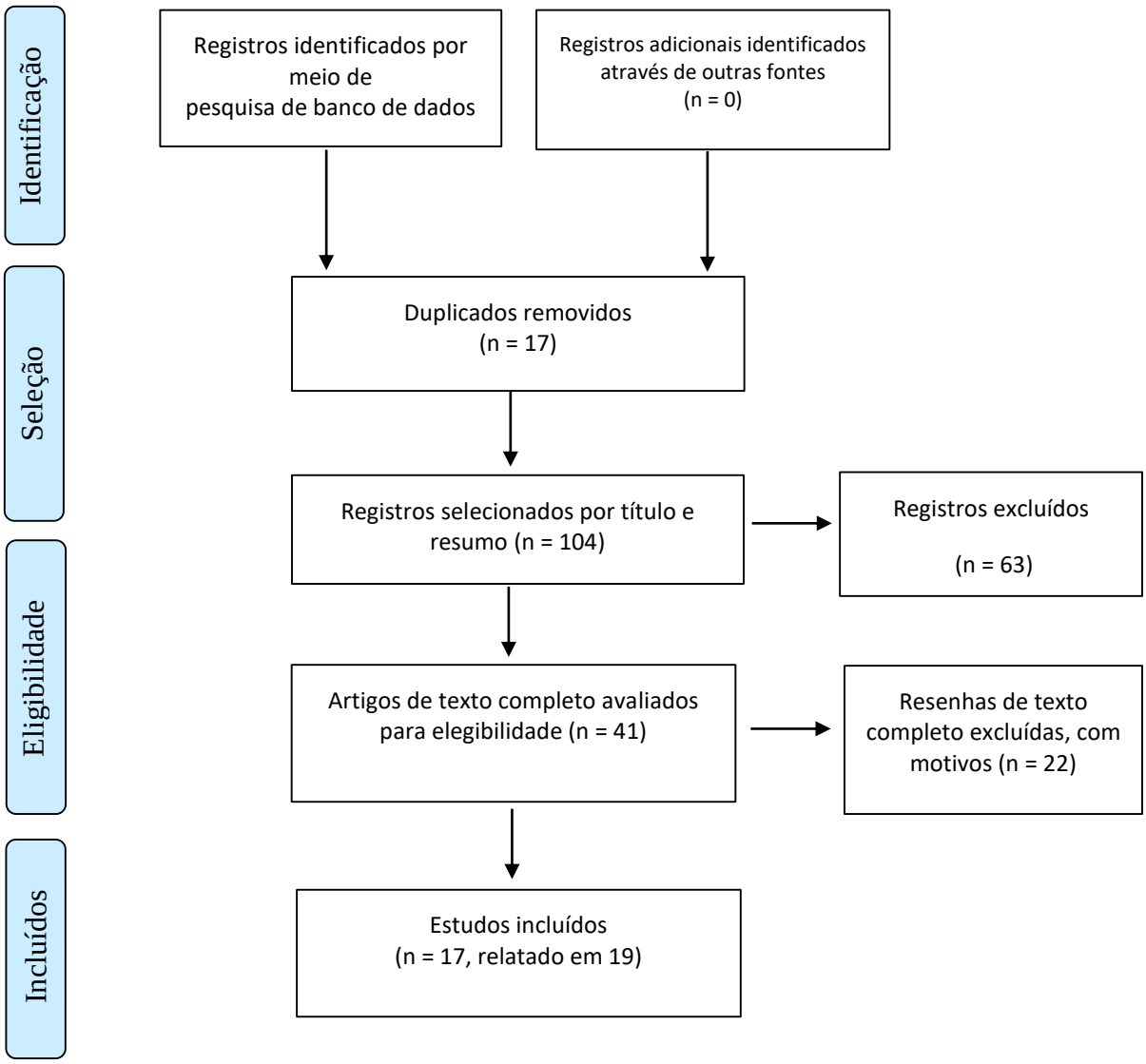

Figura 08. Fluxograma do processo de seleção dos estudos.

Tabela 02 – Características dos trabalhos selecionados.

Autor/ Ano/ País	Desenho do Estudo / Nível de Evidência	Participantes	Intervenções / Exposição	Resultados
Baram et al., 2020 Dinamarca	RCT Nível II	n = 29 mediana 65 anos DP moderado para avançado	G1: Instrução individual de higiene oral, treino de abertura mandibular, exercícios labiais e de mastigação (n = 15) G2: Apenas instruções (n = 14)	• Os pacientes do G1 melhoraram abertura da mandíbula, tempo de mastigação e higiene após 2 meses • Nenhuma mudança significativa foi encontrada nos pacientes do G2 após 2 meses
Zarpelon et al., 2019 Brasil	Transversal Nível IV	n = 50 idade entre 53 a 94 anos DP leve	Exame da cavidade oral para avaliação do uso e necessidade de próteses; índice de CPOD; CPI; PAL; e mucosa oral	• 92% de uso de prótese na arcada superior • 66% da necessidade protética na arcada inferior • 43% de dentes perdidos (CPOD) • 43% cálculo dentário (CPI) • 28% de perda de anexo (PAL) • Achados na mucosa oral: estomatite dentária, hiperplasia fibrosa inflamatória
Silva et al., 2019 Brasil	Transversal Nível IV	n = 59 idade entre 50 e 75 anos 83% DP leve	Sinais e sintomas de DTM com RDC / DTM	• Prevalência de DTM 20,3% (n = 12) • Mais frequente entre mulheres (n = 7) • Nenhuma associação significativa entre DTM e gravidade da DP
Chen et al., 2018 Taiwan	Caso-controle Nível IV	n = 4,765 com DP n = 19,060 sem DP idade 40 a 69 anos	Raspagem dentária e desenvolvimento de DP	• Pacientes sem DIP que foram submetidos a raspagem dentária por mais de cinco anos tiveram um risco significativamente menor de DP
van Stiphout et al., 2018 Países Baixos	Caso-controle Nível IV	n = 74 sem DP n = 74 com DP idade 40 a 69 anos	Estado de saúde oral e duração e gravidade da DP	• Os pacientes com DP tinham estado de saúde oral enfraquecido e cuidados de higiene oral reduzidos • A duração e a gravidade da DP foram associadas a mais problemas de saúde oral e higiene

Tiigimäe-Saar et al., 2018 Estônia	Caso-controle Nível IV	n = 12 com DP n = 13 sem DP n = 13 indivíduos saudáveis média de idade 71.1 anos	Toxina botulínica tipo A para sialorreia (glândulas parótidas e submandibulares bilaterais)	• Diminuição do fluxo salivar em 1 mês • Sem mudanças na composição salivar n • Níveis aumentados de contagem de lactobacilos • Nenhum evento adverso observado
Barbe et al., 2017 Alemanha	Caso-controle Nível IV	n = 26 com DP n = 26 sem DP media de idade 69 anos	Halitose e DP	• Mais pacientes com DP perceberam que a halitose é mais forte (77% vs 54%) • A boca seca foi maior em pacientes com DP • OHRQoL mais baixo em pacientes com DP • Pacientes com DP tiveram mais hipossalivação (87% versus 50%) • 50% relataram xerostomia e nenhum dos controles
Ribeiro et al., 2016 and 2017 Brasil	Caso-controle Nível IV	n = 17 com DP n = 17 Sem DP média de idade 69.4 idades	Reabilitação oral com prótese removível e DP	• Melhoria OHRQoL e eficiência mastigatória, dois meses após a intervenção em ambos os grupos • Sem diferenças de grupo no número de dentes restantes, CPOD, VPI ou taxa de fluxo salivar • Escores GOHAI mais baixos em pacientes com DP • Pacientes com DP tiveram autopercepções mais negativas de sua saúde oral
Liu et al., 2017 Suécia	Coorte Nível II	n = 20,175 sem DP em 1973/74, até 2012 307 PD casos depois de 27.9 anos, controle de proservação média de idade 54.1 anos	Uso de tabaco, indicadores de saúde oral e risco de DP	• Tabaco associado a menor risco de DP em homens • Sem associação para número de dentes, Biofilme ou lesões da mucosa oral e risco de DP
Barbe et al., 2017 Alemanha	Transversal Nível IV	n = 100 média de idade 71 anos	Autoavaliação do atendimento odontológico: capacidade de realizar higiene	• 49% de xerostomia, 70% de Saliva e 47% de disfagia

			oral, autoavaliação da xerostomia, problemas de sialorréia e disfagia e impacto no OHQoL.	• 29% capacidade limitada de realizar higiene oral • A xerostomia, a Saliva e a disfagia prejudicaram a QV OH • 6,1% dos participantes com xerostomia receberam conselhos sobre o manejo
Bonenfant et al., 2016 Canada/França	Transversal Nível IV	n = 203 média de idade 81,2 anos	Frequência da síndrome da boca ardente em pacientes com DP	• Baixa prevalência de BMS em pacientes com DP (4%) • O índice de saúde oral ruim foi maior em BMS em comparação com não-BMS
Pradeep et al., 2015 Índia	Caso-controle Nível IV	n = 45 com DP n = 46 sem DP média de idade 58,7 anos	Status periodontal e gravidade da DP	• Todos os parâmetros e índices clínicos periodontais avaliados se deterioram com o aumento da gravidade da DP
Cicciù et al., 2012 Itália	Caso-controle Nível IV	n = 45 com DP n = 45 sem DP média de idade 65 anos	Status periodontal e gravidade da DP	• A frequência de cáries não tratadas, doenças periodontais e dentes perdidos foi em pacientes com DP
Müller et al., 2011 Alemanha	Caso-controle Nível IV	n = 101 com DP n = 75 sem DP média de idade 66,2 anos	Saúde oral e DP	• Pacientes com DP tiveram pior: • Saúde oral (índice de sangramento da papila), • Recessão gengival, • mobilidade dentária, • Frequência mais baixas de escovação, • Mais tempo desde a última visita ao dentista, • fluxo salivar reduzido
Bakke et al., 2011 Dinamarca	Caso-controle Nível IV	n = 15 com DP n = 15 sem DP média de idade entre 62 e 81 anos	Função orofacial saúde oral em pacientes com DP	• Pacientes com DP apresentaram disfunção orofacial mais prevalente, mastigação e abertura mandibular mais pobres e impacto negativo da saúde oral na vida diária

RCT: ensaio clínico randomizado; **n**: número de participantes; **DP**: doença de Parkinson; **G**: grupo; **DMFT**: dentes cariados, ausentes e restaurados; **CPI**: Índice Periodontal Comunitário; **PAL**: Perda de inserção periodontal; **DTM**: disfunção temporomandibular; **RDC / TMD**: Critérios de diagnóstico de pesquisa para doenças temporomandibulares; **DIP**: doença inflamatória periodontal; **OHRQoL**: Qualidade de vida relacionada à saúde oral; **VPI**: índice de placa visível; **GOHAI**: Índice Geral de Avaliação de Saúde oral; **BMS**: síndrome da boca ardente

6. DISCUSSÃO

A importância da SO é conhecida por todas as pessoas e reflete na saúde geral, assim como contribui significativamente na qualidade de vida e no bem-estar dos indivíduos. O paciente portador da DP apresenta diversas situações de déficits motores e não-motores e que determinam consequências quanto ao aspecto da manutenção da SO[56].

A DP apresenta uma evolução bem descrita na literatura e que repercute negativamente na condição da saúde geral, incluindo a SO. Poucos trabalhos descrevem uma SO melhor em portadores de DP[56], enquanto a grande maioria descreve uma piora acentuada da SO quando comparados aos pacientes saudáveis.

Os estudos associando SO DP apresentam-se em número reduzido, apesar do aumento da longevidade da população ser amplamente conhecido, buscando um envelhecimento saudável. Esse fator é particularmente importante dada a relação entre idade e presença de DP, que apresenta fatores cardinais. Sabe-se que indivíduos mais idosos necessitam instruções individualizadas sobre higiene, exercícios labiais e mastigação, que podem melhorar a SO em pacientes com DP[8, 56].

A DP está associada à hipossalivação ou xerostomia (drogas autonômicas e anticolinérgicas), sialorréia (motora e disfagia) e doenças orais (halitose, cárie, entre outras)[56] Ademais, o baixo fluxo salivar pode ser aliviado por meio da saliva artificial. O trabalho multidisciplinar entre cirurgião-dentista, neurologista e outras especialidades, contribuirão para avaliar as condições e estabelecer a melhor abordagem para conduzir o tratamento[55,56,60].

Além disso, pacientes com DP, cuja evolução clínica se encontra acentuada, apresentam maior frequência de cáries não tratadas[47,39]. Tal situação, pode ser amenizada com visitas regulares ao cirurgião-dentista.

No tocante à perda dos elementos dentais, recomenda-se instalações de próteses parciais ou totais[6]. Levando-se em conta que os pacientes em quadro avançado da DP, poderão ter comprometimento funcional em relação ao uso destas próteses, e em alguns casos, há indicação de implantes osteointegrados, em decorrência, por exemplo: de tremor, rigidez, xerostomia e salivação[55,56].

Por outro lado, pacientes com DP, que utilizam prótese dentária total, ao examinarem suas cavidades orais, houve relatos de quadros clínicos de estomatite protética, hiperplasia fibrosa inflamatória[57].

Enuncia-se a Doença Periodontal com abordagem em vários tipos de quadros clínicos, assim designadas como doenças gengivais ou gengivite, quando atingem os tecidos periodontais de proteção: gengiva e mucosa alveolar e, periodontite, quando alcançam os tecidos de suporte: osso alveolar, cemento e ligamento periodontal, igualmente associada a DP[7, 12, 39 47, 57]. A terapêutica multidisciplinar se baseia em ação profilática, antibacteriana, resultando na higiene oral, em método clínico periodontal, acompanhada por visitas clínicas regulares ao cirurgião-dentista como prevenção[57].

De modo comparável, neste estudo, pacientes com DP apresentaram prevalência de Disfunção temporomandibular (DTM), em consequência da alteração postural, controle de mandíbula e progressão dos sintomas, sobretudo em mulheres. A DTM deve ser tratada, como uma necessidade especial de cada paciente, de acordo com avanço da doença. Neste sentido, não houve nenhuma associação significativa entre DTM e gravidade da DP[45].

Acrescenta-se também, a BMS sua prevalência, não seja superior a 4% em pacientes com DP, constata-se que a condição estava associada à SO precária[58]. De maneira idêntica, o mal estado periodontal está associado a um risco aumentado da DP, ou seja, para evitar uma carga adicional de BMS para pacientes com DP, aconselha-se manter uma boa SO[59].

Com efeito, a suscetibilidade às doenças, também, pode vir a ocorrer devido a fatores extrínsecos, a nicotina aumenta o risco de doença neurodegenerativa e a má SO eleva o risco de DP[58].

Outro ponto importante, é que as doenças orais não apresentam sintomas somente com manifestações na cavidade oral, mas afetam condições de muitas doenças sistêmicas. Do mesmo modo, se identifica o papel essencial da saliva, das habilidades motoras finas que prejudicam a SO, já enfraquecida pela DP[8].

7. CONCLUSÃO

O presente trabalho averigua vários estudos, ao longo dos tempos, por meio de revisão da literatura, no tocante aos diferentes aspectos da saúde oral em pacientes portadores da doença de Parkinson.

Os estudos enfatizam evidências para estes pacientes, que há uma gama de variedade de doenças orais, que devem ser prevenidas, diagnosticadas e tratadas. Entendimento norteador, que ressalta uma boa higienização oral, como um todo.

Expressa ainda, significativamente a importância da terapêutica multidisciplinar, estabelecendo um conjunto de rotinas integradas, apontando às necessidades individuais de cada paciente, assim como, buscando proporcionar uma orientação da saúde oral adequada, com visitas regulares ao cirurgião-dentista.

Direcionamento que se manterá de forma constante, visto que, a saúde oral nos pacientes portadores da doença de Parkinson, exerce uma demanda de interação entre paciente, profissionais da saúde e família, a fim de repercutir positivamente na qualidade de vida e na saúde geral.

Dessa forma, constata-se que se requer acuidade no aprimoramento dos segmentos dos estudos, em relação aos sintomas da doença de Parkinson na saúde oral, justamente por conta da sua dinâmica de seus sintomas e do próprio avanço da Ciência.

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9. ANEXOS

ANEXO 1 - ESTRATÉGIAS DE PESQUISA

Medline (via Pubmed)	#1 "Parkinson Disease"[Mesh] OR (Idiopathic Parkinson's Disease) OR (Lewy Body Parkinson Disease) OR (Lewy Body Parkinson's Disease) OR (Primary Parkinsonism) OR (Parkinsonism, Primary) OR (Parkinson Disease, Idiopathic) OR (Parkinson's Disease) OR (Parkinson's Disease, Idiopathic) OR (Parkinson's Disease, Lewy Body) OR (Idiopathic Parkinson Disease) OR (Paralysis Agitans) #2 "Oral Health" [Mesh] OR "Oral Health" #3 #1 AND #2 (71)
Cochrane Central Register of Controlled Trials - CENTRAL (via Wiley)	#1 MeSH descriptor: [Parkinson Disease] explode all trees #2 MeSH descriptor: [Oral Health] explode all trees #3 #1 AND #2 (In Trials) (1)
Embase (via Elsevier)	#1 'Parkinson disease'/exp OR 'Idiopathic Parkinson's Disease' OR 'Lewy Body Parkinson Disease' OR 'Lewy Body Parkinson's Disease' OR 'Primary Parkinsonism' OR 'Parkinsonism, Primary' OR 'Parkinson Disease, Idiopathic' OR 'Parkinson's Disease' OR 'Parkinson's Disease, Idiopathic' OR 'Parkinson's Disease, Lewy Body' OR 'Idiopathic Parkinson Disease' OR 'Paralysis Agitans' #2 'Oral health care' OR 'Oral health' #3 #1 AND #2 (38)

Literatura Latino Americana em Ciências da Saúde e do Caribe - LILACS and BBO (Bibliografia Brasileira de Odontologia) (via Biblioteca Virtual em Saúde)	#1 MH:"Doença de Parkinson" OR "Parkinson Disease" OR "Enfermedad de Parkinson" OR MH:C10.228.140.079.862.500 OR MH:C10.228.662.600.400 OR MH: C10.574.812 #2 MH:"Saúde oral" OR "Oral Health" OR "Salud Bucal" OR MH: N01.400.535 OR MH:SP2.006.097 #3 (db:("LILACS" OR "BBO")) #3 #1 AND #2 AND #3 (11)

ANEXO 2 – IMPROVEMENT OF ORAL FUNCTION AND HYGIENE IN PARKINSON´S DISEASE: A RANDOMISED CONTROLLED CLINICAL TRIAL

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ORIGINAL ARTICLE

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Improvement of oral function and hygiene in Parkinson's disease: A randomised controlled clinical trial

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Abstract

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder. It is associated with reduced oral health and impaired oro-facial function, but besides recommendations of dental visits and drooling treatment, there are little documented odontological treatment options.

Objectives: To evaluate the effect of standardised home exercise jaw opening and chewing programmes, as well as home oral hygiene measures instructed and controlled by a trained dentist.

Methods: Twenty-nine patients (median 65 years) with moderate to advanced PD participated in the project after informed consent. They were followed at a Neurology Department, were able to cooperate, and had stable medical treatment and nine also deep brain stimulation. The interventions were individual dental hygiene instruction, training of jaw opening (JawTrainer), and lip and chewing exercises (Ulmer Oral Screen and Proxident Fluoride Gum). The study was performed as a randomised controlled study. The treatment effect was evaluated after 2 and 4 months. The primary outcome was maximum unassisted jaw opening capacity, chewing time of a standardised apple slice, and the Simplified Debris Index. Results were analysed with Wilcoxon matched pairs test and Mann-Whitney *U* test (significance level $P < .05$).

Results: Jaw opening, chewing time and hygiene were significantly improved 2 months from the start of the invention, respectively, 6%, 49%, and 25%, and the improvement was still significant after 4 months. No significant changes were found after the 2-month control period without intervention.

Conclusion: The simple measures had a substantial and significant clinical effect which is promising despite the progressive nature of the PD.

KEYWORDS

chewing, home setting, jaw exercises, oral hygiene, oro-facial dysfunction, Parkinson's disease

1 | BACKGROUND

Parkinson's disease (PD) is a slow progressive, age-related, common neurodegenerative disease with loss of dopaminergic neurons in the substantia nigra of the brain. It is a multisystem disorder clinically characterised by motor and non-motor (NM) symptoms.[1] The motor symptoms of PD include four cardinal features: bradykinesia (slowness of movements), rest tremor, rigidity and postural instability or gait impairment.[2] The NM symptoms include autonomic disturbances and neuropsychiatric dysfunctions such as depression, dementia and apathy. Most therapies are oriented towards symptomatic relief and do not have significant effect on the underlying disease process with respect

to either slowing progression or restoring the affected dopaminergic neurons.[3]

Patients with PD have jaw tremor, and rigid facial and masticatory muscles as well as poorer jaw function than subjects without PD.[4,5] These disorders seem to increase with the duration and severity of the PD. Studies have also shown that patients with PD have decreased oro-facial function, jaw mobility and oral health, even when they are treated for their PD.[6-11] In levodopa-treated PD patients, the masticatory function and bite force are also significantly lower when the effect of the drug is wearing off ("off" period) than when the medication is working optimally ("on" period).[12,13] There may be decreased self-cleaning of the oral cavity and impaired oral hygiene with increased risk of caries and periodontitis.[4,13] Thus, the findings of more missing teeth, caries and poorer periodontal health in patients with PD compared with control subjects have been ascribed to the lack of muscular control in patients with PD.[7,14]

The disease often begins at the age of 50-70, and the frequency increases with age, from 0.5%-1% in 65- to 75-year-olds up to ≥3% in 85-year-olds. Because of the growth of the elderly part of the population, the incidence of PD in the population is increasing. Consequently, the oro-facial disorders and disabilities in patients with PD may become a major societal problem. There is therefore an increasing need for oro-facial interventions. However, most published reports including our own have primarily dealt with mapping and incidence of the oral problems, and the conclusions have generally been that dentists must pay more attention to preventing and treatments of these problems.[4] Development of guidelines, multidisciplinary care and incorporation of oral health into interprofessional care teams for patients with PD are discussed, but there are little documented odontological treatment options.[15-17]

The present purpose was therefore to carry out a study with oral interventions to maintain and even improve oro-facial function and oral hygiene in PD patients in terms of training of jaw mobility, chewing, and lip and cheek muscles, together with individual oral care instructions.

2 | MATERIALS AND METHODS

The investigation complies with the guidelines of the Declaration of Helsinki and was approved by the Committee on Health Research Ethics of the Capital Region (H-17039142), and of the Faculty of Health and Medical Sciences and the Danish Data Protection Agency (SUND-2017-68).

2.1 | Participants

The patients were recruited by the neurologists in the Day Hospital and Outpatient Clinic at the Department of Neurology, Bispebjerg University Hospital (Copenhagen, Denmark) in the period from February 2018 till November 2018, and the data collection ended in January 2019. The patients were chosen among the patients who fitted the inclusion

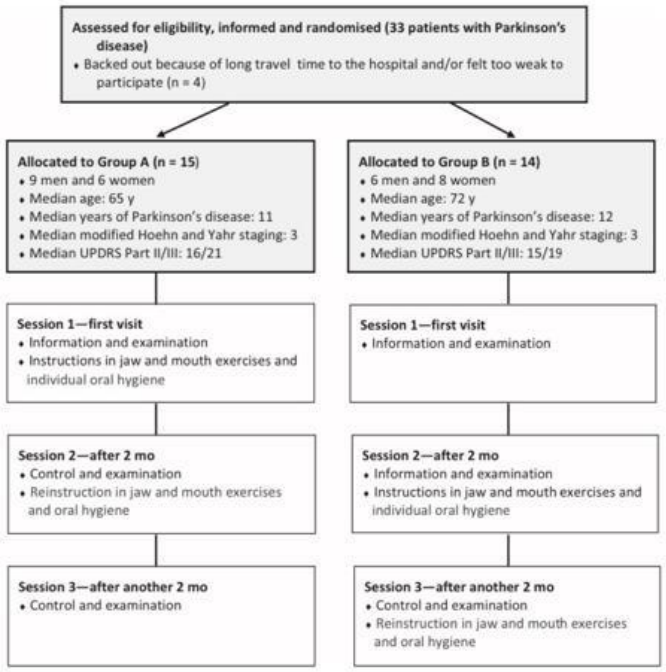

FIGURE 1 Design of the study showing dropout, randomisation and the delayed onset of the interventions in Group B (acting as a "temporary" control group) compared with Group A. UPDRS, Unified Parkinson's Disease Rating Scale[20]

criteria: moderate to advanced PD corresponding to UK Brain Bank Criteria and Hoehn and Yahr stages.[18,19] They should also be in stable medical treatment for PD motor symptoms the last month prior to inclusion and able to cooperate in the entire project. Patients were excluded if they were suffering from any other serious illness which might affect the trial results. Patients fitting the criteria were offered to participate in the study and were free to decline without any consequences for their treatment at the hospital. They were informed that no adverse events, risks or disadvantages were expected in the study. Thirty-three accepted to participate after informed consent and were randomised. However, four patients backed out later because of long travel time to the hospital and/or felt too weak to participate (Figure 1).

As a result, the study group included 29 patients, 15 males and 14 females, 32-79 years (mean 65, SD 10), with Hoehn and Yahr staging 2-4 (Table 1) and the range of the scores on the Unified Parkinson's Disease Rating Scale (UPDRS) Part II (motor aspects of experiences of daily living) were 8-23 and on the UPDRS Part III (motor examination) 12-31.[19,20] The time of the diagnosis of their PD ranged from 3 to 20 years ago (Table 1). The medication consisted typically of MAO-B inhibitors, dopamine agonists, COMT inhibitors and levodopa medicine. In patients with "on-off" fluctuation, the examination was performed in the "on" period.

The screening for oro-facial dysfunction (Nordic Orofacial Test–Screening, NOT-S) varied from none to very severe dysfunction (Table 1).[21] None had temporal joint pain or systematic pain during maximal jaw opening. Three had crepitus in one or both temporomandibular joints probably due to normal variation, ageing or remodelling of the joint (DC/TMD)[22,23] The number of present natural teeth ranged from 10 remaining teeth to a full complement of teeth. Twenty patients had tooth contact in all four occlusal support zones (Eichner's index A1-A3),[24] and nine had no occlusal contact on natural teeth, fixed prostheses or dental implants in one or two supporting zones (Eichner's index B1-B2), but only two had no occlusal contact in both molar regions.

2.2 | Study design

The study was performed as a randomised controlled clinical trial (Figure 1), and no blinding was performed. The participants were allocated by lot drawing to either Group A or Group B. Both groups received information about the study and were examined at their first visit (Session 1). Group A also received and was instructed in a standardised exercise programme for the jaw and mouth together with individualised counselling and instruction in oral hygiene in Session 1, while Group B did not receive any exercise instructions or counselling. Both groups were re-examined 2 months later (Session 2). Group A was reinstructed and re-counselled and Group B (acting as a control group the first 2 months; Figure 1) received the standardised jaw and mouth exercise and the individualised instruction in oral hygiene. Two months later, that is 4 months after the first visit, both groups came for their last visit and were re-examined (Session 3; Figure 1). In addition, Group B was also reinstructed and re-counselled. Thus, all patients received the same interventions, but Group B's interventions were delayed as they acted as a control group between Sessions 1 and 2 (Figure 1).

All three authors planned and wrote the project. MK recruited, informed and included the participants, SB examined and instructed the participants regarded training and oral care, and MB performed the statistical analyses. SB and MB wrote the first draft, and all three corrected and approved the final draft.

2.3 | Interventions

2.3.1 | Home training programme

The standardised programme consisted of three exercises to perform in a home setting to increase jaw mobility and train the masticatory, lip and cheek muscles to facilitate oral function:

- Training of the jaw opening mobility with a JawTrainer.[25] Instruction: Place the trainer between the front teeth. Press slowly on the clamp until the cheeks begin to tighten, but without pain. Keep the pressure for ½ minute, rest for ½ minute. Repeat the exercise ten times a day.
- Training of lip and cheek muscles with an Oral Screen (Ulmer model) Maxi. [26] Instructions: Place the mouth screen in front of the teeth in the mouth. Then pull the ring so that the lip muscles are tightened for ten seconds. Repeat the exercise 10 times a day.
- Training of the chewing function and the masticatory muscles with Proxident Fluoride Gum. [27] Instructions: Chew one piece of gum for ½ hour. If it is too tiring to chew a whole piece of gum, start with ½ a piece for 15 minutes and then increase the time and gum size up to the recommended week by week. Repeat the exercise twice a day.

2.3.2 | Oral hygiene programme

The individualised programme consisted of advices, counselling and instruction regarding oral hygiene for home care twice a day:

- Delivery of a special toothbrush (Dr Barman's Special) as a supplement to the patient's ordinary toothbrush or eventually a denture brush.[28,29]
- Instruction on cleaning between the teeth and demonstration of the use of dental floss with holders for removal of plaque on approximal surfaces.

2.4 | Outcomes

The primary outcome measures regarding oral function were maximum unassisted jaw opening capacity (the interincisal distance in mm taking the vertical overbite taking into account; recorded according to Diagnostic Criteria for Temporomandibular Disorders, DC/TMD and

TABLE 1 Oro-facial function, dentition and oral hygiene in 29 patients with Parkinson's disease (PD) in Session 1 without any interventions, and before instructions in jaw and mouth exercises and oral hygiene

Mean ± SD, median (range) and correlations in Session 1 without interventions	Modified Hoehn and Yahr staging: 2.9 ± 0.4 3 (2-4)	UPDRS Part II: 15.0 ± 4.5 15 (8-23)	UPDRS Part III: 20.6 ± 4.9 21 (12-31)	Years of Parkinson's disease: 11.7 ± 5.0 11 (3-20)
Nordic Orofacial Test—Screening for dysfunction (0 to 12):				
3.1 ± 2.0	r_s 0.30	r_s 0.66	r_s 0.41	r_s 0.2
3 (0-8)	*P*: .1	*P*: .0001*	*P*: .03*	*P*: .4
Chewing time of a standard apple slice (seconds):				
28.4 ± 13.5	r_s 0.06	r_s 0.41	r_s 0.04	r_s 0.32
25 (12-70)	*P*: .8	*P*: .03*	*P*: .9	*P*: .1
Maximum unassisted jaw opening capacity (mm):				
49.2 ± 6.9	r_s 0.05	r_s 0.09	r_s 0.05	r_s 0.03
50 (37-67)	*P*: .8	*P*: .6	*P*: .8	*P*: .9
Number of present natural teeth (0-32):				
25.6 ± 4.4	r_s −0.33	r_s −0.42	r_s −0.19	r_s −0.05
26 (10-32)	*P*: .08	*P*: .02*	*P*: .3	*P*: .8
Oral Hygiene Index—Simplified (DSI; 0.0 to 3.0):				
1.1 ± 0.6	r_s 0.06	r_s 0.35	r_s 0.14	r_s 0.28
1.2 (0.2-2.5)	*P*: .7	*P*: .06	*P*: .5	*P*: .1

Abbreviations: r_s, Spearman rank correlation coefficient; UPDRS, Unified Parkinson's Disease Rating Scale.[20]
*$P < .05$.

chewing time from first bite to swallow of a standardised crisp apple slice (seconds; 10 g of Granny Smith with the rind and core removed).[4,22,23,29] The secondary outcome was oral hygiene performance (0-3; Simplified Debris Index, DI-S, assessed as the degree of the average plaque coverage on the surfaces of four posterior and two anterior teeth).[30]

2.5 | Statistical evaluation

2.5.1 | Sample size

Based on clinical experience in patients with temporomandibular disorders, it was realistic to assume that the maximum unassisted jaw opening capacity may increase ≥5 mm after training of the jaw opening over a few months in half of the participants. At the same time, some random fluctuation in the measured jaw opening might also be expected, which could be set to approx. 4%. Strength calculation showed that it would require 30 patients, 15 in each group, to have a 90% chance of detecting an increase, which is significant at the 5% level after 2 months from an estimated random increase of approx. 4% in Group B (control) to 50% in Group A (experimental) after training.[31]

2.5.2 | Statistical analysis

The data were first analysed with descriptive statistics (mean, SD, median and range). Then, non-parametric analyses were performed using Statistica, version 5.0 (StatSoft) on the outcome parameters with a statistical significance accepted at $P < .05$.

The scale values in the patients on the oro-facial dysfunction, the number of natural teeth and the outcome parameters before invention were associated with the values describing the severity and duration of the PD using Spearman's rank-order correlation analysis (r_s). The changes of the outcome parameters from Session 1 to Session 2 in Group A were compared with the changes in Group B (acting as a control group the first 2 months) Mann-Whitney *U* test. The values in Sessions 2 and 3 vs Session 1 in both Group A and Group B were compared with Wilcoxon matched pair test.

3 | RESULTS

3.1 | At inclusion

The mean and median values from the whole group of participants corresponded to or deviated only slightly from reference values, but the individual values varied considerably (Table 1). The severity of oro-facial dysfunction (NOT-S) was significantly and positively correlated with general PD motor symptoms and findings (UPDRS Part II and III r_s 0.66 and r_s 0.41, $P \leq .003$; Table 1). Also the number of natural teeth was significantly, but negatively associated with the PD motor symptoms (UPDRS Part II r_s −0.42, *P*: .02; Table 1).

TABLE 2 Use of the delivered jaw and mouth training devices and the special tooth brush in 29 patients with Parkinson's disease (PD) reported in Session 3 (last visit)

	Training of the jaw opening mobility with the JawTrainer[7]	Training of lip and cheek muscles with the Oral Screen (Ulmer model) Maxi[7]	Training of the chewing function and the masticatory muscles with Proxident Fluoride Gum[7]	Tooth cleaning with Dr Barman's Special tooth brush[7]
The number of active users within the last 2 mo				
% patients	86.2	89.7	82.8	69.0
The number of days with use per week within the last 2 mo				
Mean ± SD	4.4 ± 2.8	4.6 ± 27	4.4 ± 2.8	4.6 ± 3.3

3.2 | During intervention

All participants followed instructions and applied most of the training and oral care aids. Thus, 69%-90% (Table 2) used all or several of the delivered training devices and the special tooth brush regularly, and about 4-5 days per week. No harm or side effects were detected, but a few patients found it troublesome to use the devices, for example JawTrainer due to pronounced gag reflex or the Proxident Fluoride Gum because of missing teeth or partial dentures. Others were satisfied with their own electric tooth brush and felt little need for Dr Barman's Special tooth brush (Table 2).

3.3 | After intervention

3.3.1 | Primary outcomes

The maximum unassisted jaw opening capacity and the chewing time of a standard apple slice were significantly improved 2 months after the start of the inventions (Session 2, +6 and −25% $P \leq .02$; Figure 2 and Table 3), and the levels were still significant after 4 months (Session 3, +8 and −29% $P \leq .009$).

The changes measured in Session 2 were also significantly greater in Group A than in Group B, the last acting as control the first 2 months (Group B, +0% and +0% $P \leq .03$; Figure 2 and Table 3). In Group B after 2 months of intervention, that is Session 3, the improvement was also significant (+6% and −25% $P \leq .01$; Figure 2 and Table 3).

In addition, 45% of the patients indicated chewing and swallowing problems in the NOT-S before and 35% after 2 months of training.

3.3.2 | Secondary outcome

The Simplified Debris Index was significantly reduced 2 months after the start of the inventions in Group A (Session 2, −56% *P*: .02; Figure 2 and Table 3), and the levels were still significant after 4 months (Session 3, −67% *P*: .001).

The changes measured in Session 2 were also significantly greater in Group A than in Group B, the last acting as control the first 2 months (Group B, +14% *P*: .00007; Figure 2 and Table 3). In Group B after 2 months of intervention, that is Session 3, the improvement was also significant (−43% *P*: .004; Figure 2 and Table 3).

4 | DISCUSSION AND CONCLUSION

The incidence of PD is increasing in the healthcare system due to the growing proportion of the elderly. It is therefore important to investigate and treat the oro-facial and odontological issues that patients struggle with. Our study showed that the degree of oro-facial dysfunction and dental state in the patients were either significantly associated or tended to be associated with their general PD symptoms. These findings were consistent with previous studies.[4,5] The PD patients have also reduced capability to carry out daily oral hygiene manoeuvres, which inevitably will lead to accumulation of plaque and debris, and risk of development of periodontal disease and caries.[14]

Oro-facial function as chewing is a complex process involving integrated activities of the jaw elevator and depressor muscles, the lips, cheek and tongue. [32] These activities result in patterns of rhythmic jaw movements, food manipulation and the crushing of food. The rigidity of the jaw muscles around the mouth and the slow movements impair jaw mobility and chewing, and may cause waste of food or liquid out of the mouth and limit the intake and the choice of food. Thus, the chewing problems may also contribute to the weight loss that is often seen in PD.[33] In the present study, almost half of the patients reported chewing and swallowing problems in the NOT-S. We tried to improve the integrated oro-facial function in several ways by chewing exercises and specific exercises for stretching and activation of jaw, lip and cheek muscles. This resulted in a significantly shorter chewing time with a reduction of 49% after 2 months of training, and fewer patients complained of chewing and swallowing problems. The increase of the maximal jaw opening capacity was less, 6%, probably because the capacity was already within normal range in most patients.

Healthcare professionals including dentists may not always recognise the severity and the oral consequences of PD, and no jaw and mouth exercises or hygiene instructions are generally included in the medical advices and the advocated training and exercises for PD patients. This is astonishing since gait training with treadmill walking and resistance training, that is body exercises similar to chewing and jaw exercises, are recommended as effective

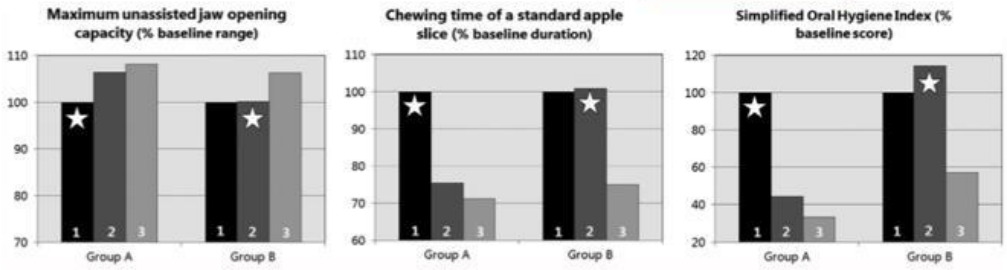

FIGURE 2 The relative change of the clinical evaluation of maximum unassisted jaw opening capacity (left; the interincisal distance taking the vertical overbite taking into account), chewing duration of apple (middle; 10 g slice of Granny Smith with the rind and core removed) and oral hygiene (right; Simplified Debris Index, the average plaque coverage on the surfaces of four posterior and two anterior teeth) compared to baseline (Session 1, 100%; black), after 2 mo (Session 2; dark grey) and after 4 mo (Session 3; light grey).[4,23,29,30] The stars indicate when the participants were instructed in the interventions after which they started the home exercises and oral care

TABLE 3 Oro-facial function and oral hygiene in 29 patients with Parkinson's disease (PD) before and after instructions in jaw exercises and oral hygiene

	Session 1 Baseline Intervention: A: instruction B: none	Session 2 +2 mo Intervention: A: reinstruction B: instruction	Wilcoxon matched pairs test: Session 2 versus Session 1	Session 3 +4 mo Intervention: A: control B: reinstruction	Wilcoxon matched pairs test: Session 3 versus Session 1
Group A: 15 patients (9 male, 6 female), median age 65 y					
Maximum unassisted jaw opening capacity (mm)					
Median (range)	50 (39-67)	52 (42-73)	*P*: .002*	53 (44-73)	*P*: .002*
Chewing time of a standard apple slice (seconds)					
Median (range)	26 (17-49)	19 (10-36)	*P*: .02*	19 (11-32)	*P*: .009*
Oral hygiene—Simplified Debris Index (DSI)					
Median (range)	1.2 (0.1-1.7)	0.3 (0.1-0.7)	*P*: .003*	0.2 (0.0-0.8)	*P*: .001*
Group B: 14 patients (6 male, 8 female), median age 72 y					
Maximum unassisted jaw opening capacity (mm)					
Median (range)	48 (37-57)	48 (35-56)	*P*: .5	51 (41-59)	*P*: .001*
Chewing time of a standard apple slice (sec)					
Median (range)	29 (12-70)	33 (11-76)	*P*: .7	24 (9-49)	*P*: .01*
Oral hygiene—Simplified Debris Index (DSI)					
Median (range)	1.5 (0.3-2.5)	1.7 (0.5-3.0)	*P*: .01*	0.8 (0.2-1.6)	*P*: .004*

*$P < .05$.

non-pharmacological aids in PD.[2,34] Thus, general stretching and flexibility exercises and rhythmic body activity improve and preserve both range of movement of the joints and gait capacity.[35,36] Our results showed that it was possible to reduce the impact of the disease on the oral function and hygiene both evaluated after 2 and 4 months. This has not been shown before. However, there is evidence that the effect of gait, and strength and resistance training in other parts of the body in PD patients may sustain for 3-6 months.[34]

Even with a small number of patients, the variation in age and number of natural teeth, and a relatively short observation time, our results are clear: patients with moderate to advanced PD can be motivated to train and increase jaw mobility and chewing ability by means of physical exercises performed at home. Thus, the JawTrainer, Oral Screen and Proxident Fluoride Gum were used on an average of 4 days per week by 83%-90% of the patients. They were also able to follow oral hygiene instructions, change their homecare habits and improve the overall oral hygiene. However, 31% preferred their electric tooth brushes and only used Dr Barman's Special tooth brush as a supplement. The relative simple training and care measures had a substantial and significant clinical effect, which is promising. The devices and dental products were relatively cheap, less than 150 US dollars, but examination and instruction were somewhat time-consuming, approximately 2 hours per patient, including one or two follow-up consultations. However with the progressive nature of the

disease, it is important to investigate whether a positive effect can be maintained over a longer period than 4 months.

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ANEXO 3 – ORAL HEALTH CONDITION OF ELDERLY PEOPLE WITH PARKINSON DISEASE

Oral health condition of elderly people with Parkinson disease

Condição de saúde bucal de idosos com doença de Parkinson

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Abstract

The oral hygiene of individuals with Parkinson disease (PD) is markedly impaired by difficulties in toothbrushing due to motor impairment and tremors. Additionally, it appears that other features associated with PD have an impact on the quality of oral health. Objective: this cross-sectional observational study characterized the oral health condition of individuals with PD. Methods: fifty individuals with PD, aged 53 to 94 years, users of medication for such condition were examined. The research participants had their oral cavities examined to assess prosthetic use and need; index of Decayed, Missing and Filled Teeth (DMFT); Community Periodontal Index (CPI); Periodontal Attachment Loss (PAL); and oral mucosa. In addition, a questionnaire was applied to obtain personal data, general health, and oral health. The data were analyzed using descriptive statistics. Results: a high prosthetic use was observed in the upper arch (92%), while the lower arch revealed high prosthetic need (66%). The DMFT index showed a high number of missing teeth, CPI showed a prevalence of 43% of dental calculus, and PAL revealed 28% of attachment loss of 4-5 mm. The most frequent findings in the assessment of oral mucosa were denture stomatitis and inflammatory fibrous hyperplasia. Conclusion: PD patients refer xerostomia and present high number of missing teeth, a minority of healthy teeth, and oral lesions, representing a target population for specialized oral health care.

Keywords: Elderly people. Oral health. Parkinson disease. Xerostomia.

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Introduction

Parkinson disease (PD) is a dementia characterized by motor symptoms, namely bradykinesia, muscle rigidity, bent posture, motor blocking, and postural instability associated with tremors. Additionally, there are cognitive deficiencies even in the initial stages of the disease. The resting tremor, in most cases, is the first symptom[1]. Its etiology is still unknown but some factors have been indicated as potential causes, such as genetic factors, environmental toxins, oxidative stress, idiopathic causes, and mitochondrial abnormalities[2].

The highest prevalence of PD involves elderly people, with an onset peak age of about 60 years[2-4]. Parkinson disease is universally distributed, affecting all ethnic groups and socioeconomic levels with an estimated prevalence of 100 to 200 cases every 100,000 inhabitants. Due to the high prevalence of the disease and the high demand for antiparkinsonian medication, PD generates a world annual cost of 11 billion dollars[5].

The standard medication for PD treatment is levodopa and it may be associated with other medications. Treatment options vary depending on the stage of the disease, the patient's age, and the cost. Physical therapy and nutritional guidance should also be included in the rehabilitation to improve quality of life. The goal of PD treatment is to prevent the disease from progressing, considering that it has no cure currently[5].

It is estimated that xerostomia affects approximately 55% of the individuals with PD because of the use of antidepressants and antipsychotics[4,6,7]. Other common oral illnesses include oral ulcerations, tong edema, change in taste, oral discomfort, or problems with prosthesis retention. The 'burning mouth syndrome' is also associated with xerostomia and the use of levodopa[4,6]. The adequate oral hygiene of PD patients may be impaired due to the motor impairment and tremors, and they might depend on family members and/or caregivers to have their oral hygiene properly done[1,4].

A debilitated oral health may be a risk factor for the development of other conditions such as cardiovascular diseases, pulmonary disease, atherosclerosis, and cerebrovascular accident[8,9,10]. In addition, pneumonia resulting from the aspiration of remnants from a poor oral hygiene is not uncommon in elderly people with PD[1,6]. It has been suggested that the orofacial function of these individuals may be impaired by the loss of motor function of the orofacial muscles and it may affect jaw mobility and the extent of mouth opening[11].

Therefore, given the high global prevalence of PD and in light of the factors that affect the correct oral care of these individuals and its consequences, this study aimed to characterize the oral health status of patients with PD and its impact on daily life.

Material and Method

Cross-sectional observational study including the elderly population with Parkinson disease (PD) in the city of Chapecó, state of Santa Catarina, southern Brazil. The study was approved by the institutional Research Ethics Committee under protocol no. 078/CEP/2013. The pharmaceutical department of the Municipal Health Service provided a list of individuals who required the medication for PD treatment. A sample of 50 elderly people received a full explanation of the objective of the study and they were invited to participate in the study through phone call. Oral health was assessed according to the World Health Organization criteria[12]:

(i) use and need of dental prostheses. Prosthetic need was characterized as the use of a non-functional, defective prosthesis; therefore, one could use prosthesis and need prosthesis in the same arch;

(ii) index of decayed, missing and filled teeth (DMFT) subdivided into coronal and root. A tooth was considered decayed when there was visual evidence of cavity that could be confirmed in occlusal, buccal, and lingual aspects of the tooth by probing with the CPI probe;

(iii) Community Periodontal Index (CPI), evaluated as the presence and depth of periodontal pockets, subgingival calculus,

and gingival bleeding in index teeth for sextants on probing with the CPI probe, designed with a 0.5 mm ball tip, a black band between 3.5 and 5.5 mm, and rings or marks at 8.5 and 11.5 mm[12]. The CPI was coded as follows: 0 (healthy), 1 (bleeding on probing), 2 (calculus detected during probing, but all the black band of the probe is visible), 3 (4-5 mm periodontal pocket and gingival margin within the black band of the probe), 4 (periodontal pocket of 6 mm or more, with the black band of the probe not visible), X (sextant excluded, less than two teeth present);

(iv) Periodontal Attachment Loss (PAL), assessed by probing of the same index teeth. It is referenced by the exposure of the cementoenamel junction, which indicates the presence of gingival recession. The PAL was coded as 0 (attachment loss of 0-3 mm, CEJ is not visible and CPI value between 0-3 mm), 1 (attachment loss of 4-5 mm, CEJ within the black band), 2 (attachment loss of 6-8 mm, CEJ between the upper limit of the black band and the 8.5 mm ring), 3 (attachment loss of 9-11 mm, CEJ between the 8.5 and 11.5 mm rings), 4 (attachment loss of 12 mm or more, CEJ beyond the 11.5 mm ring), X (sextant excluded, less than two teeth present). For both periodontal indexes the worst condition was registered;

(v) presence of mucosal oral lesions, categorized as normal mucosa or presence of lesion. It assessed upper and lower labial mucosa and labial sulci, labial part of the dorsal and ventral commissures and margins of the tongue, buccal mucosa, palate, floor of the mouth, retromolar area, and upper and lower gingiva.

The independent variables were assessed by applying a modified version of the Geriatric Oral Health Assessment questionnaire[13] and it involved data on sociodemographics, education, access to oral health services, and oral and general health data.

A specialist in periodontology and stomatology and a specialist in operative dentistry trained two dental students of the fourth year (CZ and NRSM) using slide presentations and discussion sessions for consensus. Clinical examinations for calibration were performed in eight elderly people with mean age of 74 years and of both genders. Due to the categorical nature of the variables, the inter-examiner agreement was assessed using the Kappa coefficient, which varied from 0.4 to 1.0. The student who presented the highest agreement with the gold-standard examiners conducted the clinical examinations during the fieldwork.

The research subjects were examined at home and signed a consent form after being instructed on the study objectives. Clinical examinations were performed using sterile gauze, dental mirror, and CPI probe. The examiner used a light source attached to the head. The data were tabulated and analyzed using descriptive statistics with the SPSS 20 package.

Results

The mean age of the participants was 72.9 ± 9.6 years, ranging from 53 to 94 years. Sixty-four percent of the participants were women, 52% were married, 38% widows, 6% divorced, and 4% single. Seventy-two percent were illiterate or had not completed primary education, 4% had completed primary education, 12% had not completed high school, 10% had completed high school, and 2% had completed higher education.

All the research subjects used medications daily. The most frequent medications consumed were antiparkinsonians and antihypertensives. Eighty-four percent had the last visit to the dentist within the last 3 years and 10% for more than 5 years. Fifty percent claims having received hygiene instructions from the dentist and 46% claims to brush their teeth twice a day and 48% three times a day. Figure 1 presents the frequency of prosthetic use and need and the DMFT index of the participants.

Seventy-four percent of the participants who used prosthesis in the upper arch used total dentures, followed by 12% who used removable partial dentures, 4% who used one fixed bridge, and 2% who used more than one fixed bridge. Forty-two percent of those who used prosthesis in the lower arch used total dentures, followed by 22% who used removable partial dentures, and 2% who used one fixed bridge. Most of those who needed prosthesis in the upper arch needed total dentures (42%), followed by 12% who needed a fixed or removable denture to replace one dental element, and 2% who needed a combination of either fixed or removable dentures to replace more than one dental element. Most of those who needed lower prosthesis (32%) needed a fixed bridge or a removable denture to replace more than one dental element, followed by 26% who needed total dentures, 6% who needed the combination of fixed and removable dentures to replace more than one element, and 2% who needed a fixed or removable denture to replace one dental element.

The mean total DMTF index for crown was 28.9 ± 4.0, with mean indexes of decayed, missing and filled crowns of 0.6 ± 1.4, 26.1 ± 7.2 and 2.2 ± 3.3, respectively. The mean total DMTF index for root was 26.2 ± 7.1, with mean indexes of decayed, missing and filled roots of 0.1 ± 0.5, 25.7 ± 7.6 and 0.4 ± 0.8, respectively.

Forty percent of the participants presented oral mucosal lesions, 38% presented palatal lesions, 10% in the lips, 8% in the buccal mucosa and commissures, and 6% in the labial sulci. Fifty percent of the participants presented calculus, while other 16% were considered healthy. In spite of being lower, the rate of healthy subjects, when considered as a sextant/subject ratio, was the highest observed (Table 1). Proportions of 20% and 4% were observed for the presence of 4-5 mm deep pockets and 6 mm or more, respectively. As for periodontal attachment loss, the highest rate was for healthy sextants, with 48% of the subjects, followed by 30% of the subjects presenting 4-5 mm attachment loss.

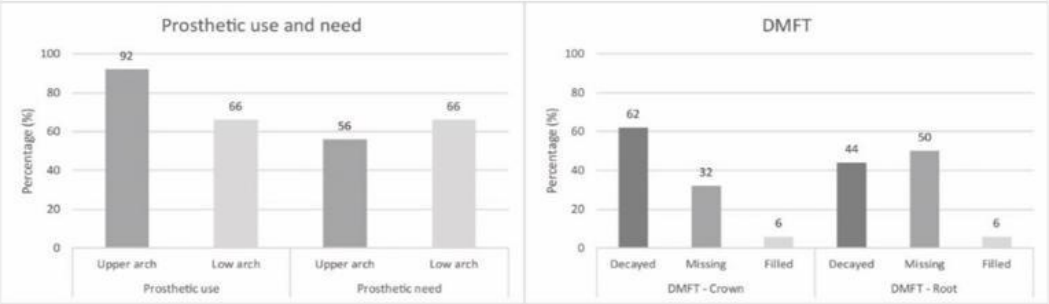

Figure 1 – Frequency of prosthetic use and need, and decayed, missing and filled teeth of the participants

Source: the authors.

Table 1 – Community periodontal index (CPI) and periodontal attachment loss (PAL) of the study participants (n=50), expressed as number of sextants, number of subjects, and sextant/subject ratio

	Sextants	Subjects	Sextant/subject ratio
Community Periodontal Index (CPI)			
0 Healthy	21	8	2.63
1 Bleeding on probing	3	3	1
2 Calculus detected during probing	35	25	1.4
3 Pocket of 4-5 mm	18	10	1.8
4 Pocket of 6 mm or more	3	2	1.5
Periodontal Attachment Loss (PAL)			
0 Healthy – attachment loss of 0-3mm	53	24	2.21
1 Attachment loss of 4-5 mm	23	15	1.53
2 Attachment loss of 6-8 mm	5	4	1.25
3 Attachment loss of 9-11 mm	0	0	0
4 Attachment loss of 12 mm or more	0	0	0

Source: the authors.

Table 2 presents results regarding oral health impact and Table 3 shows the data for the oral health impact on feeding and dietary habits. When asked whether they had a regular intake of fermentable sugar-rich food, pasty food, and soft drinks, 48%, 94%, and 76% answered affirmatively, respectively.

Table 2 – Perceived oral health impact of the study participants (n=50)

	N (%)
How do you classify the salivary flow in your mouth?	
Low (dry mouth)	33 (66%)
Normal	15 (30%)
High (hypersalivation)	2 (4%)
Do you feel your mouth burning?	
Always	1 (2%)
Sometimes	11 (22%)
Never	38 (76%)
Are your teeth or gingiva sensitive when in contact with cold, warm, or sweet?	
Always	4 (8%)
Sometimes	12 (24%)
Never	34 (68%)
Do you feel your speech is impaired due to your teeth or prosthesis?	
Always	0 (0%)
Sometimes	13 (26%)
Never	37 (74%)
Have you noticed any mobility in your teeth?	
Yes	5 (10%)
No	45 (90%)
Have you had any tooth, restoration, or prosthesis fractured due to tremors?	
Yes	2 (4%)
No	48 (96%)
Do you bite your tongue, lips, or cheeks?	
Yes	12 (24%)
No	38 (76%)
Have you used any medication to relieve the discomfort in your mouth?	
Yes	3 (6%)
No	47 (94%)

Source: the authors.

Table 3 – Oral impact on feeding of the study participants (n=50)

	N (%)
Do you limit the type and/or amount of food intake due to problems with your teeth or prostheses?	
Always	5 (10%)
Sometimes	22 (44%)
Never	23 (46%)
Do you have any difficulty in chewing solid food, such as meat or an apple?	
Always	10 (20%)
Sometimes	15 (30%)
Never	25 (50%)
Do you swallow comfortably?	
Always	31 (62%)
Sometimes	16 (32%)
Never	3 (6%)
Can you eat without any discomfort?	
Always	22 (44%)
Sometimes	25 (50%)
Never	3 (6%)

Source: the authors.

Discussion

Descriptive studies are performed to describe the occurrence of a condition or the health status of a certain population[14]. Characterizing the health condition of a population is the first step for planning health promotion activities. In this study, a specific sample including subjects with Parkinson disease (PD) had their oral health assessed, considering the specificities of the disease and their impact on oral health management. This study identified a high number of missing teeth associated with a low number of healthy teeth, high need of prosthesis in the lower arch, and high prevalence of oral mucosal lesions. Most participants also referred xerostomia.

Parkinson disease is an age-related condition that rarely manifests in individuals under 40 years old. It most commonly begins in older adults with an onset age of about 60 years and it presents a lifetime risk of about 2%[2]. In the present study, the age of PD patients ranged between 53 and 94 years, with a mean of 73 years old, which confirms the aging trend aforementioned.

There is also a tendency for increased use of medication as age advances, due to the incidence

of new diseases. The most common medications PD patients use include antidepressants, antihistamines, antiparkinsonians, antipsychotics, diuretics, antihypertensives, anticholinergics, and antineoplasics[15]. In this study, all research subjects reported daily use of antihypertensives and antiparkinsonians, and levodopa was the mostly used.

Sixty-six per cent of our research participants referred dry mouth (Table 2). Xerostomia, which is characterized by the subjective sensation of dry mouth, is one of the most frequently reported oral manifestations in elderly people with PD[16,17]. The prevalence of xerostomia, which is of 3-5% in the general population and 20% in elderly people with no neurological disorders, raises up to 55% in subjects with PD[16]. Regardless of the fact that the mechanism behind this condition is not fully understood at the moment, it appears to occur due to a dysfunction in the center of salivary control in the brain[18] and it has also been associated with the use of levodopa and with its dose[17].

Saliva plays an important protective role in the oral cavity, working as a natural lubricant that washes out bacteria and biofilm from mucosal and dental surfaces. It also has a buffer effect that helps controlling the oral pH and it is an ion carrier, storing and providing ions for the process of tooth remineralization[17,18]. Therefore, the reduction of salivary flow has a negative impact on the oral health condition of subjects with PD, considering its protective effect against caries and periodontal diseases decreases[17,18].

Burning mouth syndrome is another condition commonly associated with the elderly (prevalence of approximately 40%)[19], including those with PD[20]. Twenty-four per cent of our sample referred the feeling of burning mouth, but only one subject referred it as a constant occurrence. The burning mouth syndrome is a challenging condition to health professionals because it lacks diagnostic criteria, a clear understanding of its etiology and risk factors, and a well-established clinical guideline indicating the adequate treatment options[19]. Additionally, it affects the quality of life of the subjects, which is determined by severity[21]. Some hypotheses for the causes of burning mouth syndrome include the organic deficiency of vitamins and minerals, hormonal dysfunction, candida infection, parafunctional habits, and depression[21]. However, it is worth noting that some of these conditions are differential diagnoses for burning mouth syndrome and they should be properly acknowledged for a correct diagnosis. Although xerostomia may be associated with burning mouth syndrome, a potential further etiological role requires clarification[21]. In fact, in our study, the prevalence of xerostomia was more than twice higher than that of burning mouth and the subjects referring burning pain in their mouths did not necessarily manifest dry mouth symptoms.

Although the rate of individuals with decayed teeth and restorative need ranged from 40% to 62%, for root and crown, respectively (Figure 1), the mean index of decayed teeth was 0.62 for crowns and 0.12 for roots. The National Oral Health Survey – SBBrasil[22] (2010) revealed a 0.23 average of decayed roots in individuals aged 65-74 years. The oral health of subjects with PD has shown to be poorer than for those with no neurological impairment[1,11,18,23]. In this sense, oral health maintenance, especially the control of caries and periodontal disease, strongly rely on satisfactory oral hygiene. Several features associated with PD may affect the quality and frequency of oral hygiene procedures, namely the impaired fine motor skills that interfere with hand performance during toothbrushing and flossing. Motor difficulties include tremor, akinesia, and muscle rigidity[23,24]. Swallowing dysfunctions and cognitive disturbances such as dementia and apathy may also interfere with the oral hygiene routine of PD patients[18,23].

Nevertheless, Fukayo et al.[6] (2003) observed that PD patients with mild symptoms presented higher toothbrushing frequency than the control subjects and concluded that the features of PD may not entirely explain the differences in oral health status. In our study, for instance, 94% of the subjects with PD stated brushing their teeth twice or three times a day and 50% acknowledged having received oral hygiene instructions from their dentists. One likely explanation for the low index of decayed teeth is the high missing component of the DMFT index. Thirty-two

percent of the subjects presented missing crowns and 50% presented missing roots.

The general DMFT index of individuals aged 65-74 years by the National Oral Health Survey – SBBrasil[22] (2010) was 27.53, with the missing component accounting for 92% of the total index. In our study, missing teeth accounted for 90% and 98% of the DMFT index for crown and root, respectively. The total DMFT index of the study was similar to that reported by the epidemiological survey. Significantly, poorer nutrition has been associated with edentulous people in comparison to those with natural teeth[14].

The periodontal status of the subjects with PD was evaluated by the Community Periodontal Index and the Periodontal Attachment Loss index[12]. The analysis of CPI revealed that 73% of the research subjects presented excluded sextants. This indicates the absence of the index teeth in the sextant and it reinforces the high tendency of edentulism observed by the National Oral Health Survey – SBBrasil[22] (2010) in individuals aged 65-74 years. Our study presented a higher rate of subjects with lower scores when compared to other studies[1,23].

The Periodontal Attachment Loss index provides information about the accumulated tissue destruction throughout the life of the periodontal attachment[10]. Most subjects (48%) were considered healthy as to the periodontal attachment loss (0-3 mm loss) and 30% revealed loss of 4-5 mm, which was similar to the average loss presented by PD subjects in another study (ranged from 3.14 to 6.74 mm)[25]. The impaired motor skills for oral hygiene is considered the primary risk factor for the development of periodontal disease in subjects with PD[26]. As a result, the literature has extensively reported a compromised periodontal health status. Moreover, emphasis should be given to the quality of oral health care that most PD patients receive from caregivers, who commonly become responsible for oral health care measures[27].

The adequate prosthetic replacement of missing teeth is key for proper nutrition, communication, and social interaction[4]. Our results indicated a higher rate of prosthetic use in the upper arch (Table 5), most of them constituted by total dentures. It is speculated that such higher prevalence in the upper arch would indicate a concern about social and communicational issues. However, approximately 60% of upper arch prostheses required replacement, indicating that the functional aspect had not been considered. This is reinforced by the fact that a lower proportion of prosthetic use was observed in the lower arch, similar to the rate of prosthetic need. One of the most common indications for prosthetic replacement was poor fitting and retention, which might be aggravated by the typical tremors of subjects with PD. Ill-fitting dentures generate socialization difficulties, as they affect pronunciation and cause nutritional impairment, leading to weight loss and diet shift[4].

The tremor of orofacial muscles may generate tooth abrasion, orofacial pain, discomfort in the temporomandibular joint, tooth fractures, and involuntary bites in the tongue, cheeks, or lips[4]. Episodes of fractures in teeth, restorations, or prosthetic crowns were identified in 4% of the subjects, while biting the tongue, lips, and cheeks was observed in 24% of the cases (Table 3). As PD progresses, tremors and dyskinesia impair the ability of subjects to have a meal on his own, requiring changes in dietary habits and the usual need for having their food cut by the caregivers[28]. In our study, 10% of the subjects reported some kind of limitation related to the amount or type of food, due to problems with teeth or prostheses. As for masticatory ability, 50% of subjects never had problems to bite or chew solid food, but 50% reported feeling some kind of discomfort during eating (Table 3).

Our results also showed that 88% of the participants consumed sugar-rich foods and 76% drank sugar-rich soft beverages. Miller et al.[28] (2006) highlights the need to assess swallowing capacity during all the phases of PD to maximize function and stop or slow down the onset of preventable problems for feeding and swallowing. Our study identified 6% of individuals with problems for swallowing. The implications of swallowing difficulties are dietary changes, with a tendency of increasing the amount of pasty food intake, including fermentable-sugar rich foods[1,4].

Regarding the health status of the oral mucosa, the most prevalent lesions found were prosthetic stomatitis and inflammatory fibrous hyperplasia. None of these conditions are specific to subjects with PD, but both have been associated with poor oral hygiene and lack of adequate care with total and partial removable dentures. In this sense, the concern with oral health should not be restricted only to situations involving oral-related pain. Poor oral health conditions were observed among older people with and without PD[29], suggesting similar oral health care demands. Perhaps the ideal condition would involve interdisciplinary health care for individuals with PD, including dentists among the health professionals providing periodical assistance to these subjects.

Conclusion

Individuals with PD presented a high number of missing teeth, a minority of healthy teeth, and oral lesions. They also referred dry mouth symptoms and, to a lower extent, difficulty for eating and swallowing. This study suggests a target population for specialized oral health care.

Resumo

A higiene bucal de indivíduos com doença de Parkinson (DP) é claramente prejudicada por dificuldades na escovação devido ao comprometimento motor e aos tremores. Além disso, outros aspectos relacionados à doença parecem impactar a qualidade da saúde bucal. Objetivo: este estudo observacional seccional caracterizou a condição de saúde bucal de indivíduos com DP. Métodos: foram examinados cinquenta indivíduos com DP, com idades variando entre 53 e 94 anos, que utilizavam medicamentos para DP. Os participantes da pesquisa foram submetidos a exame bucal para avaliar: uso e necessidade de prótese, índice de dentes cariados, perdidos e obturados (CPOD), Índice Periodontal Comunitário (IPC), Índice de Perda de Inserção Periodontal (PIP) e mucosa bucal. Além disso, foi aplicado um questionário para obtenção de dados pessoais e sobre saúde geral e saúde bucal. Os dados foram analisados usando estatística descritiva. Resultados: observou-se alto percentual de uso de prótese superior (92%), enquanto o arco inferior apresentou elevada necessidade de prótese (66%). O CPOD revelou um alto número de dentes perdidos; o IPC apresentou prevalência de 43% de cálculo dentário; e o PIP revelou 28% de perda de inserção de 4-5 mm. Os achados mais frequentes na avaliação da mucosa bucal foram estomatite por dentadura e hiperplasia fibrosa inflamatória. Conclusão: os indivíduos com DP mencionam xerostomia, apresentam alto número de dentes faltantes, um número reduzido de dentes saudáveis e lesões bucais, representando uma população-alvo para o cuidado de saúde bucal especializado.

Palavras-chave: Idoso. Saúde Bucal. Doença de Parkinson. Xerostomia.

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ANEXO 4 – IMPACT IN ORAL HEALTH AND THE PREVALENCE OF TEMPOROMANDIBULAR DISORDER IN INDIVIDUALS WITH PARKINSON´S DISEASE

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Original Article

Impact in oral health and the prevalence of temporomandibular disorder in individuals with Parkinson's disease

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Abstract. [Purpose] The aims of the present study were to investigate the prevalence of temporomandibular disorder (TMD) in a group of patients with Parkinson's disease (PD), and to analyze oral health according to the severity of the disease. [Methods] Signs and symptoms of TMD were evaluated using the Research Diagnostic Criteria for Temporomandibular Disorders, and oral health impact was measured using the Oral Health Impact Profile. The unpaired Student's t-test was used to compare groups with and without TMD. Pearson's correlation coefficients were calculated to determine correlations between the level of functional independence and oral health impact. Fisher's exact test was used to test the association between TMD and the severity of symptoms of PD. [Results] Fifty-nine individuals with PD were analyzed. The prevalence of TMD was 20.33%. No statistically significant associations were found between TMD and the severity of PD. Oral health impact was considered weak, but a statistically significant difference between groups with and without TMD was found for psychological disability ($p = 0.003$). No significant correlation was found between the level of functional independence and oral health impact. [Conclusion] The prevalence of TMD among patients with Parkinson's disease was 20.33%. A statistically significant difference between groups with and without TMD was found regarding the psychological disability domain.
Key words: Parkinson's disease, Oral health, Temporomandibular joint disorder

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INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive condition of the central nervous system characterized by the degeneration of dopaminergic neurons that leads to a reduction in dopamine and produces the major signs of the disease: trembling, especially in the upper limbs and extending to the neck and face; bradykinesia (slowness of voluntary motor actions), muscle stiffness resulting from the ineffective inhibition of antagonist muscles; and postural instability, which occurs due to the progressive loss of balance and postural reflexes[1, 2)]. Axial impairment is considered one of the major indictors of disability in individuals with PD[3)]. Motor symptoms are related to the development of postural abnormalities characterized by forward lean and flexion of the cervical spine, thoracic hyperkyphosis, protraction and abduction of the shoulders, and flexion of the arms[1, 4, 5)].

Studies have demonstrated that changes in neck posture can lead to alterations in the biomechanics of the temporomandibular joint, affecting both stomagnathic function and postural control[6, 7)]. Deficient axial control and mandibular movements due to the progression of motor symptoms in individuals with PD[8, 9)] indicate that such individuals are subject to the development of temporomandibular disorder (TMD), which is defined as a set of clinical manifestations of mandibular dysfunction with or without pain caused by damage to the morphological or functional integrity of the temporomandibular system[10)]. TMD has a multifactorial etiology and is related to myofunctional alterations, muscle and postural imbalances[11)], as well as parafunctional habits[12)], such as nail biting and clenching of the teeth, which cause muscle hyperactivity and microtraumas in the temporomandibular joint[13)]. It is estimated that the prevalence of TMD in the elderly population is approximately 21%[14)].

Functional alterations related to the symptoms of TMD, such as orofacial pain affecting the temporomandibular joint and masticatory muscles, limited or deviated mandibular movements, and joint sounds[15, 16)], contribute to a perception of poor oral health. Indeed, the severity of the symptoms of TMD is reported to exert an impact on oral health[17, 18)], with a negative effect on the performance of activities of daily living. Moreover, the chronic, progressive nature of PD leads to impaired motor control, which has a negative impact on the maintenance of adequate oral hygiene[3, 9, 19)] and likely accounts for the greater impact on oral health among such individuals[9)].

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Considering the evidence that characteristic clinical impairment in individuals with PD can lead to alterations in the stomatognathic system, the aims of the present study were to investigate the prevalence of TMD in a group of patients with PD at a rehabilitation center and analyze the oral health impact according to the severity of the disease.

SUBJECTS AND METHODS

A cross-sectional study was carried out involving patients at the Brazilian Parkinson's Association in the city of Sao Paulo, Brazil. Male and female individuals were recruited from the physical therapy sector of the rehabilitation center. The following were the inclusion criteria: age 50 to 75 years, medical diagnosis of idiopathic PD, and adequate cognitive state based on the Brazilian version of the Mini Mental State Examination as assessed by, adopting the cutoff points proposed by Bertolucci et al.[20]: 13 for illiterate individuals, 18 for those with a low to medium level of schooling and 26 for those with a high level of schooling. Individuals with missing teeth, dentofacial deformities or signs and symptoms of TMD prior to the diagnosis of PD were excluded from the study.

Considering daily variations in motor symptoms in individuals with PD due to the "on-off" phenomenon, the decision was made to perform the evaluations during the "on" period of medication. The evaluations were performed by a single examiner who had undergone a training exercise. Due to the clinical characteristics of the sample, the questionnaires were administered in interview format. The questions were always read in the same order and the response options for each question were presented.

Demographic data (age, sex, evolution of PD) were recorded on standardized charts. All individuals were evaluated for the effect of medications used to control the symptoms of PD. The modified Hoehn & Yahr[21] scale was used for the classification of signs and symptoms of PD. This scale allows the classification of each individuals into seven stages of severity. Stages 1, 1.5 and 2 indicate mild disability; stages 2.5 and 3 indicate moderate disability and stages 4 and 5 indicate severe disability.

The Functional Independence Measure (FIM) was employed, which has been translated and validated for use on the Brazilian population was used to assess the subjects. The evaluation consists of the self-reported degree of assistance required from others for the performance of motor and cognitive tasks. Each activity is rated on a seven-point scale, for which 1 denotes complete dependence and 7 denotes complete independence[22]. As adequate cognitive capacity was one of the inclusion criteria, only the motor subscale was employed in the present study. Thus, the total score ranged from 13 to 91 points and the cutoff was 78 points, with lower scores indicating some degree of dependence and scores of 78 or higher indicating functional independence.

Signs and symptoms of TMD were evaluated using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), which is the gold standard for this type of evaluation. The RDC/TMD is made up of two axes. Axis I consists of an intraoral and extraoral clinical examination involving the analysis of mandibular movements and joint sounds as well as palpation of trigger points in the masticatory muscles. Axis II consists of a psychosocial questionnaire made up of 31 items. The diagnosis is determined with the aid of a correction key based on data from both axes[23].

The Oral Health Impact Profile (OHIP-14)[24] questionnaire was conducted. This measure is composed of 14 items distributed among seven subscales (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap) addressing oral health status and its impact on social aspects. Each item has four response options: never (0 points), hardly ever (1 points), occasionally (2 points), fairly often (3 points) and very often (4 points). The total ranges from 0 to 56 points. Each item is attributed a weight. Oral health impact is considered weak when the score is between 0 and 9 points, moderate when the score is between 10 and 18 points and strong when the score is 19 points or higher[25].

This study was according to the ethical principles of Declaration of Helsinki and the Regulating Guidelines and Norms for Research Involving Human Subjects stipulated in Resolution 196/96 of the Brazilian National Health Board. The study received approval from the Human Research Ethics Committee of University Nove de Julho, Brazil (process number: 437980). All participants signed a statement of informed consent.

Descriptive statistics (mean and standard deviation [SD]) were used for the characterization of the sample and distribution of the scores. The Kolmogorov-Smirnov test was used to determine the normality of the data distribution. The FIM results were dichotomized as "some degree of dependence" (< 78 points) and "independent" (≥ 78 points). The unpaired Student's t-test was used to analyze differences in OHIP-14 scores between the groups with and without TMD. Pearson's correlation coefficients were calculated to determine correlations between the FIM subscales and the OHIP-14. Fisher's exact test was used to test the association between TMD and the severity of symptoms of PD. The Statistical Package for Social Sciences (SPSS) 15.0 for Windows was employed for all statistical tests, with a level of significance of to 5% ($p < 0.05$).

RESULTS

All individuals in the physical therapy sector of the Parkinson's rehabilitation center were recruited. After the exclusion of those who did not meet the eligibility criteria, the final sample was made up of 59 individuals (Fig. 1).

Among the 59 participants evaluated, 50.84% were male and their mean age was 65.41 ± 8.77 years. The mean time elapsed since the diagnosis of PD was 7.11 ± 4.05 years. According to the Hoehn & Yahr scale, 83% of the sample had mild PD. Thirty-eight subjects were categorized as independent with regard to functional activities (Table 1).

The prevalence of TMD was 20.33% (n = 12) and this disorder was more frequent among the women (n = 7). Table 2 displays the distribution of the cases classified under diagnostic subtypes based on the RDC/TMD and distribution between sexes.

Fisher's exact test revealed no significant association between TMD and PD severity (Table 3).

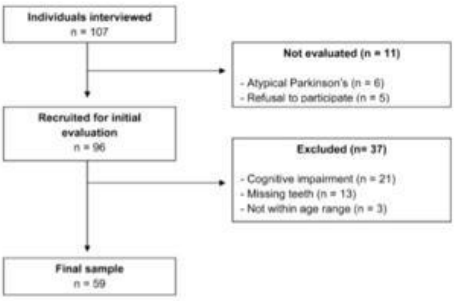

Fig. 1. Flowchart of sample selection procedure

Table 1. Characterization of sample

Variable	n	Mean ± SD
Age (years)		65.4 ± 8.7
Time since diagnosis of PD		7.1 ± 4.0
Gender (male/female)	(30/29)	
Motor impairment (Hoehn & Yahr)		
Mild	49	
Moderate	10	
Total FIM score		77.1 ± 5.8
Some dependence < 78 points (n)	21	
Independent ≥ 78 points (n)	38	

FIM: functional independence measure; PD: Parkinson's disease; SD: standard deviation

Table 2. Distribution of sample according to RDC/TMD and sex

Diagnosis	Male	Female	Total
RDC/TMD			
Ib	2	-	2
IIa	2	4	6
IIb	-	2	2
IIIc	1	1	2

Ib: myofascial pain with limited mouth opening; IIa: disc displacement with reduction; IIb: disc displacement without reduction; IIIc: osteoarthrosis; RDC: research diagnostic criteria

Table 3. Severity of PD according to presence or absence of TMD

Severity of PD (Hoehn & Yahr)	TMD	
	Present	Absent
Mild	11	35
Moderate	1	12
Total	12	47

TMD: temporomandibular disorder; PD: Parkinson's disease Fisher Exact Test.

Table 4. Impact of oral health based on each OHIP-14 subscale

Subscale	Mean ± SD
Functional limitation	0.78 ± 0.62
Physical pain	0.99 ± 0.54
Psychological discomfort	1.07 ± 0.56
Physical disability	1.02 ± 0.59
Psychological disability	0.82 ± 0.47
Social disability	0.92 ± 0.61
Handicap	0.50 ± 0.27
Total OHIP-14	6.14 ± 1.94

SD: standard deviation

Table 5. OHIP-14 subscale scores in groups with and without TMD

Dimension	Without TMD (n = 47) Mean ± SD	With TMD (n = 12) Mean ± SD	
Functional limitation	0.71 ± 0.65	1.04 ± 0.45	
Physical pain	0.97 ± 0.55	1.11 ± 0.49	
Psychological discomfort	1.05 ± 0.61	1.16 ± 0.24	
Physical disability	1.00 ± 0.63	1.12 ± 0.38	
Psychological disability	0.77 ± 0.51	1.05 ± 0.17	*
Social disability	0.86 ± 0.64	1.15 ± 0.41	
Handicap	0.49 ± 0.28	0.55 ± 0.20	

TMD: temporomandibular disorder; SD: standard deviation. *: statistical significance.

Analyzing the entire sample (n = 59), oral health impact was weak for all OHIP-14 subscales. The greatest impacts were on the "physical disability" and "psychological discomfort" subscales (Table 4).

A weak negative correlation was found between the severity of symptoms of PD and oral health impact ($r = -0.167$, $p = 0.207$). Comparing oral health impact between the groups with and without TMD, statistically significant differences were found regarding the "functional limitation", "psychological discomfort", "physical disability" and "psychological disability" subscales (Table 5).

DISCUSSION

Despite evidence that individuals with PD exhibit deficits in axial control and mandibular function[8, 9], to the best of our knowledge, there are no previous reports in the literature on the investigation of signs and symptoms of TMD in this population. The hypothesis of the present study was that common clinical manifestations in individuals with PD would be associated with TMD and the prevalence of this disorder would be greater than that found among elderly individuals with no neurological disease.

The prevalence of TMD in the present sample was 20.33%. Moreover, the disorder was more frequent among

women (58.33%). This finding is in agreement with data reported in the literature that demonstrating a greater prevalence of TMD among females gender[16].

The mean age of the present sample was 65.11 years. Abud et al.[14] evaluated signs and symptoms of TMD in a sample of community-dwelling individuals aged 60 years and older with no neurological diseases and found a 21.9% prevalence rate of mild signs of TMD. Physiological changes in oral motor function stemming from the ageing process may be one of the factors linked to the occurrence of TMD in the elderly population[26]. Moreover, Bakke et al.[9] found that orofacial functions of individuals with PD can be compromised due to the severity of the motor symptoms, which may also exert an influence on the occurrence of TMD in this population. However, no significant associations were found between motor impairment and a diagnosis of TMD in the present study. This may be partially explained by the fact that the sample was made up mostly of individuals in the mild stage of PD. A more in-depth evaluation of other factors, such as changes in posture and muscle tone, should be carried out for a better analysis of this relationship.

It is important to consider the impact of oral problems on quality of life and studies have shown that functional alterations associated with symptoms of TMD contribute to greater oral health impact, especially among individuals with orofacial pain[17, 27, 28]. The OHIP-14 has been used in recent studies to investigate the impact of TMD due to the satisfactory psychometric properties of this assessment tool[17].

Oral health is influenced by a number of factors, including perceptions regarding general health. Brennan and Singh[29] found an association between the perception of general health and oral health in a sample of elderly individuals, demonstrating that oral health is highly influenced by a poorer state of general health. In the present study, however, no significant correlation was found between motor impairment and oral health impact. This finding is in disagreement with data described by Bakke et al.[9], who evaluated the impact of oral health in patients in moderate to advanced stages of PD. In the present sample, the majority of individuals were in less advanced stages of the disease, were only semi-dependent, and had good perceptions of their general health, with no impact on the performance of activities of daily living, as demonstrated by their high FIM scores. Moreover, participation in the social and preventive activities, to which individuals are submitted at Parkinson's institutions perform, may have exerted influence on the findings.

In the comparison of oral health impact between individuals with and without TMD, higher OHIP-14 scores were found among those with TMD, despite the weak impact indicated by the different subscales. This difference was significant with regard to psychological disability. It has been demonstrated that all diagnoses resulting from the RDC/TMD have a significant impact on oral health[30]. Moreover, orofacial pain is reported to be the main factor related to a greater negative oral health impact[17, 27, 28, 30]. This may explain the present findings, as only two individuals were classified with myofascial pain.

Although we did not find demonstrate significant differences in the present data, it should be stressed that evaluations and interventions involving individuals with PD mainly address motor aspects (such as gait)[31] and cognitive aspects[3], which may sometimes make such individuals overlook symptoms of equal importance to their health and quality of life. This may influence the measurement of symptoms of TMD and the perception of oral health, as these aspects are generally analyzed based on self-reports.

The present study had the inherent limitations of a cross-sectional design, which only allows the establishment of associations and does not permit conclusions regarding causality. Thus, longitudinal studies should be carried out to determine the cause-and-effect relationships of the variables analyzed. Studies should also be carried out to investigate other factors with a more global therapeutic approach for individuals with PD. Such investigations could offer valuable information on the efficacy of therapeutic and prevention strategies for this population.

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ANEXO 5 – PERIODONTAL INFLAMMATORY DISEASE IS ASSOCIATED WITH THE RISK OF PARKINSON´S DISEASE: A POPULATION-BASED RETROSPECTIVE MATCHED-COHORT STUDY

PeerJ

Periodontal inflammatory disease is associated with the risk of Parkinson's disease: a population-based retrospective matched-cohort study

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ABSTRACT

Background. The cause–effect relation between periodontal inflammatory disease (PID) and Parkinson's disease (PD) remains uncertain. The purpose of our study was to investigate the association between PID and PD.
Methods. We conducted a retrospective matched-cohort study by using Taiwan's National Health Insurance Research Database. We identified 5,396 patients with newly diagnosed PID during 1997–2004 and 10,792 cases without PID by matching sex, age, index of year (occurrence of PID), and comorbidity. Cox proportional hazard regression was used to evaluate the risk of subsequent PD.
Results. At the final follow-up, a total of 176 (3.26%) and 275 (2.55%) individuals developed PD in the case and control groups, respectively. Patients with PID have a higher risk of developing PD (adjusted hazard ratio = 1.431, 95% CI [1.141–1.794], $p = 0.002$).
Discussion. Our results show that PID is associated with an increased risk of developing PD. Whilst these findings suggest that reducing PID may modify the risk of developing PD, further study will be needed.

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INTRODUCTION

Parkinson's disease (PD) is a disabling neurodegenerative disease, which is progressive, and is caused by a loss of dopaminergic neurons in the substantia nigra (*Pradeep et al., 2015*). Onset is generally after the age of 40 years, and predominantly affects males, with an incidence that increases with age (*Van Den Eeden et al., 2003*). In Taiwan, the prevalence was 84.8 per 100,000 in 2004, and 147.7 per 100,000 in 2011, with an annual growth rate of 7.9%. The highest prevalence was among individuals over 80 years of age. Over the past decade, Japan, France, and Israel have also reported similar findings (*Liu et al., 2016*).

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Previously, several studies have emphasized inflammatory responses in the progression of PD (*Ferrari & Tarelli, 2011*; *Perry, 2010*), and have proposed that chronic conditions and infections, such as diabetes mellitus (*Yang et al., 2017*) and periodontal problems (*Wu et al., 2016*), resulting in inflammatory reactions, may be one of the etiological factors in the pathogenesis of PD. In a previous study, after adjustment for age, periodontal disease was significantly higher in men than women (56.4% vs. 38.4%) (*Eke et al., 2012*). Periodontal inflammatory disease (PID), which comprises two major forms, i.e., chronic gingivitis (CG) and chronic periodontitis (CP), is a form of peripheral inflammation with potentially systemic effects. It involves mechanisms mediated by periodontal pathogenic microbes and inflammatory responses. CG is primarily caused by accumulated dental bacterial plaque and may develop into CP (*American Academy of Periodontology–Research et al., 2005*). The products of periodontal pathogens cause host cells to generate and release pro-inflammatory mediators, such as IL-1, IL-6, TNF- α, and reactive oxygen species (ROS) (*Ebersole & Cappelli, 2000*) and the mediators might induce dopaminergic neuronal necrosis or apoptosis, PD initiation and progression, and then cause movement and cognitive disorders (*Kaur, Uppoor & Naik, 2016*).

Periodontal bacterial cell wall components including Helicobacter pylori (HP), such as the endotoxin lipopolysaccharides (LPS) of Gram-negative strains, are well known as potent inflammatory agents. Bacterial LPS is widely used in model studies of PD induction. In addition, HP infection can aggravate the neurodegenerative process in PD (*Kell & Pretorius, 2015*; *Nielsen et al., 2012*; *Tan et al., 2015*). However, there is no direct evidence to date to indicate that PID plays a role in PD pathogenesis (*Kaur, Uppoor & Naik, 2016*). Although few articles have addressed the relationship between periodontal problems and PD in cross-sectional studies (*Barbe et al., 2017*; *Cicciu et al., 2012*; *Muller, Palluch & Jackowski, 2011*; *Pradeep et al., 2015*) the cause-effect relationship remains unclear. In 2013, *Liu et al. (2013)* first reported an increased risk of parkinsonism after CP in a cohort study. However, only patients with CP were enrolled in their cohort study and a lack of information of CG leaves the exact relationship between PID and PD unclear. Moreover, parkinsonism is a general term that not only indicates PD (*Dickson, 2012*). Therefore, we here conducted a cohort study using the National Health Insurance Research Database (NHIRD) of Taiwan to determine the risk of developing PD after PID.

MATERIALS & METHODS

Data sources

The National Health Insurance Program (NHIP) was developed and managed for research purposes since 1995 and provides universal and comprehensive health care for about 99% of Taiwanese residents (*Ho Chan, 2010*). The NHIRD data from 1996 to 2013 were selected. The data used in the present study were retrieved from the data of one million randomly selected subjects in the whole NHIRD, representing about 4.5% of the population from the entire NHIRD enrollee population (*Hsu et al., 2011*). There was no significant difference in age and gender between the

one million random-sampled data sets and enrollees in the NHIRD. The demographic information gathered included encrypted identification numbers, sex, dates of birth and death, diagnostic data, and procedures. The diagnostic data included the dates of dental procedures and the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic and procedure codes (*Romano, Roos & Jollis, 1993*).

The study was approved by the Institutional Review Board (IRB) in Chung Shan Medical University (CS2-15071).

Study design and sampled participants

This study was a retrospective matched-cohort design. Patients who were aged ≥40 years, new diagnosed between January 1, 1997, and December 31, 2004, based on the ICD-9-CM diagnostic criteria code: 523.1 (CG) and 523.4 (CP), were recruited. In addition, each enrolled patient had been diagnosed at least at three outpatient clinics with PID (CG or/and CP) during a 1-year study period (*Tzeng et al., 2016*). Exclusion criteria were as follows: age and gender unknown, and PID diagnoses made before 1997. In addition, the patients being diagnosed with PD (ICD-9-CM code: 332.0) (*Liu et al., 2016*) before 1997 or before the first visit for PID were also excluded. In the interests of accuracy patients were excluded if they had not accessed health services for more than one year, as the NHIRD does not record deaths. A total of 5,396 patients with PID were recruited and 10,792 patients without PID were matched by gender, age, and index years as a control group, at a 1:2 ratio.

Both cohorts were followed from the index date until the PD diagnosis, death, or the end of December 31, 2013, whichever came first, as shown in Fig. 1. The covariates included gender and age group (40–49, 50–59, 60–69, and ≥70 years). According to the definition of urbanization issued by the National Institutes of Health in Taiwan, all 365 townships in Taiwan are divided into seven clusters according to the following variables: population density (people/km^2), the proportion of the population with college or above educational levels, population ratio of elderly people (over 65 years old), the population ratio of people who are agricultural workers and the number of physicians per 100,000 people. In the present study, we operationally defined townships of 1–2 clusters as level 1, 3–4 clusters as level 2, and 5–7 clusters as level 3 (*Liu et al., 2006*).

The PD-related comorbidities include hypertension (ICD-9-CM codes: 401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.1, and 405.9), hyperlipidemia (ICD-9-CM codes: 272.0–272.9), chronic kidney disease (ICD-9-CM codes: 580, 581–589, 753, 403, 404, 250.4, 274.1, 440.1, 442.1, 447.3, 572.4, 642.1, and 646.2), depression (ICD-9-CM code: 311), stroke (ICD-9-CM codes: 433, 434, and 436) and traumatic brain injury (ICD-9-CM codes: 800–804, 850–854, 905.0, 950.1, 950.3, 907.0, 959.01, 959.9, 310.2, and V15.52) (*Chang et al., 2016*; *Goodarzi et al., 2016*; *Hsu et al., 2016*; *Liu et al., 2013*; *Wu et al., 2016*). We also recorded the Charlson Comorbidity Index (CCI), which contains 17 weighted comorbidities and was calculated for each participant (*Charlson et al., 1987*).

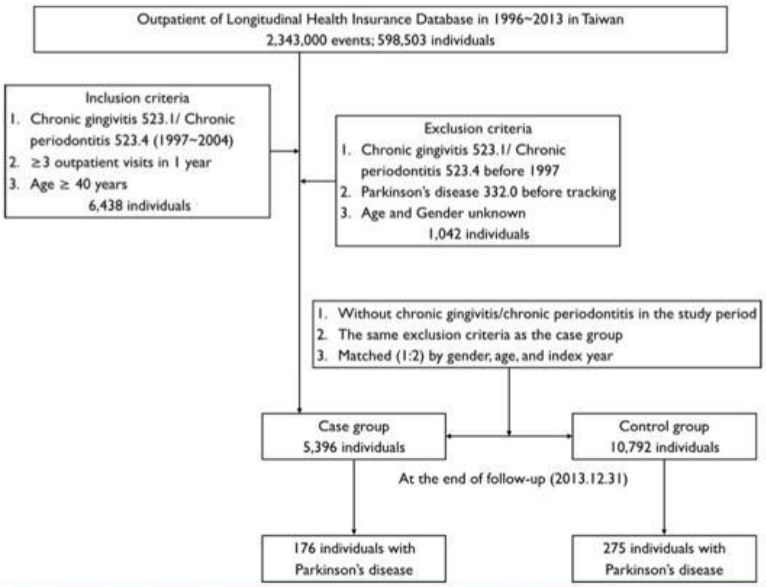

Figure 1 **Flowchart of cohort selection of patients from the National Health Research Institute.**

Statistical analysis

The *t*-test and chi-square test were used to compare the demographic and clinical characteristics of patients with PD vs. those without PID. Univariate and multivariate models were then used to calculate the hazard ratio (HR) and the 95% confidence interval (CI) with stratified Cox regression models. Multivariable models were adjusted for PD-related comorbidities, CCI score, and urbanization level. The incidence rate (IR) and incidence rate ratio (IRR) (per 100,000 person-years) was calculated by dividing the number of events of current PD by the person-years (PYs) observed for each patient. The Kaplan–Meier method was used to assess the survival probability in PD between the case and control cohorts. The log-rank test was used to compare their differences.

In sensitivity analysis, we identified patients with PID that occurred ≥1-year after the diagnosis of PID and the incidence of PD during the 5-year period after a diagnosis of CG and CP (*Liu et al., 2013*). We performed sensitivity analysis, excluding patients diagnosed with PD <1–5 years after a diagnosis of CG or CP, to ensure the stability and accuracy of the statistical model (*Wong et al., 2016*). All statistical analyses were performed in SAS version 9.3 (SAS Institute, Cary, NC, USA) and SPSS software version 22 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined by a *p*-value <0.05.

RESULTS

The baseline demographic characteristics at the beginning of the study were shown in Table 1. The patients with PID had a higher prevalence of hyperlipidemia, depression, CCI score, and urbanization level than the control cohort. The mean ages for the case and control cohorts were 54.1 ± 10.5 and 54.2 ± 10.5 years, respectively. The mean follow-up time for the case and control cohorts was 11.9 ± 2.6 and 12.2 ± 2.6 years, respectively.

A total of 176 (3.26%) and 275 (2.55%) patients were diagnosed with PD in the case and control cohorts, respectively (Fig. 1). Table 2 shows the Cox regression analysis of risk factors associated with development of PD. More people developed PD in the PID cohort than in the control cohort and the adjusted HR was 1.431 (95% CI [1.141–1.794], $p = 0.002$; Table 2). Patients with hypertension, depression, stroke, traumatic brain injury and CCI score ≥3 tended to have a higher risk of development of PD and the adjusted HR was 1.746, 2.116, 2.257, 1.645 and 4.207 respectively (all $p < 0.05$; Table 2).

Table 3 shows subgroups stratified by gender, age, comorbidities, CCI score and urbanization level during a 1-year period. The IRR of PD was significantly higher among the case cohort than it was among the control cohort, in the following subgroups: male gender, age ≥60 years, hypertension, stroke, CCI score 1, and CCI score ≥3. Both the patients with and without hyperlipidemia, chronic kidney disease, and traumatic brain injury in the case group were at higher risk of PD than were the control group. Level 1 and level 2 carried greater significant risk than did level 3 in terms of urbanization. However, PID subjects who were male, aged ≥70 years, hypertension, no hyperlipidemia, no depression, stroke, with/without chronic kidney disease, traumatic brain injury, CCI score ≥3, and the highest urbanization level 1, were associated with significant higher risk of PD after adjusting the HR.

Applying sensitivity analysis to the strategic evaluation by using the Cox proportional hazards regression model for examining the risk of PD after CG and CP were shown in Table 4. We performed sensitivity analysis after excluding patients diagnosed with PD <1 and <5 years after diagnosis of CG and CP. The association between CG/CP and PD remained consistent (adjusted HR of 1-year and 5-year was 1.431 and 1.395 respectively.)

Figure 2 shown the Kaplan–Meier for cumulative risk of PD in the case and control groups. The difference between the case and control groups reached statistical significance difference between the case and control group in the 1st year of follow-up ($p < 0.05$ with log-rank test).

DISCUSSION

To the best of our knowledge, this is the first nationwide population-based matched-cohort study to find that patients with newly diagnosed PID had an increased risk of developing PD (adjusted HR = 1.431) regardless of comorbidities, CCI score, and urbanization level. Overall, our study found that hypertension, depression, stroke, traumatic brain injury, and CCI score ≥3 were independent risk factors for PD.

Periodontal microorganisms mainly comprise the gram-negative bacteria with endotoxin LPS, which leads to breakdown of the blood brain barrier (BBB). PID can

Table 1 Demographic characteristics of the study cohort at baseline.

Variable	Total		Periodontal inflammatory disease				*p*-value
			With (case)		Without (control)		
	n	%	*n*	%	*n*	%	
Total	16,188	100	5,396	100	10,792	100	
Gender							
Female	7,461	46.09	2,487	46.09	4,974	46.09	>0.999
Male	8,727	53.91	2,909	53.91	5,818	53.91	
Age (years)							
40–49	6,808	42.06	2,269	42.05	4,539	42.06	>0.999
50–59	4,610	28.48	1,537	28.48	3,073	28.47	
60–69	2,939	18.16	980	18.16	1,959	18.15	
≥70	1,831	11.31	610	11.3	1,221	11.31	
Hypertension							
No	7,461	46.09	2,487	46.09	4,974	46.09	0.1834
Yes	8,727	53.91	2,909	53.91	5,818	53.91	
Hyperlipidemia							
No	13,015	80.4	4,198	77.8	8,817	81.7	<0.0001
Yes	3,173	19.6	1,198	22.2	1,975	18.3	
Chronic kidney disease							
No	11,256	69.53	3,727	69.07	7,529	69.76	0.3651
Yes	4,932	30.47	1,669	30.93	3,263	30.24	
Depression							
No	13,829	85.43	4,522	83.8	9,307	86.24	<0.0001
Yes	2,359	14.57	874	16.2	1,485	13.76	
Stroke							
No	13,434	82.99	4,478	82.99	8,956	82.99	>0.999
Yes	2,754	17.01	918	17.01	1,836	17.01	
Traumatic brain injury							
No	13,517	83.5	4,545	84.23	8,972	83.14	0.0773
Yes	2,671	16.5	851	15.77	1,820	16.86	
CCI score							
0	1,719	10.62	541	10.03	1,178	10.92	0.0010
1	2,455	15.17	747	13.84	1,708	15.83	
2	2,583	15.96	872	16.16	1,711	15.85	
≥3	9,431	58.26	3,236	59.97	6,195	57.4	
Urbanization level							
1	10,479	64.73	6,662	61.71	3,817	70.79	<0.0001
2	4,337	26.79	3,076	28.49	1,261	23.39	
3	1,372	8.48	1,058	9.8	314	5.82	

Notes.
CCI, charlson Comorbidity Index.

Table 2 Covariates associated with Parkinson's disease at the end of follow-up with univariate and multivariable Cox-regression analysis.

Variable	Univariate analysis			Multivariable analysis		
	Crude HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
Periodontal inflammatory disease						
Control	Reference			Reference		
Case	1.422	1.165–1.737	0.0005	1.431	1.141–1.794	0.002
Hypertension						
No	Reference			Reference		
Yes	2.566	1.727–3.813	<0.0001	1.746	1.114–2.735	0.015
Hyperlipidemia						
No	Reference			Reference		
Yes	2.566	1.727–3.813	<0.0001	1.018	0.763–1.36	0.9019
Chronic kidney disease						
No	Reference			Reference		
Yes	1.358	1.063–1.735	0.0144	0.992	0.746–1.32	0.9586
Depression						
No	Reference			Reference		
Yes	2.654	1.995–3.53	<0.0001	2.116	1.55–2.888	<0.0001
Stroke						
No	Reference			Reference		
Yes	2.981	2.289–3.881	<0.0001	2.257	1.693–3.007	<0.0001
Traumatic brain injury						
No	Reference			Reference		
Yes	2.035	1.548–2.676	<0.0001	1.645	1.217–2.224	0.0012
CCI score						
0	Reference			Reference		
1	3.778	0.979–14.584	0.0538	3.433	0.85–13.873	0.0834
2	4.202	1.156–15.282	0.0293	2.829	0.753–10.635	0.1238
≥3	9.472	2.821–31.808	0.0003	4.207	1.171–15.107	0.0276
Urbanization level						
1	Reference			Reference		
2	1.288	0.977–1.696	0.0722	1.230	0.905–1.671	0.1862
3	1.187	0.804–1.752	0.3891	1.133	0.713–1.799	0.5981

Notes.
CCI, Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval.

lead to the induction of pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α. These cytokines can activate microglial cells, which produce nitric oxide and ROS, leading to death of dopaminergic neurons (*Kaur, Uppoor & Naik, 2016*). Our findings showing increased PD after PID support the reports stating that LPS, produced by gram-negative bacteria, may be an important contributor to the development and progression of PD (*Bohatschek, Werner & Raivich, 2001*). Similar findings were reported from several studies, where the correlation between periodontal problems and PD were revealed. They reported that periodontal problems are frequently found in patients with PD by using cross-section observation, because these patients with PD progressively showed less self-care capability

Table 3 Incidence and hazard ratios of Parkinson's disease with periodontal inflammatory disease at the end of follow-up period, stratified by variables listed in the table with Cox-regression analysis.

Variable	Periodontal inflammatory disease						IRR	95% CI	Adjusted HR	95% CI	*p*-value
	With (case)			Without (control)							
	Event	PYs	IR	Event	PYs	IR					
Gender											
Female	62	29,547	209.8	119	60,748	195.9	1.07	0.88–1.30	1.145	0.839–1.564	0.3932
Male	114	34,501	330.4	156	70,786	220.4	1.50*	1.26–1.78	1.557*	1.216–1.993	0.0004
Age (years)											
40–49	5	27,514	18.2	18	56,114	32.1	0.57	0.32–1.01	0.716	0.264–1.946	0.5129
50–59	26	18,099	143.7	48	37,100	129.4	1.11	0.88–1.41	1.414	0.867–2.306	0.1657
60–69	64	11,575	552.9	107	23,884	448.0	1.23*	1.09–1.39	1.204	0.878–1.651	0.2483
≥70	81	6,860	1180.8	102	14,437	706.5	1.67*	1.52–1.83	1.615*	1.198–2.177	0.0017
Hypertension											
No	17	23,513	72.3	24	46,242	51.9	1.39	0.97–1.99	1.563	0.815–2.997	0.1785
Yes	159	40,534	392.3	251	85,292	294.3	1.33*	1.14–1.55	1.365*	1.115–1.671	0.0026
Hyperlipidemia											
No	133	49,693	267.6	214	10,7219	199.6	1.34*	1.12–1.61	1.471*	1.180–1.833	0.0006
Yes	43	14,354	299.6	61	24,315	250.9	1.19*	1.01–1.41	1.097	0.739–1.629	0.6457
Chronic kidney disease											
No	86	44,191	194.6	141	91,486	154.1	1.26*	1.02–1.56	1.363*	1.037–1.793	0.0266
Yes	90	19,857	453.2	134	40,049	334.6	1.35*	1.17–1.55	1.370*	1.044–1.797	0.0232
Depression											
No	113	53,832	209.9	184	11,3417	162.2	1.29*	1.05–1.58	1.408*	1.108–1.788	0.0050
Yes	63	10,216	616.7	91	18,117	502.3	1.23*	1.09–1.38	1.313	0.946–1.822	0.1038
Stroke											
No	70	53,310	131.3	123	10,9094	112.7	1.16	0.90–1.49	1.209	0.896–1.633	0.2144
Yes	106	10,737	987.2	152	22,440	677.4	1.46*	1.32–1.61	1.479*	1.149–1.904	0.0024
Traumatic brain injury											
No	112	54,111	207.0	186	10,9259	170.2	1.22*	1.00–1.49	1.213	0.956–1.539	0.1121
Yes	64	9,936	644.1	89	22,276	399.5	1.61*	1.42–1.82	1.690*	1.215–2.350	0.0018
CCI score											
0	1	6,346	15.8	2	14,132	14.2	1.11	0.54–2.27	1.495	0.025–88.223	0.8468
1	6	8,767	68.4	8	20,399	39.2	1.75*	1.18–2.59	2.139	0.711–6.439	0.1762
2	9	10,343	87.0	17	20,698	82.1	1.06	0.78–1.43	1.463	0.636–3.365	0.3706
≥3	160	38,591	414.6	248	76,305	325.0	1.28*	1.11–1.48	1.328*	1.084–1.626	0.0061
Urbanization level											
1	124	45,606	271.9	144	81,426	176.8	1.54*	1.27–1.86	1.467*	1.151–1.871	0.0020
2	44	14,747	298.4	84	37,197	225.8	1.32*	1.11–1.57	1.426	0.986–2.062	0.0593
3	8	3,695	216.5	47	12,911	364.0	0.59*	0.50–0.70	0.581	0.272–1.241	0.1606

Notes.

*$p < 0.05$.

CCI, Charlson Comorbidity Index; PYs, person-years; IR, incidence rate (per 10^5 PYs); IRR, incidence rate ratio (per 10^5 PYs); CI, confidence interval; HR, hazard ratio.

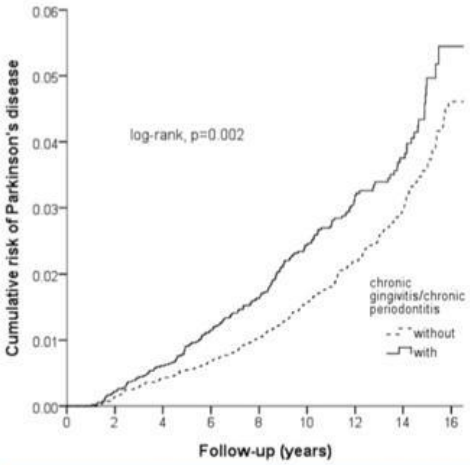

Figure 2 **Kaplan–Meier model based on the Cox-regression analysis for the cumulative risk of Parkinson's disease among the case and control cohort with the log-rank test.**

Table 4 **Sensitivity analysis of Cox-regression model for Parkinson's disease.**

Periodontal inflammatory disease	Crude HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
1-year period after a diagnosis	1.422	1.165–1.737	0.0005	1.431	1.141–1.794	0.002
5-year period after a diagnosis	1.364	1.079–1.725	0.0095	1.395	1.067–1.825	0.015

Notes.
HR, hazard ratio; CI, confidence interval.

and reduced dental appointments (*Barbe et al., 2017*; *Cicciu et al., 2012*; *Muller, Palluch & Jackowski, 2011*; *Pradeep et al., 2015*; *Schwarz, Heimhilger & Storch, 2006*). In addition, a previous study found that patients with PD frequently have oral gram-negative bacteria. Their oral flora differed considerably from that of healthy people (*Gosney et al., 2003*). Moreover, patients with PD often suffer from xerostomia, drooling, and dysphagia, which impair their quality of life (*Barbe et al., 2017*). Therefore, periodontal disease is also one of the important issues affecting the quality of life in patients with PD (*Cicciu et al., 2012*). Nonetheless the cause–effect relationship between periodontal problems and PD remained uncertain until *Liu et al. (2013)* reported, using a cohort study, that revealed increased Parkinsonism five years following a diagnosis.

Unfortunately, patients with CG were not enrolled and the definite HR for a time-period less than 5 years after diagnosis of PID was not reported in their study. We emphasize the importance of enrolling CG because gingivitis is caused by accumulated dental-bacterial plaque and inflammation of gingiva, and CP may develop in PID. CG does not directly result in tooth loss and may be considered reversible with appropriate care. However, CP is always preceded by CG and any resulting clinical loss of attachment and alveolar bone loss

due to CP cannot be reversed. In our study, we found that patients with PID (mainly CG and CP) had an almost 1.4-fold increased risk of developing PD, not only in the CP stage. Therefore, greater care should be paid, to educating the oral hygiene and plaque control methods for patients with PD because periodontal pathology presented a high prevalence in the early stages of gingivitis.

As shown in Table 3, we found male gender, age ≥70 years, hypertension, stroke, traumatic brain injury, CCI score ≥3, and urbanization level 1 in patients with PID were significantly associated with the risk of developing PD. Our findings agree with recent studies which found that PD incidence was higher among males than females (*Smith & Dahodwala, 2014*). The possible explanations suggested that women carry recessive susceptibility genes on the X chromosome, estrogen has neuroprotective effects, women have a lower rate of toxic exposure, and less incidence of traumatic brain injury, than men (*Smith & Dahodwala, 2014*). The patients with and without chronic kidney disease were related with the increased risk of development in PD (*Linnemann Jr & First, 1979*).

PID is a chronic inflammatory condition of the supporting structures of the teeth resulting from a dental plaque biofilm attached to teeth surfaces. Previous study has indicated the presence of a significant association between periodontitis and hyperlipidemia (*Cutler et al., 1999*). According to an earlier study (*Chung et al., 2014*), we adjusted for the selected comorbidities including hyperlipidemia in the Cox-regression model. However, in the subgroups stratified by gender, age, comorbidities, CCI score and urbanization (Table 3), the patients without hyperlipidemia were associated with a higher risk of developing PD (adjusted HR = 1.471). Therefore, further investigation will be required to confirm and clarify the mechanism.

Our results showed higher IRR and adjusted HR for urbanization level 1 (1.54 and 1.467, respectively) in the case group for developing PD. It may be explained by the urban–rural differences in terms of lifestyle, availability of medical resources, and convenience of medical access due to urban patients having better health care (*Liu et al., 2016*). We performed sensitivity analysis to evaluate the role of PID in the development of PD. We further demonstrated and confirmed the adjusted HR during the 1-year and 5-year follow-up period for individuals with PID were 1.431 and 1.395 relative to the control group. However, in a previous study, the patients exposed to CP had significantly greater adjusted HR than did the control group after the 5-year follow-up period (*Liu et al., 2013*). Based on our findings, we suggest that it is necessary to control inflammatory components of patients in the early phase, to potentially reduce the risk of PD.

Our research has the following advantages: (1) We applied a nationwide database and recruited a large number of sample sizes in highlighting the HR and IR over the 16-year long-term follow-up. (2) Taiwanese NHIRD provides continued coverage for the whole population of Taiwan and thus avoids selection bias in the cohorts, (3) the use of the NHIRD eliminates the need to minimize patients in the cohort that were lost to tracing, (4) in socio-demographic characteristics, it is easy to obtain geographically dispersed large samples, which avoids the estimated regional discrepancy (*Liu et al., 2006*), (5) we applied a rigorous definition to identify patients with PD (ICD-9-CM code: 332.0), such that statistical analysis would be more robust and reliable.

However, there were some limitations to our study (1) We excluded patients who had PD before tracing. However, we could not differentiate between primary and secondary Parkinsonism in analyzing NHIRD on the diagnostic code from a representative cohort (*Liu et al., 2016*), (2) we did not access medical records of all defined PID and PD cases, because all the medical records from the NHIRD was de-identified due to ethics approval. We had no clinical information regarding image findings, clinical photographs and examinations of the periodontal disease, laboratory data or treatment response in the defined patients. (3) Periodontal treatment in clinics, oral hygiene from caregivers improved education regarding good oral hygiene practices may help to prevent PD by reducing inflammation (*Pradeep et al., 2015*); however, personal details about periodontal therapy were not included in the NHIRD. (4) Finally, our methods to extract data from the NIHRD enable long-term follow-up periods of sufficiently large cohorts to correlate risk for PD in the context of PID and in the future, could incorporate additional factors such as environmental exposures, lifestyle (e.g., smoking) and genetic polymorphisms. Accurate risk assessment for PD in the context of PID is necessary if it is to influence healthcare planning and national health insurance policy.

CONCLUSIONS

Individuals exposed to PID were 1.431 times more likely to develop PD than those who were not exposed. However, future long-term, larger or national data sets combined with genes, environmental exposure, lifestyle changes, dietary habits, and accurately defined PD diagnosis should be investigated to support the current research results.

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Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Chang-Kai Chen conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, wrote the paper, prepared figures and/or tables, reviewed drafts of the paper.
- Yung-Tsan Wu conceived and designed the experiments, performed the experiments, wrote the paper.

- Yu-Chao Chang conceived and designed the experiments, performed the experiments, contributed reagents/materials/analysis tools, reviewed drafts of the paper.

Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

The study was approved by the Institutional Review Board (IRB) of Chung Shan Medical University.

Data Availability

The following information was supplied regarding data availability:

The raw data has been deposited at the National Health Insurance Research Database in LHID 2010, and has been uploaded as Supplemental Information 1.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.3647#supplemental-information.

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ANEXO 6 – ORAL HEALTH OF PARKINSON´S DISEASE PATIENTS: A CASE-CONTROL STUDY

Hindawi
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Research Article

Oral Health of Parkinson's Disease Patients: A Case-Control Study

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The aim of the study was to examine the oral health status of Parkinson's disease (PD) patients, to compare their oral health status to that of a control group, and to relate it to the duration and severity of PD. *Materials and Methods*. 74 PD patients and 74 controls were interviewed and orally examined. Among PD patients, the duration and the Hoehn and Yahr stage (HY) of the disease were registered. *Results*. More PD patients than controls reported oral hygiene care support as well as chewing/biting problems, taste disturbance, tooth mobility, and xerostomia, whereas dentate patients had more teeth with carious lesions, tooth root remnants, and biofilm. Both longer duration and higher HY were associated with more chewing problems and, in dentates, more teeth with restorations. In dentates, longer duration of the disease was associated with higher number of mobile teeth. Higher HY was associated with more oral hygiene care support as well as biting problems and, in dentates, more teeth with carious lesions and tooth root remnants. *Conclusions*. Comparatively, PD patients had weakened oral health status and reduced oral hygiene care. Both duration and severity of the disease were associated with more oral health and hygiene care problems.

1. Introduction

Parkinson's disease is a progressive degenerative neurological disorder, characterized by motor and nonmotor symptoms. The motor symptoms include akinesia, bradykinesia, rigidity, and tremor, which remain not restricted to the trunk and extremities, but may also occur in the orofacial system [1–3]. Motor impairments of the orofacial system include dysphagia, masticatory dysfunction, orofacial dyskinesia, and oromandibular dystonia [4–7]. In addition, related to oral health, the potentially impaired dexterity of arms and fingers may hamper the required daily oral hygiene care [8].

Advances in oral health care and treatment during the past few decades have resulted in a reduced number of edentulous individuals. The proportion of adults who retain their teeth until late in life has increased substantially [9]. Consequently, a still increasing number of dentate older people experience oral health problems, such as dental caries, periodontal disease, and substantial wear of hard tooth tissues (tooth wear). Furthermore, many older people have been treated with oral implants and/or sophisticated tooth- and/or implant-supported fixed and/or removable dental prostheses. Hence, these older people are in continuous need of both preventive and curative oral health care. The complexity of oral health status, the potential presence of systemic diseases, and the use of several medications make older people more vulnerable to oral problems when compared to younger age groups, particularly in those who are cognitively impaired [10, 11]. In addition, weakened oral health due to neglected oral hygiene care and reduced oral health care utilization has previously been found in older people [11–14].

Oral diseases, such as dental caries and periodontal disease, not only have oral effects, for example oral pain and oral functioning problems, but may also impact a number of systemic conditions. Emerging evidence suggests that poor oral health influences the initiation and/or progression of

diseases, such as atherosclerosis, diabetes mellitus, Alzheimer's disease, and rheumatoid arthritis [15]. Aspiration of oropharyngeal bacteria may cause pneumonia [15–17]. Concerns were expressed about relationships between older people's poor oral health status and nutrition [18].

Study of the international literature revealed that, when compared to control subjects, Parkinson's disease patients generally had a lower number of teeth, more dental carious lesions, poorer periodontal health, higher objective periodontal treatment needs, more subjective chewing difficulties, more subjective swallowing difficulties, more subjective denture discomfort, more limited active mouth opening, and more negative impact of oral health on daily life (Table 1) [19–28]. However, each of the aforementioned studies investigated only few aspects of oral health; none investigated the whole picture of the oral health status. Furthermore, the relationships between aspects of oral health and the duration and severity of Parkinson's disease have not been addressed.

Therefore, the aim of the current study was to examine the most relevant aspects of the subjective and objective oral health status of Parkinson's disease patients, to compare their oral health status to that of an optimally gender-, age-, social background-, and lifestyle-matched control group, and to relate their oral health status to the duration and severity of Parkinson's disease.

2. Materials and Methods

2.1. Study Population. The current cross-sectional, case-control, optimally gender-, age-, social background-, and lifestyle-matched study was approved by the Medical Ethical Committee of Leiden University Medical Center, Leiden, the Netherlands, approval number P13.079. Assuming a power (1-β) of 0.80 and an α of 0.05 and an objective to detect a prevalence difference of 25% between groups across a range of different hypothetical prevalence rates, a sample size calculation indicated that 69 persons per group of Parkinson's disease patients and control subjects would be sufficient.

Patients with Parkinson's disease, without severe comorbidity according to classes III and IV of the Physical Status Classification System of the American Society of Anesthesiologists, were requested to participate when they visited the Department of Neurology of the Leiden University Medical Center, Leiden, the Netherlands, for a routine periodic consultation. The Parkinson's disease patients who agreed to participate, were subsequently requested to identify a control person, for instance a family member or other close relative, who had no Parkinson's disease or other severe systemic diseases according to classes III and IV of the Physical Status Classification System of the American Society of Anesthesiologists, who had approximately the same age (±5 years) as well as a similar social background and lifestyle, and who would likely be prepared to participate. The group of control subjects was also optimally gender matched, meaning that men with Parkinson's disease preferably indicated men and women with Parkinson's disease preferably indicated women. Assuming that not every person proposed by a Parkinson's disease patient as control subject would agree to participate, initially 74 Parkinson's disease patients were included. All Parkinson's disease patients and indicated control subjects were visited at their homes to inform them about the research project. Luckily, all of them provided informed consent and were subsequently interviewed and examined.

After the interview and the examination, every participant received information on his/her actual oral health condition and was recommended consultation with a dentist in case the actual oral health condition required attention and/or treatment.

2.2. Assessments. Using a common history form, data were gathered about educational level (primary, secondary, and tertiary), smoking habits, length of time since the last oral health consultation, number of oral health consultations during the previous five years, daily oral hygiene care (whether or not supported by a professional or voluntary care provider), type of toothbrush used, chewing problems, biting problems, taste disturbance, burning mouth, xerostomia, halitosis, remaining food particles, tooth mobility, toothache, tooth sensitivity, painful gums, and bleeding gums. Persons with an edentulous maxilla/mandible were requested to indicate the duration since the last teeth in the maxilla/mandible had been removed, the number of years during which a current complete maxillary/mandibular removable dental prosthesis was functioning, and their potential experience with a loose coming complete maxillary/mandibular removable dental prosthesis during oral movements.

An experienced dentist performed an oral health examination in all participants, using a common oral screening form. Variables included were edentulousness, soft tissue lesions, complete or partial maxillary/mandibular removable dental prostheses, number of teeth, number of teeth with carious lesions, number of teeth with restorations, number of tooth root remnants, amount of biofilm and food, periodontal health, and number of posterior functional tooth units, including (implant-supported) single- and multiunit fixed dental prostheses.

The amount of biofilm and food on teeth and soft tissues was assessed by a simple 3-points scale: 1 = hardly any biofilm and food; 2 = thin layer of biofilm and food; 3 = thick layer of biofilm and food.

Periodontal health was assessed using the tooth mobility scoring system. This clinically easy-to-determine system differentiates three grades: grade I: mobility in a horizontal direction more than 0.2 mm and less than 1 mm; grade II: mobility in a horizontal direction of 1 mm or more; and grade III: mobility in vertical direction [29].

The number of posterior functional tooth units is an important proxy for masticatory efficiency. One maxillary and one mandibular premolar in occluding contact constitute one posterior functional tooth unit. One occluding maxillary and mandibular molar are equivalent to two posterior functional tooth units [30].

In persons with an edentulous maxilla/mandible, the reduction of the edentulous residual alveolar ridge was clinically classified as moderate reduction, high degree of reduction, or extensive reduction, using a standard set of edentulous alveolar ridge models [31].

Table 1: Studies on Parkinson's disease and oral health, available in the international literature.

Publication	Country	Research design	Population	Results of PD patients when compared to controls	OR	95% CI	P
Nakayama et al., 2004 [19]	Japan	Questionnaire survey by mail	104 with PD 191 controls	Gender- and age-adjusted:			
				More chewing difficulties	6.0	2.8–12.8	
				More denture discomfort	3.9	1.9–8.0	
				More edentulousness	3.5	1.8–6.8	
				Less daily denture care	10.5	2.9–37.3	
				50% swallowing problems			
Schwarz et al., 2006 [20]	Germany	Case-control, age-matched	70 with PD 85 controls	Higher scores on indices of the Community Periodontal Index for Treatment Needs (CPITN)			<0.05
Einarsdóttir et al., 2009 [21]	Iceland	Case-control	67 with PD 55 controls	Lower number of teeth			<0.036
				More dental carious lesions			<0.007
				More biofilm	3.13	1.4–6.9	<0.004
				Poorer periodontal health	2.28	1.0–4.9	0.035
				Greater number of cariogenic bacteria in saliva			<0.05
Hanaoka and Kashihara, 2009 [22]	Japan	Case-control, age-matched	89 with PD 68 mild cognitively impaired 60 with ischemic stroke	Lower number of teeth			<0.05
				More dental carious lesions			<0.001
				More deep periodontal pockets			<0.001
Bakke et al., 2011 [23]	Denmark	Case-control, age-matched, gender-matched	15 with moderate to advanced PD 15 controls	Overall objective orofacial function			<0.001
				Poorer subjective masticatory ability			<0.001
				Poorer active mouth opening			<0.001
				More negative impact of oral health on daily life			<0.001
Müller et al., 2011 [24]	Germany	Case-control	101 with PD 75 controls	Lower gingival index			<0.001
				Lower frequency of daily tooth brushing			<0.01
				More dental carious lesions			<0.01
				Longer time since last dental visit			<0.001
				Lower salivary flow rate			<0.001
				More gingival recession			<0.001
				More tooth mobility			<0.001
Cicciù et al., 2012 [25]	Italy	Case-control, age-matched	45 with mild to moderate PD 45 controls	More dental carious lesions			not reported
				Higher gingival index			not reported
				Higher sulcus bleeding index			not reported
				Higher biofilm index			not reported
Pradeep et al., 2015 [26]	India	Case-control, age-matched	45 with PD 46 controls	More periodontal pockets			<0.001
				More periodontal attachment loss			<0.001
				Lower gingival index			<0.001
				Lower biofilm index			<0.001
Ribeiro et al., 2016 [27]	Brasil	Case-control	Wearers of complete removable dental prostheses 17 with PD 20 controls	Poorer self-perception of oral health			<0.04
Barbe et al., 2017 [28]	Germany	Questionnaire survey	100 with PD Frequencies compared with results of other studies	Poorer oral health impact profile, among others due to complaints of xerostomia, drooling and dysphagia			

For Parkinson's disease patients, the duration of the disease (since the onset of motor symptoms) and the severity of the disease expressed by the Hoehn and Yahr stage were registered from the patients' medical records [32]. The duration of the disease was categorized as less than 5 years, between 5 and 9 years, and 10 years or longer.

2.3. Statistical Analysis. Data were analyzed using SPSS version 22.0 (SPSS, Inc., Chicago, IL). Numbers and percentages were compared between groups using a Chi-square test (χ^2). An independent-samples Student's t-test was only used to compare the age of Parkinson's disease patients and control subjects. Mann–Whitney U test was used to compare

Table 2: Frequencies, including percentages, of the general subjective aspects of oral health and the often/occasional oral health complaints of the (dentate) Parkinson's disease patients (PD) and the (dentate) control subjects (control) and the results of the Chi-square test carried out to assess statistically significant differences (∗) between PD and control.

Variables	PD	Control	Chi-square test
All persons: general subjective variables	$n = 74$	$n = 74$	
Educational level			
(i) primary	18 (24%)	12 (16%)	
(ii) secondary	21 (29%)	35 (47%)	
(iii) tertiary	34 (46%)	27 (37%)	
(iv) missing value	1 (1%)	—	$\chi^2_{(7)} = 11.947$; $P = 0.102$
Smoking status	6 (8.1%)	6 (8.1%)	—
Length of time since the last oral health consultation			
(i) less than half a year	52 (70.3%)	49 (66.2%)	
(ii) between a half and two years	15 (20.3%)	22 (29.8%)	$\chi^2_{(5)} = 5.704$; $P = 0.336$
Number of oral health consultations during the previous five years			
(i) 0	4 (5.4%)	2 (2.7%)	
(ii) 1–5	13 (17.6%)	17 (23.0%)	
(iii) 6–10	30 (40.5%)	36 (48.6%)	
(iv) 11 or more	27 (36.5%)	19 (25.7%)	$\chi^2_{(6)} = 6.607$; $P = 0.359$
Daily oral hygiene care supported by a professional or voluntary care provider	11 (14.9%)	1 (1.4%)	$\chi^2_{(1)} = 9.069$; $P = 0.003^*$
Electric toothbrush used	36 (48.6%)	30 (40.5%)	$\chi^2_{(3)} = 3.091$; $P = 0.378$
All persons: oral health complaints	$n = 74$	$n = 74$	
Chewing problems	22 (29.7%)	3 (4.1%)	$\chi^2_{(4)} = 18.973$; $P = 0.001^*$
Biting problems	26 (35.1%)	7 (9.5%)	$\chi^2_{(4)} = 15.047$; $P = 0.005^*$
Taste disturbance	17 (23.0%)	1 (1.4%)	$\chi^2_{(4)} = 19.523$; $P = 0.001^*$
Burning mouth	3 (4.1%)	0	$\chi^2_{(4)} = 8.0290$; $P = 0.091$
Xerostomia	48 (64.9%)	24 (32.4%)	$\chi^2_{(4)} = 19.510$; $P = 0.001^*$
Halitosis	14 (18.9%)	9 (12.2%)	$\chi^2_{(4)} = 7.037$; $P = 0.134$
Remaining food particles	52 (70.3%)	51 (68.9%)	$\chi^2_{(4)} = 2.877$; $P = 0.579$
Dentate persons: oral health complaints	$n = 65$	$n = 65$	
Tooth mobility	12 (18.5%)	2 (3.1%)	$\chi^2_{(3)} = 11.215$; $P = 0.011^*$
Toothache	10 (15.4%)	6 (9.2%)	$\chi^2_{(3)} = 2.000$; $P = 0.572$
Tooth sensitivity	17 (26.2%)	11 (16.9%)	$\chi^2_{(4)} = 4.500$; $P = 0.343$
Painful gums	12 (18.5%)	7 (10.8%)	$\chi^2_{(4)} = 2.810$; $P = 0.590$
Bleeding gums	13 (20.0%)	12 (18.5%)	$\chi^2_{(4)} = 5.826$; $P = 0.213$

ordinal or nonnormally distributed continuous variables between groups. Kruskal–Wallis test was used to examine group differences of nonnormally distributed continuous variables with three or more categories. Statistical significance was accepted at $P < 0.05$. Given the exploratory character of the study, no attempt was made to control for multiple comparisons.

3. Results

3.1. Participants. Interviews and oral health examinations were performed in 26 women and 48 men with Parkinson's disease and in 35 female and 39 male control subjects ($\chi^2_{(1)} = 2.259$, $P = 0.133$). Mean age ± standard deviation was 70.2 ± 8.8 years in the Parkinson's disease patients and 67.9 ± 10.1 years in the control subjects (Student's t-test; $P = 0.641$).

3.2. Subjective Variables. Table 2 presents frequencies and percentages of the subjective variables of the Parkinson's disease patients and the control subjects. When compared to the control subjects, statistically significantly more Parkinson's disease patients reported daily oral hygiene care support by a professional or voluntary care provider, chewing problems, biting problems, taste disturbance, and xerostomia. When compared to the dentate control subjects, statistically significantly more dentate Parkinson's disease patients reported tooth mobility.

The Parkinson's disease patients and control subjects with an edentulous maxilla (and mandible) showed no statistically significant group differences with regard to length of time since the last teeth had been removed, number of years during which a current complete maxillary/mandibular removable dental prosthesis was functioning, and persons' experiences with a loose coming complete maxillary/mandibular removable dental prosthesis during oral movements.

3.3. Objective Variables. Table 3 presents frequencies and percentages of the objective variables of the Parkinson's disease patients and the control subjects. Statistical analysis of the data of dentate persons did point out that the

Table 3: Frequencies, including percentages, of the objective oral health variables of the Parkinson's disease patients (PD) and the control subjects (control) and statistically significant group differences.

Variables	PD	Control	Statistical test
All persons	$n = 74$	$n = 74$	
Number of persons with an edentulous maxilla	14 (18.9%)	14 (18.9%)	
Number of persons with an edentulous maxilla and mandible	9 (12.2%)	9 (12.2%)	
Number of persons with a soft tissue lesion	20 (27.0%)	18 (24.3%)	
Number of complete maxillary removable dental prostheses	14	15	
Number of complete mandibular removable dental prostheses	9	9	
Number of partial maxillary removable dental prostheses	8	7	
Number of partial mandibular removable dental prostheses	10	9	
Dentate persons	$n = 65$	$n = 65$	
Mean number of teeth	21.2	22.5	
Number of teeth with carious lesions	74	12	Mann–Whitney U test; $U = 1526.500$, $P \leq 0.001$
Number of teeth with restorations	466	518	
Number of tooth root remnants	24	5	Mann–Whitney U test; $U = 1818.000$, $P < 0.022$
Amount of biofilm and food (scores 2 and 3)	39 (60%)	20 (31%)	$\chi^2_{(2)} = 18.127$; $P < 0.001$
Mean number of posterior functional tooth units, including (implant-supported) single- and multiunit fixed dental prostheses	3.2	2.8	

Parkinson's disease patients had statistically significantly more teeth with carious lesions, a greater number of tooth root remnants, and a greater amount of biofilm and food when compared to the control subjects.

Only few Parkinson's disease patients and control subjects had teeth with grades II and III of tooth mobility, 11 and 6 persons, respectively. Therefore, comparisons of periodontal health between Parkinson's disease patients and control subjects were not performed.

The persons who had an edentulous maxilla/mandible, showed no statistically significant differences between Parkinson's disease patients and control subjects with regard to grades of reduction of the edentulous residual alveolar ridges.

3.4. Parkinson's Disease Patients. The distribution of the Parkinson's disease patients across duration and Hoehn and Yahr stage of the disease is presented in Table 4.

The mean duration of the disease was 9.1 ± 6.4 years. Reported chewing problems were statistically significantly positively related to the duration of the disease ($\chi^2_{(8)} = 17.690$, $P = 0.024$). In dentate patients, the number of teeth with restorations and the number of teeth with mobility grade II or III were statistically significantly related to the duration of the disease (Kruskal–Wallis test; resp. $H_{(2)} = 6.398$, $P = 0.041$ and $H_{(2)} = 8.058$, $P = 0.018$).

For subsequent statistical analysis, the Hoehn and Yahr stages were dichotimized, resulting in a group of 47 patients with the mild stages 1 and 2 and a group of 27 patients with the moderate/severe stages 3, 4, and 5. The reported chewing and biting problems as well as the reported daily support for oral hygiene care by a professional or voluntary care provider were statistically significantly positively related to the Hoehn and Yahr stage of the disease (resp. $\chi^2_{(4)} = 14.045$, $P = 0.007$; $\chi^2_{(4)} = 10.939$, $P = 0.027$; $\chi^2_{(1)} = 11.457$, $P = 0.001$). Furthermore, the number of teeth with carious lesions, the number of teeth with restorations, and the number of tooth root remnants appeared statistically significantly higher in dentate patients with the moderate/severe Hoehn and Yahr stages 3–5, when compared to dentate patients with the mild Hoehn and Yahr stages 1-2 (Mann–Whitney U test; resp., $U = 246.500$, $P = 0.001$; $U = 252.500$, $P = 0.004$; $U = 311.000$, $P = 0.002$).

Table 4: Distribution, including percentages, of the Parkinson's disease patients by duration (D) and Hoehn & Yahr stage (HY) of the disease.

D/HY	Number of patients	Percentage
D less than 5 years	20	27
D between 5 and 9 years	19	26
D 10 years or more	35	47
HY1	16	22
HY2	31	42
HY3	11	14
HY4	12	16
HY5	4	6

4. Discussion

This is the first study which examined the most relevant aspects of the subjective as well as the objective oral health status of a large group of Parkinson's disease patients, which compared these findings with the same data of an optimally gender-, age-, social background-, and lifestyle-matched control group and which related the oral health status of the Parkinson's disease patients to the duration and severity of the disease. The findings demonstrate that more Parkinson's disease patients than control subjects reported daily oral hygiene care support by a professional or voluntary care provider, as well as chewing problems, biting problems, taste disturbance, tooth mobility, and xerostomia. Objectively, the dentate Parkinson's disease patients had a greater number of teeth with carious lesions, a greater

number of tooth root remnants, and a greater amount of biofilm and food, when compared to the dentate control subjects. These findings represent symptoms of weakened oral health and reduced oral hygiene care, probably due to Parkinson's disease impairments. Within the group of Parkinson's disease patients, both longer duration and higher Hoehn and Yahr stage of the disease were associated with more chewing problems and, in dentate persons, with more teeth with restorations. Additionally, in dentate persons, longer duration of the disease was associated with a higher number of teeth with mobility grade II or III, whereas a higher Hoehn and Yahr stage of the disease was associated with more daily oral hygiene care support by a care provider as well as biting problems and, in dentate persons, with more teeth with carious lesions and more tooth root remnants. These findings reflect symptoms of weakening oral health, probably due to the reducing ability to manage oral hygiene care as the disease advances.

Existing data on the oral health of Parkinson's disease patients, as presented in Table 1, are extended by the results of the current study. Novel identified oral health problems include taste disturbance and more oral health problems in advanced stages of the disease. Together, these data indicate that weakening oral health and its potential negative impact on several systemic conditions are serious problems in Parkinson's disease patients, which demand more attention worldwide by the multidisciplinary Parkinson's disease medical management teams as well as standard referrals to oral health-care providers.

Chewing and biting problems, more reported by Parkinson's disease patients than control subjects, predominantly in advanced stages of the disease, may reflect (increasing) motor impairments of the orofacial system. Consequently, it is recommended to consider research of chewing and biting problems in Parkinson's disease patients with the objective to manage or reduce these problems. Other impairments of the orofacial system of Parkinson's disease patients may present as temporomandibular dysfunction. A recent study among a group of Parkinson's disease patients found temporomandibular dysfunction in about one-fifth of the patients [33]. Nevertheless, since diagnosing and classifying temporomandibular dysfunction is a rather complicated and time-consuming activity [34], we decided consciously not to include temporomandibular dysfunction as a research variable in our study. A separate and specific study on this topic is in preparation by the research groups involved in the current study.

When considered in relation to oral health, taste disturbance is certainly a novel finding in Parkinson's disease patients since none of the studies mentioned in Table 1 reported this problem. However, olfactory loss as well as smell and taste loss are well-known neurological problems in Parkinson's disease. Results of a recent (neurological) study suggest that the problems are caused by a decline of central brain networks rather than a damage of the peripheral olfactory system [35]. Previously, the olfactory deficit was demonstrated to be independent of Parkinson's disease severity and duration and preceding clinical motor symptoms by years. For this reason, taste disturbance was even suggested to be used for assessing the risk of Parkinson's disease in otherwise asymptomatic individuals [36]. From an oral health perspective, taste ability may change due to deterioration of oral health status, deficient oral hygiene, and impaired masticatory ability [37]. Additionally, saliva is of great importance since it acts as a solvent of taste substances, affects taste sensitivity, and maintains the health and function of the taste receptors. Consequently, hyposalivation results, among others, in significant altered taste sensation or taste disturbance [38]. Hyposalivation may induce oral health problems, such as tooth wear, oral soft tissue lesions, dental caries, candidiasis, and periodontal disease [39]. Nearly 65% of the Parkinson's disease patients in our study reported xerostomia (Table 2), confirming previous results demonstrating or suggesting that xerostomia and the commonly underlying hyposalivation are prevalent complications of Parkinson's disease [28, 40]. Another saliva complication of Parkinson's disease patients is drooling. Most likely, impaired intraoral saliva clearance is the basis of its pathophysiology. However, research to explore the exact pathophysiology and to develop standard diagnostic criteria and assessment tools are needed [41]. Therefore, taste disturbance, xerostomia, hyposalivation, and drooling are topics challenging collaboration between movement disorders specialists and dentists.

Several results of the current study suggest a reduced ability to manage oral hygiene care due to Parkinson's disease impairments, which increases as the disease advances. This assumption concurs with the finding of impaired dexterity in Parkinson's disease, predominantly in advanced stages of the disease [8]. Furthermore, a recent study proved that fine motor skills in Parkinson's disease patients are impaired, predominantly in patients with mild cognitive impairment [42]. Probably, at a certain, difficult to predict stage of Parkinson's disease, patients become dependent on professional or voluntary care providers for proper daily oral hygiene care. In the current study, 15% of the Parkinson's disease patients reported as such. Unfortunately, oral hygiene care is generally not prioritized, either by the professional care providers, or by the patients themselves. Even providing a guideline to nursing home care providers and supervised implementation of this guideline did not result in a general improvement of oral hygiene of nursing home residents [43]. Subsequently, it was recommended to better integrate professional oral hygiene care into professional general health care (also in Parkinson's disease patients) in order to prevent poor oral health to become a new geriatric syndrome [44].

A retrospectively ascertained weakness of this study is the lack of data on social background and lifestyle of both the Parkinson's disease patients and the control subjects. Although the patients were requested to identify a family member or other close relative who had a similar social background and lifestyle as a control person, these variables were not actually assessed. Therefore, some selection bias cannot be ruled out.

5. Conclusions

The results of the current study reveal that the Parkinson's disease patients had a weakened oral health status and

reduced oral hygiene care, when compared to an optimally gender-, age-, social background-, and lifestyle-matched control group. Additionally, both longer duration of the disease and more severe disease were associated with more oral health and oral hygiene care problems, altogether suggesting that their weakened oral health and reduced oral hygiene care are due to Parkinson's disease impairments. The authors recommend worldwide multidisciplinary Parkinson's disease medical management teams to pay more attention to their patients' oral health including standard referrals to oral health-care providers, to establish research of chewing and biting problems, taste disturbance, xerostomia, hyposalivation, and drooling in Parkinson's disease patients through collaboration of movement disorders specialists and dentists, and to integrate professional oral hygiene care into professional general health care for Parkinson's disease patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The intention of this research project has been presented at the XX World Congress on Parkinson's Disease and Related Disorders in Geneva, Switzerland, 8–11 December 2013. On 4–7 December 2014, the design of this research project has been presented at the 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders in Nice, France. Some preliminary results of the study have been presented at the XXII World Congress on Parkinson's Disease and Related Disorders in Ho Chi Minh City, Vietnam, 12–15 November 2017.

Conflicts of Interest

The authors report no conflicts of interest.

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ANEXO 7 – SALIVA CHANGE IN PARKINSON´S DISEASE PATIENTS AFTER INJECTION OF BOTULINUM NEUROTOXI TYPE A

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ORIGINAL ARTICLE

Saliva changes in Parkinson's disease patients after injection of Botulinum neurotoxin type A

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Abstract
Patients with Parkinson's disease (PD) are compromised by poor oral condition due to oropharyngeal bradykinesia, dysphagia, and the side effects of treatment. Intrasalivary gland injections of Botulinum neurotoxin type A (BNT-A) have been known to treat sialorrhea effectively in these patients. However, the decreased amount of saliva reduces self-cleaning ability that deteriorates oral hygiene and increases dental caries. The aim of this study was to determine the changes in the oral microflora and saliva in patients with PD treated for sialorrhea by means of sonography-controlled BNT-A injections into the bilateral parotid and submandibular glands. Altogether, 38 persons participated in the study: 12 PD patients who were injected with BNT-A for treatment of sialorrhea and passed salivary tests before and 1 month after the injections; and 13 PD patients and 13 healthy subjects who were not injected with BNT-A and passed salivary tests once. The condition of oral health was measured by the amount of saliva, salivary flow rate, and salivary composition. A good outcome with a significant decrease in salivary flow rate occurred at 1-month follow-up in the BNT-A-treated group while no significant change was found in salivary composition. BNT-A treatment did not change the *Streptococcus mutans* levels in saliva but there was statistically significant increase in levels of *Lactobacilli*. BNT-A injections can effectively treat sialorrhea while considering the change of oral microflora, and the patients should be under dentists' care more frequently. EudraCT clinical trial number: 2015-000682-30.

Keywords Sialorrhea · Botulinum neurotoxin type A · Parkinson's disease · Saliva · *Streptococcus mutans* · *Lactobacilli*

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Introduction

Although the clinical diagnosis of PD is based upon a defined motor syndrome (bradykinesia, rigidity, rest tremor), also, non-motor features are present in most patients in the early stages of the disease already, and often can dominate among clinical manifestations [1–3]. As the disease progresses, the burden of non-motor symptoms rises, affecting substantially the quality of life of patients with PD [4, 5]. Some of the non-motor features, such as autonomic and neuropsychiatric disturbances, seem to preferentially affect patients with non-tremor-dominant subtypes of PD [6].

Drooling is not among the most frequent non-motor symptoms with its prevalence ranging from 10 to 84% across different studies and it may affect the quality of life remarkably [7–10]. It is defined as the inability to control oral secretions, resulting in excessive saliva accumulation in the oropharynx. Usually, the main problem in PD with saliva excess is related to the dysfunctional oral motor control when the glutation process is abnormal due to the weak muscle function [7–9, 11]. Based on yet unpublished data of the PD prevalence study

in Estonia, excessive drooling was commonly described affecting 47% patients but mostly not as a severe symptom.

Higher odds of the occurrence of drooling have been found among patients with older age, more severe PD, and longer disease duration [8]. Several case-control studies have demonstrated that patients with PD have lower salivary flow [12, 13], but increased excretion velocity to stimulus [7] compared to healthy controls. Drooling may also be associated with oropharyngeal bradykinesia [9], hypomimia, and dysphagia [8, 9]. There is some evidence that levodopa might stimulate salivary flow rate and lead to excessive amount of saliva [12].

Saliva has a purifying and disinfective effect due to its lysosomal content. As the parotid gland produces water, electrolytes, and proteins, saliva is serous. Saliva is also viscous as the submandibular and sublingual glands produce mucopolysaccharides [14]. The physiology of swallowing consists of three phases: voluntary oral, and involuntary pharyngeal and esophageal [10]. Complaints of PD patients depend largely on disturbances occurring in the oropharyngeal phases. Reduced fine motor skills due to the disease may lead to inadequate cleaning of teeth and poor oral condition [15].

Botulinum neurotoxin type A (BNT-A) injections into the salivary glands have been proven to effectively reduce drooling according to several clinical studies [16–18]. This treatment method may also affect the oral condition since a change in the amount of saliva is frequently accompanied by changes in salivary pH, oral flora, and saliva characteristics [10]. A decrease in the amount of saliva is thought to be associated with increased incidence of dental caries.

The aim of the present study was to assess the salivary parameters along with the saliva flow in order to improve the knowledge of the oral health management of elderly people and patients with PD and through that evaluate the impact of BNT-A injection therapy on the oral health of PD patients.

Subjects and methods

Thirty-eight study subjects (16 female and 22 male; age range 58–88 years, mean age of 71.1 years) screened at the Tartu University Hospital from April 2015 to January 2016 were enrolled in the prospective, clinical trial. The subjects were selected from the cohort of patients included in the PD epidemiology study at the Department of Neurology and Neurosurgery of Tartu University. Thirteen healthy, age-matched controls (7 female and 6 male) were recruited from the Department of Stomatology.

The patient recruitment was based on screening by the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) questionnaire, Item 2.2 from Part II (Non-Motor Aspects of Experiences of Daily Living) [19]. Demographic and clinical data including age at PD onset, disease duration, clinical motor phenotype, and information on antiparkinsonian treatment were collected for all the PD patients. The clinical motor phenotype of disease was classified on the basis of the presence of leading symptoms: tremor-dominant, akinetic-rigid-dominant, or postural instability and gait disorder-dominant (PIGD). All except one PD patient was clinically thoroughly examined with the use of parts II and III of the MDS-UPDRS and the Hoehn and Yahr Scale [20].

All subjects were divided into three groups: group 1 consisted of 12 PD patients (9 male and 3 female) who suffered from sialorrhea and received BNT-A injections into the salivary glands, group 2 consisted of 13 PD patients without hypersalivation (7 male and 6 female) and who did not receive BNT-A injections, and group 3 consisted of 13 age-matched healthy controls (6 male and 7 female). Group 1 patients passed salivary tests before and 1 month after the injections. Groups 2 and 3 passed salivary tests once.

Inclusion criteria of the study groups were defined as follows. BNT-A injections into salivary glands were used to treat patients suffering from average or severe hypersalivation when logopedical treatment with chewing muscle and orbicularis oris myogymnastics had not been effective in decreasing the saliva flow. PD patients with sialorrhea who scored 1 to 4 based on item 2.2 of the Part II of the MDS-UPDRS were included in group 1. PD patients without sialorrhea whose score of item 2.2 of the MDS-UPDRS was 0 were included in group 2. All the controls in group 3 were healthy volunteers chosen from the similar age group as the PD patients. Patients who received any other sialorrhea treatment were excluded from the study. Another exclusion criterion was the use of any medication during the study that could influence the severity of drooling. One patient from group 1 was excluded from the study because of his refusal of the second follow-up examination.

Intervention

Group 1 was injected with BNT-A (a total of 250 units Dysport) into the salivary glands to treat hypersalivation. The procedure was performed by a maxillofacial surgeon. 27-G needles were placed in the anteroposterior direction into each submandibular and parotid gland under an ultrasound guidance (Fig. 1). Groups 2 and 3 did not receive any treatment influencing the salivary glands. All participants were interviewed about changes in saliva.

To investigate the salivary parameters, saliva from all the study participants was collected in a cup during 5 min; the amount, composition, and microbial state were compared between the groups. The samples were taken before noon, 2 h after the last meal. Patients were instructed not to brush their teeth on the morning before the investigation.

Saliva analysis consisted of the measurement of both resting and stimulated saliva. To measure the amount of

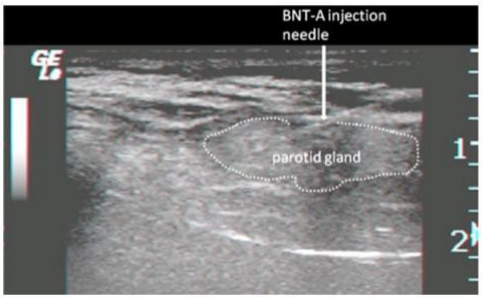

Fig. 1 The ultrasound sonography of BNT-A injection to the salivary gland

stimulated saliva production, the patients chewed a piece of wax for 5 min before the collection of saliva, which accumulated in the oral cavity. Resting saliva was tested by its hydration level, consistency, and pH. Quantity and buffering capacity of stimulated saliva were measured. Salivary levels of the cariogenic bacteria *Streptococcus mutans* were measured using the Dentocult SM test, and *Lactobacilli* were measured by using the Dentocult LB test (Orion Diagnostica Co Ltd., Epsom, Finland) [21]. Microbial tests were evaluated by counting colony-forming units (CFU/ml): class $0 = < 10^3$; class $1 = 10^3$–10^4; class $2 = 10^4$–10^5; class $3 = > 10^5$.

Analysis of saliva composition was performed using the Saliva-Check BUFFER in Vitro Test (GC EUROPE N.V. B-3001 Leuven, Belgium) [22] by the instructions. The change in the amount and composition of saliva during 1 month (before and 1 month after the injection) was measured among patients of group 1 who received BNT-A injections. The results for groups 1, 2, and 3 were compared to assess differences in saliva in PD patients with sialorrhea treated with BNT-A, the PD patients without sialorrhea, and the healthy controls.

Statistical analysis

Data analysis was performed using the IBM SPSS Statistics V20 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were expressed as estimates of percentages, means with standard deviation (SD), and medians with ranges. The Kruskal–Wallis test or ANOVA was used for multiple comparisons. To compare the differences of the variables of interest between the two independent groups, the two-sample *t* test, the two-proportion *z* test, and Mann–Whitney test were used as appropriate. Wilcoxon matched pairs signed-ranks test was used for the analysis of non-parametric data, while paired *t* test was used for parametric data analysis. The Pearson correlation analysis was used to evaluate the associations between variables. The *p* values < 0.05 were considered statistically significant.

Ethics approval

The study was conducted in accordance with the national and international ethics standards, and was approved by the Research Ethics Committee of the University of Tartu (Protocol No. 221/T-15). Written informed consent was obtained from all participants. As the patients of group 1 received BNT-A injections, the study was approved by the Estonian State Agency of Medicines (Protocol No. 01-09.02.15; EudraCT number: 2015-000682-30).

Results

The mean age for group 1 was 71.3 years (SD 8.5); for group 2, 71.5 years (SD 8.1); and for group 3, 70.6 years (SD 9.0). These differences were statistically insignificant by ANOVA ($p = 0.966$). The summary of the clinical characteristics of the PD patients from group 1 and group 2 is demonstrated in Table 1. According to the Kruskal–Wallis test and ANOVA, there were no statistically significant differences between the three groups in resting saliva formation ($p = 0.372$), consistency ($p = 0.585$), amount of saliva collected during 5 min ($p = 0.493$), pH ($p = 0.635$), and buffering capacity ($p = 0.183$).

By the Pearson correlation analysis, the amount of saliva was larger in patients who were treated with levodopa ($p = 0.016$), and less in the patients who received MAO-B treatment ($p = 0.020$). The mean duration of levodopa treatment was significantly longer among patients in group 1 who received BNT-A treatment for sialorrhea, compared to patients in group 2 (Table 1) that indicates to the association between levodopa treatment duration and sialorrhea.

Resting time saliva formation was slower in patients of later disease onset of PD. Resting saliva formation shows the time how quickly a drop of saliva appears from the minor salivary gland of the lower lip. The values before the BNT-A injections were somewhat lower compared to the corresponding values 1 month after the injections (Table 2). The Pearson correlation analysis showed an association between the initial amount of 5-min saliva and the leading symptom ($p = 0.016$) comparing PD patients in groups 1 and 2. Akinesia-rigidity was the most frequent disease subtype among patients in group 1, and tremor was the most frequent leading PD symptom among patients in group 2 (Table 1).

All patients in group 1 reported saliva thickening 1 month after BNT-A injections. Drooling was very intensive at the baseline; however, after 1 month of treatment, the patients reported a decrease in drooling to the moderate level ($p = 0.01$). The consistency of saliva did not change significantly according to the Mann–Whitney *U* test ($p = 0.059$). However, the amount of the 5-min saliva showed a significant decrease from pre-injection to 1-month post-injection assessment (Table 2). In group 1, comparison of pH values revealed no

Table 1 Characteristics of the study participants according to the group

Characteristic	Group 1 ($n = 12$)	Group 2 ($n = 13$)	p value
PD onset age (yr)[a]	57.7 ± 9.6	63.7 ± 8.1	0.102
PD duration (yr)[a]	13.4 ± 6.6	7.8 ± 4.6	*0.019*
Clinical subtype of PD, *n* (%)			
Tremor-dominant[b]	1 (8)	9 (69)	*0.0018*
Akinetic-rigid[b]	8 (67)	4 (31)	*0.005*
PIGD[b]	3 (25)	0 (0)	0.055
HY (median)[c]	3 (2–4)	2.5 (1.5–3)	*0.005*
MDS-UPDRS Part II[a]	17.7 ± 7.7	9.9 ± 4.1	*0.004*
Item 2.2. saliva and drooling[a]	2.9 ± 1.1	0.2 ± 0.4	*< 0.001*
MDS-UPDRS Part III[a]	50.1 ± 19.8	27.2 ± 9.6	*0.001*
Antiparkinsonian treatment, *n* (%)			
Amantadine[b]	7 (58)	3 (23)	0.074
MAO-B inhibitors[b]	3 (25)	3 (23)	0.907
Dopamine agonists[b]	7 (58)	8 (62)	0.838
Levodopa[b]	11 (92)	9 (69)	0.151
LEDD (mg)[a]	1024.8 ± 576.5	405.4 ± 288.3	*0.002*
Levodopa daily dose (mg)[a]	568.2 ± 234.8	355.6 ± 142.4	*0.029*
Duration of levodopa treatment (yr)[a]	9.2 ± 5.2	4.5 ± 3.7	*0.034*

Statistically significant values in italics

PD, Parkinson's disease; *sd*, standard deviation; *yr*, years; *PIGD*, postural instability and gait disorder; *HY*, Hoehn and Yahr stage; *MDS-UPDRS*, Movement Disorders Society Unified Parkinson's Disease Rating Scale; *LEDD*, levodopa equivalent daily dose

[a] Mean ± sd; two-sample t test for statistical significance

[b] Number (proportion) of patients; two proportion z test for statistical significance

[c] Median (ranges); Mann–Whitney U test for statistical significance

difference before and 1 month after the injection ($p = 1.000$), which is an evidence of preserved normal pH. Buffering capacity was higher 1 month after BNT-A treatment compared to the pre-injection value ($p = 0.037$) (Table 2). It shows that the ability of saliva to maintain the normal oral pH was better after injection than before.

According to the Mann–Whitney U test, there was no significant change in the count of *S. mutans* values, but

Table 2 Change in saliva parameters between groups and before and 1 month after the BNT-A injection in group 1

	Group 1			Group 2	Group 3
	Before BNT-A injection	1 month after BNT-A injection	p		
Resting saliva formation time (s)[a]	15 (5–60)	25 (16–75)	*0.05*	20 (7–78)	26 (10–60)
Amount of 5-min collected saliva (ml)[b]	8.6 ± 6.79	4.8 ± 4.09	*0.018*	6.0 ± 3.5	6.3 ± 4.0
Buffering capacity[a]	5 (2–12)	9 (3–12)	*0.037*	9 (3–12)	8 (2–12)
Consistency[a]	3 (2–3)	2.5 (2–3)	0.059	3 (3)	3 (2–3)
pH[b]	7.0 ± 0.74	7.0 ± 0.95	1.00	7.3 ± 0.86	7.2 ± 0.8
Dentocult LB[a]	1 (0–3)	2 (0–3)	*0.047*	2 (0–3)	1 (0–2)
Dentocult SM[a]	2 (0–3)	2 (2–3)	0.206	2 (0–3)	2 (0–3)

Statistically significant values in italics

BNT-A, Botulinum neurotoxin type A

[a] Median (ranges); Wilcoxon matched pairs signed-ranks test for statistical significance

[b] Mean ± sd; paired t test for statistical significance

Lactobacilli counts rose (Table 2): the Dentocult SM values were similar before, and 1 month after the BNT-A treatment, and the Dentocult LB values increased, being higher 1 month after the injection.

PD patients and their carers were asked to report adverse events after the BNT-A injections but there were no adverse events, and the treatment was generally well tolerated. There were no complaints of swelling or pain in group 1.

Discussion

This study focused on BNT-A treatment for sialorrhea in PD patients, and the aim of the study was to evaluate the impact of BNT-A injection therapy on the saliva properties. Other parameters of the general oral condition were not assessed. There is a number of specific orofacial problems affecting patients' oral condition even without possible BNT-A treatment complications, but associated with PD, including muscular hypokinesia, rigidity, and malnutrition in a case of decreased liquid intake and eating soft sticky food [15]. Oral implications like xerostomia, bruxism, dry throat, gingivitis, tongue edema, abnormal taste, glossitis, and orthostatic hypotension may result from the adverse effects of PD medications [23, 24]. Patients with PD have more food debris and poorer oral clearance, as well as more dental plaque, caries, and poor periodontal health [25]. This leads to more missing teeth and various denture problems, which have been ascribed to lack of orofacial muscular control, hyposalivation, and compromised manual skillfulness. PD patients report more often oral health-related problems compared to age- and gender-matched control subjects, and the problems increase significantly with increasing UPDRS score for motor impairment [26]. Caries, periodontal disease, and tooth loss may occur due to the inability to perform proper oral hygiene; also, the chewing process is less efficient because of tremor, rigidity, and hypokinesia [9]. Reduced jaw mobility and slowness of jaw movements as well as dysphagia-related food retention are common problems [26]. Patients with PD may be apathetic, depressive, or demented, and thus may not notice their dental problems. Poor oral and periodontal health is a risk factor for general health problems, including cardiovascular diseases, ischemic stroke, diabetes mellitus, atherosclerosis, pulmonary diseases, and rheumatoid arthritis [27, 28].

The standard medication of PD is levodopa. However, the effect of treatment decreases with time, and after 5–10 years, treatment complications may occur [4, 5, 26]. Earlier studies have shown that most patients with PD produce less saliva compared to healthy controls [10, 16, 26]. This can be explained with dopamine deficiency that modulates salivary secretion [15, 29]. Levodopa stimulates the rate of both basal and reflex salivary flow and leads to saliva excess in some cases of PD [12, 30]. The prevalence of drooling in PD patients ranges widely, from 10 to 84% [10, 16]. Our study showed that PD patients who experienced drooling were statistically more often on levodopa treatment supporting the findings by Ou et al. [31].

However, there are little data on the association between drooling and motor subtypes of the disease. Current study revealed that PD patients with tremor-dominant subtype of disease reported drooling less frequently than those with akinetic-rigid and PIGD-dominant subtype of PD. This is consistent with the results by Karakoc et al. showing that bradykinesia scores in MDS-UDPRS Part III were significantly higher in droolers than those in non-droolers [9]. PIGD and akinetic-rigid subtypes of PD have been linked with higher burden of non-motor features; therefore, the management of those patients might be more complex than of those who predominantly experience tremor [6].

Treatment of drooling with BNT-A injections has an effect on the amount and condition of saliva and leads to the changes of oral environment and health. Our results are in line with previous studies showing that BNT-A reduces drooling [18, 31–34]. There are no data from earlier studies on saliva composition and microbial changes after BNT-A.

Submandibular and parotid glands have been chosen for targets of BNT-A injections to treat sialorrhea because in the resting state, the saliva is mostly produced by the submandibular gland (71%), also by the parotid gland (25%), and less by the sublingual gland (4%) [10] and after stimulation, 63% of saliva is produced by the submandibular gland, 34% by the parotid gland, and 3% by the sublingual gland [14]. Our results on resting saliva formation indicate that the oral cavity remained hydrated and healthy during the treatment with BNT-A. This can be explained by the fact that the salivary flow from the greater salivary glands was affected but not from the minor salivary glands. In our study, no significant alterations in salivary pH were demonstrated after the BNT-A injections. Salivary buffering capacity shows how quickly the oral pH can reach its normal value after a meal. Saliva possesses buffering capacity for neutralizing acids present in the mouth. It can be attributed to several systems such as the phosphate system and the carbonic acid/bicarbonate system. That is why saliva can maintain its usual pH after a meal. Salivary buffers are resistant to changes in pH [14]. Buffering capacity increased during the study period, indicating improvement in salivary defense ability. Saliva's normal pH is 6.7–7.4 [14]. When the pH of saliva drops below 5.5, demineralization of tooth enamel usually follows. In the acid oral pH state, there is a higher risk for dental caries, and in the alkaline pH condition, a higher risk for the dental calculus [30]. Beside the low pH and buffering capacity values, cariogenic bacterial appearance plays a key role in caries formation and progression. Most important of them are *S. mutans* and *Lactobacilli*. Our study showed no change in *S. mutans* values, but *Lactobacilli* counts were increased 1 month after the injection. Some earlier studies have reported periodontal disorders and a worsened dental condition in subjects with PD [15, 35]. However, studies of oral and

dental health with a focus on the microbial status and salivary health of patients with PD have so far been lacking. It is generally known that the most effective way to prevent progression of periodontal disease is brushing of teeth. Consequently, maintaining the oral condition can be improved through the use of powered toothbrushes or special antimicrobial rinses that minimize oral infections. For PD patients, routine regular cleaning of teeth with powered toothbrushes could be easier to perform, and not affected too much by motor and cognitive dysfunctions including tremor, akinesia, rigidity, and dementia. When recommending mouth rinses, caution should be advised as rinsing may lead to aspiration because of the dysfunction of the oral musculature. Also, the use of fluoridated products and calcium phosphate can reduce the risk of caries and help strengthen the enamel; sodium fluoride may reduce the risk of root caries [23].

Patients with PD have poor oral health depending on the symptoms of the main disease. Although, the results of the study showed no statistically significant changes in salivary composition before and after BNT-A injections, the level of *Lactobacilli* counts raised after BNT-A injections. The main limitation of the study is the relatively small sample size of the study groups that could be a source of low statistical power. Another limitation is the fact that only limited parameters of saliva including cariogenic microflora were assessed but not the oral health in more details. Future research to evaluate different *Lactobacilli* subtypes and their influence to the oral health should be done. Also, there is a need for studies containing periodontal pathogens. In parallel with achieved therapeutic effect of the BNT-A, the treatment remains a risk for poorer oral condition and decreased self-cleaning ability. Caregivers and patients should cooperate with dentists, to improve oral hygiene and maintain good oral health [15, 34].

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Compliance with ethical standards

The study was conducted in accordance with the national and international ethics standards, and was approved by the Research Ethics Committee of the University of Tartu (Protocol No. 221/T-15). Written informed consent was obtained from all participants. As the patients of group 1 received BNT-A injections, the study was approved by the Estonian State Agency of Medicines (Protocol No. 01-09.02.15; EudraCT number: 2015-000682-30).

Conflict of interest The authors declare that they have no conflict of interest.

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ANEXO 8 – SUBJECTIVE AND OBJECTIVE HALITOSIS AMONG PATIENTS WITH PARKINSON´S DISEASE

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ORIGINAL ARTICLE

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Subjective and objective halitosis among patients with Parkinson's disease

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Objectives: Parkinson's disease (PD) affects oral health, but prevalence of subjective and objective halitosis and the influence of hyposalivation remain unclear. We aimed to explore whether patients with PD suffer from halitosis and to define correlations between halitosis and hyposalivation. We hypothesised that patients with PD suffer more often from halitosis compared to healthy controls, influenced by dry mouth.

Materials and methods: Subjective (halitosis, xerostomia visual analogue scale [VAS], short German Oral Health Impact Profile [OHIPG]-14) and objective scales (e.g., organoleptic score, volatile sulphur compounds [VSCs], stimulated whole saliva [SWS]) were assessed from 26 patients with PD and 26 healthy controls.

Results: The mean organoleptic score was 0.7 (SD: 0.7) in all patients, and VSCs were either comparable or significantly lower (dimethyl sulphide, $P = .010$) in PD patients compared with controls, yet more patients with PD perceived halitosis to be stronger (77% vs 54%, respectively; $P = .059$). Dry mouth was significantly more likely in patients with PD than controls: mean xerostomia VAS 4 (SD: 2) vs 1 (SD: 2), $P = .010$; SWS 0.4 (SD: 0.4) vs 0.7 (SD: 0.6) mL/min, $P < .05$); SWS did not correlate with subjective or objective halitosis. Oral health-related quality of life (OHRQoL) was lower in patients with PD than controls (mean OHIPG-14 score 12 (SD: 0.2) vs 5 (SD: 7.0), respectively; $P < .05$).

Conclusions: Patients with PD suffer from subjective and objective halitosis, dry mouth and impaired OHRQoL. Dry mouth problems do not correlate with prevalence or intensity of halitosis.

KEYWORDS
dry mouth, movement disorders, oral health-related quality of life, oral malodours, OralChroma™, volatile sulphur compounds

1 | INTRODUCTION

Idiopathic Parkinson's disease (PD) is a progressive neurodegenerative disease that affects around 1% of adults over the age of 60 years worldwide, making it one of the most common movement disorders.[1] Recent evidence suggests that PD is a multisystem brain disease in which non-dopaminergic transmitter systems might be affected at motor onset and become more prominent in later disease stages.[2] When PD becomes clinically overt, tremor, rigidity, bradykinesia and postural instability are considered the cardinal disease symptoms. The disease is chronic and progressive and may be complicated by a wide range of motor and non-motor features

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that contribute to increased disability and diminished quality of life (QoL).[3]

These issues are of importance to dentists, as PD has a detrimental impact on oral health (OH). Reports have shown that patients with PD suffer from hyposalivation (objective finding of decreased salivary production) and xerostomia (abnormal subjective dryness of the mouth due to insufficient secretions) more often than healthy controls.[4,5] This can have an adverse impact on the microflora balance; the lack of constant salivary flow may lead to a disappearance of the antimicrobial activity of the saliva and an increasing shift of the microflora towards gram-negative species.[6] Studies have reported a correlation between dry mouth and halitosis (bad breath).[7,8] As the disease progresses, and patients with PD become less able to perform oral hygiene procedures, the risk of developing halitosis may increase as the oral clearance function might be disturbed.[9] Patients with PD also suffer more frequently from oral symptoms such as periodontitis and caries,[10] which may further increase the risk of suffering from halitosis.[11] Anosognosia in PD, defined as a lack of awareness or denial of deficits and symptoms of dementia, may also impact OH.[12] Additionally, the underreporting of non-motor symptoms among patients with PD has been reported in a recent series,[13] and there may be a problem of detecting and thus treating halitosis. It has been shown that having bad breath may impair OH-related QoL (OHRQoL),[14,15] but this has not been investigated in patients with PD. As yet, there is no scientific data on the prevalence and burden of halitosis among patients with PD.

Therefore, we conducted a clinical comparison between a group of patients with PD and a group of sex- and age-matched healthy controls to measure subjective and objective halitosis (organoleptic scales and volatile sulphur compounds), stimulated salivation rates, xerostomia levels as well as OHRQoL. Based on previous data, we hypothesised that patient with PD suffer more often from halitosis compared to healthy controls influenced by their dry mouth conditions and that OHRQoL is impaired by halitosis compared to healthy controls.

2 | MATERIALS AND METHODS

2.1 | Ethics

The University of Cologne local ethics review board (Study number 15-026) granted approval for the study. The study was registered at the DRKS German registry of clinical trials (registration number DRKS00009314).

2.2 | Sample size calculation

In a previous study, we observed a mean difference within matched pairs of 0.46 (SD: 0.51) mL for stimulated whole saliva (SWS).[5,16] This corresponds to a (large) standardised effect of 0.9. We assume that this effect goes along with a slightly weaker effect on halitosis, that is, 0.6. To detect this effect size with 80% power at two-sided significance level 5%, the paired *t*-test requires 24 data pairs.[17] To account for missing values and possibly reduced efficiency of non-parametric methods, 26 patients with PD and 26 matched healthy controls were included.

2.3 | Participants

All patients and healthy controls that were eligible and willing to participate were included in the study, starting from October 2016. Patients with PD were recruited from the outpatient clinic of the Department of Operative Dentistry and Periodontology and from the Parkinson's outpatient clinic of the Department of Neurology, University of Cologne, Germany. Controls (matched by age and sex) were also recruited from the outpatient clinic of the Department of Operative Dentistry and Periodontology, where they received regular prophylactic control appointments. Controls were eligible to participate if they did not have any diagnosed diseases and did not take any daily medications. Inclusion criteria for patients with PD were as follows: a minimum of 18 years of age, diagnosis of PD diagnosed by a neurologist, being able to self-complete the questionnaires, and provision of written informed consent before study participation. Exclusion criteria were as follows: evidence of a persisting or recurrent malignant disease in the head and neck region or radiation/chemotherapy in the medical history, diagnosis of diabetes, Sjögren's syndrome or other direct medical causes of xerostomia or halitosis, all dental problems such as periodontal abscesses, fistulas, unstable prosthetic situations, caries with pain or inflammation within the last 3 months requiring dental treatment, planned extensive dental treatment, deep brain stimulation and pregnancy or planned pregnancy during the study. The intake of prescribed medications of PD participants was documented according to the medical file.

2.4 | Parameters assessed

2.4.1 | Clinical characteristics

The community periodontal index of treatment needs (CPITN), the plaque index (PI) and gingival index (GI) were obtained as described in detail elsewhere[18,19] and served as characterisation of the study population.

2.4.2 | MDS-UPDRS II

The severity of PD was assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scale.[20] Part II of this scale contains self-evaluation of activities of daily life, including speech, swallowing, handwriting, and dressing, hygiene, falling, salivating, turning in bed, walking and cutting food.

2.4.3 | Levodopa equivalent daily dose

To address the problem of the different drug regimens of PD, conversion factors were calculated for antiparkinsonian drugs, to yield a total levodopa equivalent daily dose (LEDD).[21]

2.4.4 | Questionnaires

All questionnaires were completed in a quiet room without help or interference. Participants could take as much time as they needed. The questionnaires were finalised and collected before the clinical examinations. The questionnaires consisted of four sections: (i) clinical characteristics of PD, MDS-UPDRS-II (self-assessment of disease progression);[20] (ii) OHRQoL (German version of the Oral Health Impact Profile, OHIPG-14);[22] (iii) self-assessment of halitosis (German Society of Halitosis); (iv) a 10 cm visual analogue scale (VAS) of xerostomia ("completely normal saliva" to "no saliva at all").[23]

2.4.5 | Halitosis self-assessment

According to the subjective questionnaire of the "German Society Halitosis—DGZMK" (www.ak-halitosis.de), patients were asked a selection of five questions regarding their subjective estimation of their own bad breath: (i) "Do you suffer from bad breath?" (Possible answers were as follows: "never," "sometimes," "often"). (ii) "How do you know that you suffer from bad breath?" (Possible answers were as follows: "just know," "non-verbal body language of others," "somebody told me"). (iii) "Do you suffer from halitosis in the morning?" (iv) "Do you suffer from halitosis in the afternoon or evening?" (Possible answers for questions 3 and 4 were as follows: "never," "rarely," "sometimes," "often"). (v) "How intensive is your bad breath?" (Possible answers were as follows: "weak," "average," "strong"). Additionally, they were asked two yes/no questions: "Do you suffer from halitosis?" and "Do you have olfactory impairments?" We included the question regarding olfactory impairments as hyposmia is correlated with PD[24] and the impaired ability to smell may influence the patient's perception regarding the own bad breath.

2.4.6 | German version of the OHIPG-14

Oral health was measured with the OHIPG-14 questionnaire.[22] The questions of the OHIPG-14 monitor pain, physical, psychological and social limitations and disabilities on a five-level scale ranging from never (score 0), hardly ever (1), occasionally (2), fairly often (3) and always (4). The results are expressed as the sum of the scores for the 14 questions (maximum 56).

2.4.7 | Organoleptic score

A distance organoleptic score[25] was used: Grade 0, halitosis not detected; Grade 1, halitosis only diagnosed when the subject was breathing through an open mouth and the observer approached to a distance of about 10 cm; Grade 2, halitosis only detected at a distance of about 30 cm from the subject's mouth; Grade 3, halitosis already diagnosed on welcoming the subject, with a distance of approximately 1 m between the examiner's nose and the subject's mouth. To standardise the procedure and to avoid adaptation of the examiner's sense of smell to possibly detectable odours, there was an interval of at least 5 minutes between each examination for the examiner.

2.4.8 | Volatile sulphur compounds

A portable gas chromatograph, the OralChroma™, was used which can discriminate the three most important volatile sulphur compounds (VSC), namely hydrogen sulphide (H_2S), methyl mercaptan (MM) and dimethyl sulphide (DMS). It is equipped with an indium oxide semiconductor gas sensor and does not need a carrier gas like standard gas chromatographs, but instead uses room air as carrier for the chromatographic column. To ensure the validity of VSC-measurements, the OralChroma was calibrated by the manufacturers (Abilit Corporation, Japan) before examinations started. Sample collection occurred by use of a disposable syringe (0.5 mL), two-thirds of which was inserted into the oral cavity of the patient (30 seconds). The plunger was pulled out slowly, then pushed in and pulled out again to take the sample, which was injected into the device. After 8 minutes, the processing was complete and the concentration of the VSC was displayed in parts per billion (ppb) by the software packet OralChroma Data Manager. All organoleptic and instrumental measurements were carried out by the same examiner (HCDD). As the cognitive threshold values are reported differently in the literature, we defined them as 112 ppb for H_2S and 26 ppb for MM.[26,27] The value for DMS was defined as 8 ppb according to studies from a Japanese university hospital (not published). These values correspond to the values that are suggested by the manufacturer.

2.4.9 | Stimulated whole saliva

All saliva collections took place between 9 and 11 AM in a quiet room in the Department of Operative Dentistry and Periodontology and were performed by the same examiner (AGB). The participants did not consume any food or drinks 2 hours prior to the examination and did not brush their teeth during this time. The clinical collection of chewing-stimulated whole saliva samples has been outlined in detail elsewhere.[28,29] In brief, stimulated saliva sampling was started by flushing in tap water followed by chewing on paraffin wax (Ivodent Vivodent AG, Liechtenstein) (1 g) for 30 seconds. Subsequently, participants were instructed to spit continuously for 5 minutes in a sterile plastic cup to obtain the rate (mL/min), and during the last few seconds of the 5 minutes, the resting amount of saliva also was collected. The volumes collected (mL) were determined using luer slip syringes (BD Discardit II, Becton, Dickinson and Company, Europe). Saliva produced at a rate <0.7 mL/min was defined as objective hyposalivation.[30] Previous studies have investigated the association between stimulated and unstimulated salivary flow rates in patients with PD.[4,31] Our experience with the PD patient study population has shown that it is seldom possible to assess unstimulated and stimulated flow rates at the same clinical examination. Unstimulated flow rates are hard to assess due to their main symptoms of tremor and the difficulty to remain without chewing for longer time periods. Additionally, it was necessary to keep examination times as short as possible to be able to finish the whole clinical examination; therefore, we decided in advance to only include the stimulated salivation rate in our study protocol.

2.4.10 | Xerostomia

Self-assessed xerostomia could be classified by answering "yes" or "no". Additionally, a VAS score (0-10 cm) was obtained from the participants, where they rated their subjective burden from 0 (completely normal saliva) to 10 (no saliva at all).[32]

2.5 | Statistical analysis

Continuous variables are summarised by mean (standard deviation, SD) or median (interquartile range, IQR), contingent on distributional characteristics. Qualitative variables are described by count and percentage. The correlation of subjective and objective values was calculated according to Spearman's ρ and was reported if ρ > .3 and/or showed statistical significance. Altogether, about 50 correlation coefficients were calculated, thus by chance alone we expect 50*5%, that is 2 to 3, correlations to reach the significance level of 5%. Alternatively, the reader may apply a Bonferroni correction to the *P* -values, that is, comparing each *P* -value with the reduced significance level 0.05/50 = .001. Considering the small sample size, the correlations are essentially descriptive. Distributions of paired data were compared by rank-based methods, that is. Wilcoxon signed-rank test and McNemar-Bowker test, respectively. All calculations were performed with SPSS Statistics 24 (IBM Corp., Armonk, NY, USA). Data were entered twice and reconciled in case of inconsistencies. *P* -values <.05 were considered to indicate statistical significance (comparison-wise type I error control).

3 | RESULTS

3.1 | Clinical characteristics

Twenty-six patients with PD and 26 healthy controls provided written informed consent and participated in and finished the study (Table 1). Of the PD participants, 46% were female, the mean age was 69 (SD: 9) years and the mean disease duration was 9 (SD: 4) years. All participants had regular medical and dental health insurance. In patients with PD, the mean self-reported MDS-UPDRS-II score was 13 (SD: 9), the mean LEDD was 680 (SD: 385) mg/d and participants used a mean of 6 (SD: 2) prescribed medications. 85% of patients with PD used dopamine agonists. Regarding the clinical examination, patients with PD had a mean PI of 1.7 (SD: 0.9), a mean GI of 1.9 (SD: 0.8) and 68% suffered from periodontitis. Among patients with PD, GI was correlated with the number of prescribed medications (ρ = .4, *P* = .047). An impaired organoleptic sense was identified in 58% (15/26) of patients with PD 4% (1/25) of controls (*P* < .001).

3.2 | Subjective halitosis

More PD patients subjectively reported bad breath compared with controls (*P* = .059). Bad breath was "never experienced" in 23% (6/26) of patients with PD vs 46% (12/26) of controls, "sometimes experienced" in 65% (17/26) of patients with PD vs 54% (14/26) of controls and "often experienced" in 11% (3/26) of patients with PD (but not reported as such in any controls) (Table 2). If participants reported halitosis, 55% (11/20) of patients with PD "just know" that they had bad breath vs 80% (12/15) of healthy controls. Participants said they had been told they had bad breath in 40% (8/20) of patients with PD compared with 20% (3/15) of healthy controls. Compared with controls, more patients with PD perceived their bad breath to be stronger *P* = .049).

TABLE 1 Clinical characteristics

	Patients with PD, n (%)	Healthy controls, n (%)	*P* -value
Gender			
Male	14 (54)	14 (54)	
Female	12 (46)	12 (46)	
Dopamine agonists	22 (85)	N.a.	
Periodontitis	17/25 (68)	15/25 (60)	.502
Xerostomia	13/26 (50)	3/26 (12)	.006*,1
	Mean (SD)	Mean (SD)	
Age, y	69 (9)	69 (9)	
Disease duration, y	9 (4)	N.a.	
MDS-UPDRS-II total score	13.0 (9)	N.a.	
LEDD, mg/d	680 (385)	N.a.	
Plaque index	1.7 (0.9)	1.0 (0.8)	.046*,2
Gingivitis index	1.9 (0.8)	0.8 (1.1)	.001*,2
Organoleptic score	0.7 (0.9)	0.7 (0.7)	.726

LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; N.a., not applicable for patients with non-PD; PD, Parkinson's disease; SD, standard deviation.
[1]McNemar's test.
[2]Wilcoxon signed-ranks test.
*P < .05.

3.3 | Objective halitosis

The greater subjective halitosis was not reflected by the mean organoleptic score of 0.7 for all participants (Table 1). Furthermore, VSCs were either comparable (H_2S and MM) or lower (DMS; *P* = .010) in PD patients compared with controls (Table 3).

3.4 | Xerostomia and hyposalivation

Higher mean VAS values for xerostomia were recorded in patients with PD than in controls (4 (SD: 2) vs 1 (SD: 2), respectively; *P* = .010) (Table 4). The objective SWS measurements indicated that saliva volumes were lower in patients with PD than in controls (0.4 mL/min (SD: 0.4) vs 0.7 mL/min (SD: 0.6), respectively; *P* = .010).

3.5 | Impact on oral health-related quality of life

The mean OHIPG-14 total score was 12 (SD: 10) in participating patients with PD vs 5 (SD: 7) in controls (*P* = .005) (Table 4). All but one

TABLE 2 Answers to the subjective halitosis self-assessment of the questionnaire of the "German Society Halitosis—DGZMK" (www.ak-halitosis.de)

	Patients with PD, n (%)	Healthy controls, n (%)	*P* -value
Do you suffer from bad breath?			
Never experienced	6 (23)	12 (46)	.346[1]
Sometimes experienced	17 (65)	14 (54)	
Often experienced	3 (11)	0	
How do you know?			
Just know	11 (55)	12 (80)	.655[1]
Non-verbal body language of others	1 (5)	0	
Somebody told me	8 (40)	3 (20)	
Do you suffer from halitosis in the morning?			
Never	0	4 (21)	.238[1]
Rarely	9 (45)	10 (53)	
Sometimes	7 (35)	4 (21)	
Often	4 (20)	1 (5)	
Do you suffer from halitosis in the afternoon and evening?			
Never	4 (20)	5 (26)	.416[1]
Rarely	8 (40)	10 (53)	
Sometimes	6 (30)	4 (21)	
Often	2 (10)	0	
How intensive is your bad breath?			
Weak	12 (60)	20 (83)	.030*[,1]
Average	6 (30)	4 (17)	
Strong	2 (10)	0	

PD, Parkinson's disease.
[1]McNemar-Bowker test.
*$P < .05$.

TABLE 3 Volatile sulphur compounds among patients with Parkinson's disease and healthy controls

VSCs, ppb	Patients with PD, mean (SD)	Healthy controls, mean (SD)	*P* -values	Cognitive threshold values, ppb
H_2S	80 (179)	51 (72)	.818[a]	112[29,30]
MM	25 (54)	14 (24)	.551[a]	26[29,30]
DMS	10 (19)	28 (34)	.010*[,a]	8

DMS, dimethyl sulphide; ppb, parts per billion; H_2S, hydrogen sulphide; MM, methyl mercaptan; PD, Parkinson's disease; SD, standard deviation; VSCs, volatile sulphur compounds (measured by OralChroma™).
Healthy controls were sex- and age-matched.
[a]Wilcoxon signed-ranks test.
*$P < .05$.

OHIPG-14 subitems were higher in patients with PD compared to controls, eight of them significantly higher ($P < .05$).

3.6 | Correlations with objective halitosis

Certain VSC values correlated with the total number of medications (DMS: $\rho = .5$, $P = .019$), xerostomic VAS values (MM: $\rho = .4$, $P = .218$, DMS: $\rho = .5$, $P = .102$), the intake of dopamine agonists (H_2S: $\rho = .4$, $P = .065$) and the answer to the question "How intensive is your bad breath?" (H_2S: $\rho = .4$, $P = .079$; MM: $\rho = .5$, $P = .014$, DMS: $\rho = .5$, $P = .027$) (Table 5). Patients with PD did not show any correlations between VSCs and organoleptic scores.

Organoleptic scores among PD patients correlated with xerostomic VAS values ($\rho = .6$, $P = .027$), subjective halitosis among PD

TABLE 4 Subjective and objective measurements of salivation and OHIPG-14 total score among patients with Parkinson's disease and healthy controls and associations between these parameters

	Patients with PD, mean (SD)	Healthy controls, mean (SD)	*P* -values
Xerostomia VAS, cm	4 (2) N = 13	1 (2) N = 13	.010*
SWS, mL/min	0.4 (0.4) N = 26	0.7 (0.6) N = 23	.010*
OHIPG-14 total score	12 (10)	5 (7)	.005*
Correlations (Spearman's ρ, *P* -values)			
OHIPG-14 total score-VAS	.416, *P* = .157	.450, *P* = **.036***	
OHIPG-14 total score-SWS	.196, *P* = .337	.514, *P* = **.014***	
VAS-SWS	.315, *P* = .295	.314, *P* = .177	

OHIPG-14, German version of the Oral Health Impact Profile; PD, Parkinson's disease; SD, standard deviation; SWS, stimulated whole saliva; VAS, visual analogue scale (0-10 cm).
Healthy controls were sex- and age-matched.
*$P < .05$ (Wilcoxon signed-ranks test).

patients correlated with LEDD (ρ = .4, *P* = .028), and SWS (ρ = .4, *P* = .073) (Table 3).

3.7 | Correlations with SWS

Among patients with PD, subjective and objective halitosis measurements did not correlate with SWS. PD patients with stimulated flow rates below 0.7 mL/min did not show correlations with VSCs, while those with stimulated flow rates above 0.7 mL/min showed correlation with H_2S (ρ = .5, *P* = .667) and DMS values (ρ = .9, *P* = .333).

3.8 | Correlations with OHIPG-14

Among patients with PD, OHIPG-14 total score correlated with VAS values (ρ = .4, *P* = .157), but not with SWS (ρ = .2, *P* = .337), VSCs (H_2S: ρ = .2, *P* = .266; MM: ρ = .2, *P* = .283; DMS: ρ = .3, *P* = .151) or subjective halitosis (ρ = .3, *P* = .159). Among healthy controls, correlations between OHIPG-14 total score and VAS (ρ = .5, *P* = .036), SWS (ρ = .5, *P* = .014) and subjective halitosis (ρ = .6, *P* = .001) could be shown.

TABLE 5 Correlations between clinical oral findings, clinical characteristics of Parkinson's disease, xerostomia and hyposalivation, and quality of life

	H_2S	MM	DMS	Subjective halitosis	Organoleptic score
Clinical oral findings					
Periodontitis	0.010	0.352	0.170	0.025	0.217
Plaque index	0.042	0.040	0.073	0.176	0.242
Gingival index	0.033	0.114	0.166	0.314	0.296
Characteristics PD					
Age, y	0.303	0.216	0.069	0.113	0.185
MDS-UPDRS-II	0.049	0.100	0.263	0.310	0.030
LEDD	0.035	0.257	0.362	**0.432***	0.102
Years since first diagnosis	0.203	0.102	0.090	0.138	0.142
Total number medications	0.063	0.283	**0.473***	0.165	0.061
Xerostomia and hyposalivation					
VAS (0-10 cm scale)	0.313	0.384	0.494	0.062	**0.610***
SWS, mL/min	0.025	0.160	0.109	0.357	0.102
QoL					
OHIPG-14 total score	0.236	0.228	0.303	0.285	0.266

DMS, dimethyl sulphide; H_2S, hydrogen sulphide; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MM, methyl mercaptan; OHIPG-14, German version of the Oral Health Impact Profile; PD, Parkinson's disease; QoL, quality of life; SWS, stimulated whole saliva; VAS, visual analogue scale.
Findings with statistical significance (*$P < .05$) are the associations between LEDD and halitosis self-assessment, total number of medications and DMS, as well as xerostomic VAS and organoleptic scores. Among healthy controls, only the OHIPG-14 total score was correlated with subjective halitosis (ρ = .628, $P < .05$).
Bold values show Spearman's rho>0.4.

4 | DISCUSSION

Although the prevalence of neurodegenerative disorders worldwide is known to be very high,[1] and will increase even further in the future, there are only limited data available regarding the oral health situation among patients with PD. Our data will help to improve the knowledge of oral health in the PD population.

The patients with PD in our study were more likely to subjectively report halitosis, and these malodours were rated to be stronger than among healthy controls—even though the organoleptic score (the common gold standard in the diagnosis of halitosis) was the same. Regarding dry mouth, patients with PD reported higher xerostomia VAS values and lower SWS than controls, similar to other reports.[4,5] Among our PD population, SWS did not correlate with the organoleptic scale or VSC levels. Only PD patients with stimulated salivation rates above 0.7 mL/min (no hyposalivation) correlated with H_2S and DMS. Therefore, an association between dry mouth and halitosis among this population could not be shown.

In our study, H_2S and MM were comparable in both groups, although they tended to be higher in patients with PD (not significant); MM almost reached the cognitive threshold value of 26 ppm. Higher values of H_2S and MM are the main causes of oral malodour and may indicate bacteria on the tongue, high plaque, gingivitis and periodontitis levels, and increased concentrations of MM might indicate poor oral hygiene.[11] These values are supported by our findings of higher plaque and gingivitis levels that may be the result of manual impairments in oral hygiene manoeuvres. As the lingual topography may also affect the amount of coating, and patients suffering from dry mouth might be at high risk of developing deep-grooved surfaces, it also underlines the risk of suffering from high VSC concentrations. However, it is not yet clear how PD and the medical treatment itself might influence the ecological conditions in the mouth and the oral microbial flora, independent from oral hygiene.

DMS levels among our participants were above the cognitive threshold values suggested in the literature,[26,27] but were significantly lower in patients with PD than in controls. DMS values might be an indicator for systemic diseases, metabolic disorders or medication intake, and often indicate bacteria arising from the digestive system. Therefore, our findings may be explained by Parkinsonian medication intake and the increased number of prescribed daily medications. Accordingly, we found that the DMS values correlated with the total number of prescribed medications. The finding of higher DMS levels among healthy controls was surprising, as our controls were healthy people without medication intake as defined in the inclusion criteria. One reason might be our missing data regarding actual medical problems that could have potentially influenced the DMS levels. Sinus conditions, mouth breathing, rhinitis or tonsil infections are frequently associated with non-oral halitosis in breath clinics.[33,34] Another hypothesis might be that PD or its medical treatment might independently establish ecological conditions that lead to lower bacterial production of DMS.

Patients with PD had higher plaque and gingival indexes, and the GI correlated with a high number of prescribed medications with daily intake, a finding that seems feasible: multimorbidity with higher drug intakes, potentially combined with increasing difficulties in performing oral hygiene manoeuvres, might lead to oral health problems. Additionally, GI and PI are factors that are well known to promote oral bad breath among other populations.[35] However, we could not show clear correlations between PI and objective halitosis measurements. We conclude that oral hygiene impairments might not be the only cause of halitosis among patients with PD.

An early key symptom in neurodegenerative diseases, and especially PD, is the impairment of olfactory senses,[36] as was reported among our study participants. Therefore, one might expect that patients with PD would show little sensitivity regarding their halitosis symptoms. Fifty-eight per cent of our patients with PD reported an impaired olfactory sense; nevertheless, subjective halitosis was reported more often in patient with PD and its intensity correlated with their VSCs. Therefore, we suggest that self-estimation of oral malodour is a reliable diagnostic factor among patients with PD, as has been shown by Pham et al[37] for the general population.

The patients with PD in our study reported more xerostomia and hyposalivation, similar to other reports,[4,5] and SWS did not correlate with the organoleptic scale or VSC levels. No relationship between dry mouth and halitosis could be shown. Only PD patients without hyposalivation showed correlation with H_2S and DMS. This finding is in contrast to those from Koshimune et al[8] who could not show a significant correlation between VSCs and stimulated and unstimulated salivary flow rates; only an extreme reduction in resting saliva influenced the generation of MM and H_2S in mouth air, and VSC levels of subjects with stimulated salivation rates above 0.7 mL/min did not correlate with VSC generation. Most patients in our study were at an earlier stage of disease, where salivation rates were significantly lower than controls, but might not have been low enough (as might be expected in later disease stages) to show a possible impact on objective halitosis measurements.

It has been reported that patients with PD suffer from an impaired OHrQoL.[38] Although the OHIPG-14 total score was higher among our patients with PD, no correlation with halitosis besides a weak correlation with the DMS values could be shown. The impaired QoL might, therefore, represent the effects of PD and its medication itself, rather than the single effect of increased DMS values. In addition, bad breath might count as a non-motor symptom that takes a back seat in the perception of patients, either because it is not strong enough or because other PD-related problems might be of more relevance to the patients.

4.1 | Limitations

As the aetiology of halitosis is multifactorial, there are other confounding factors such as tongue coating, fungal infections, diabetes, special diets or smoking that we have not further investigated but which may have altered the results.[33] Further studies should investigate more of these clinical parameters. Another limitation of our study might be a reduced classification of disease severity via MDS-UPDRS II. According to the study setting in a dental department, we collected self-evaluated MDS-UPDRS-II values that could be easily completed

in the outpatient setting of our study. As the MDS-UPDRS-II is a good approximation of disease severity and has been shown to be a useful parameter in dental studies, we had decided to include it in our study protocol.[38] Previous studies have investigated the association between stimulated and unstimulated salivary flow rates. We only collected stimulated saliva, and results might have been different with unstimulated flow rates.

4.2 | Clinical implications

Patients with PD suffer from stigmatisation, caused not only by their visible cardinal symptoms (tremor, rigidity, bradykinesia and postural instability) but also through symptoms directly affecting the face or oral region such as hypomimia and drooling.[39] Having bad breath might even increase this stigmatisation, particularly in the later stages of disease when patients become dependent on close interaction with caregivers.[40] Being told they had bad breath was more common in patients with PD than in controls, highlighting the importance of relatives and caregivers. These oral symptoms can be treated or prevented, and dentists and their teams need to be aware of their increased prevalence in patients with PD. Unlike in healthy people, who might be offended if they are told they have bad breath,[41] the dental team should realise that informing a patient with PD might rather be seen as helpful advice and very well appreciated. It is important that relatives and caregivers are involved in the management of dental problems, especially in later disease stages. Patients with PD should be seen on a short recall basis, as already suggested by Muller et al[42] because of other oral health problems, to detect possible symptoms earlier. These symptoms should be managed early so that patients can concentrate on the treatment of their main PD-related motor symptoms and to maintain their health and social life for themselves and their caregivers.

More studies with PD patients in later disease stages, and therefore even lower salivation rates, are required. Additionally, the unstimulated salivation rates should be taken into account regarding future research.

5 | CONCLUSIONS

Patients with PD suffer from subjective and objective halitosis, dry mouth and impaired OHRQoL. Dry mouth problems do not correlate with prevalence or intensity of halitosis.

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ANEXO 9 – ORAL HEALTH IN ELDERS WITH PARKINSON´S DISEASE

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Oral Health in Elders with Parkinson's Disease

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This study aimed to evaluate objectively and subjectively the oral health of elders with Parkinson's disease (PD), using clinical oral assessments and the General Oral Health Assessment Index (GOHAI). Subjects included 37 removable prosthesis wearers, 17 with PD (mean age 69.59±5.09 years) and 20 without PD (mean age 72.00±5.69 years). The objective assessment included an evaluation of oral characteristics, including the number of remaining teeth, decayed, missing and filled teeth (DMFT), visible plaque index (VPI), salivary flow rate and removable prosthesis conditions. The subjective assessment included self-perception of oral health collected using the GOHAI index. The number of remaining teeth, DMFT, VPI, salivary flow rate and GOHAI data were compared between the groups using t-tests. Removable prosthesis conditions were analyzed using χ^2 tests ($p<0.05$). There were no group differences in the number of remaining teeth, DMFT, VPI or salivary flow rate ($p>0.05$). Greater maxillary prosthesis defects were observed in the control group ($p=0.037$). GOHAI scores were low for the PD group and moderate for controls, yielding a group difference ($p=0.04$). In conclusion, elders with PD have similar oral health to controls. Although all elders had few remaining teeth, high DMFT and high VPI, PD elders had more negative self-perceptions of their oral health than did the controls.

Key Words: Parkinson's disease, oral hygiene, oral health, removable dental prosthesis.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is characterized by intracellular α-synuclein-positive inclusions called Lewy bodies and by nigrostriatal cell loss, which cause motor and non-motor symptoms (1). Cardinal motor symptoms include resting tremor, bradykinesia, rigidity and postural instability (2), and diagnosis requires the presence of at least two of these symptoms, coupled with asymmetric symptom onset and a good response to levodopa (1). Non-motor symptoms occur in over 90% of patients across all stages and include neuropsychiatric and autonomous dysfunction, such as depression, anxiety, apathy, cognitive and sleep disturbances, sensory symptoms, fatigue and pain (3).

Motor symptoms may interfere with automated small hand movements (4), causing impairment in toothbrushing ability, which is considered a primary risk factor for deteriorated oral health in PD patients (5). In addition to non-motor symptoms, such as dementia or apathy, altered motor behavior and particularly motor fluctuations may influence the quality and frequency of daily oral hygiene care by these patients (5).

Results of studies assessing oral health in patients with PD have been controversial (5,7-9). Surveys with larger number of participants showed that PD patients have more missing teeth, caries, dental biofilm (7) and poorer periodontal health (5,8) compared with individuals without the disease (7). In contrast, Fukayo et al. (6) found that PD patients had significantly more teeth and less caries than a control group of similar age (6). These controversial results underscore the need for further studies of oral health in PD patients.

Oral health means more than good teeth; it is a component of general health essential for well-being (8). Assessment of oral health, based solely on clinical diagnosis by dentists, often leads to an overestimation of the true need for treatment in elders (9) because it does not evaluate self-perceptions about oral health. Self-perception of oral health is a multidimensional measurement that reflects individuals' subjective experience of their functional, social and psychological well-being (10), and often motivates seeking dental treatment (11). Subjective assessments (12,14) were developed to enhance the clinicians' ability to assess self-perception of oral health and oral health-related quality of life in elders.

Previous studies in patients with PD assessed subjective data using a structured questionnaire (13) and Oral Health Impact Profile (OHIP) (9,16). The former (13) demonstrated that compared with the controls, PD patients complained more about their oral health due to chewing difficulties, denture discomfort and problems with oral health behavior. Subjective assessments using OHIP (14,15) also showed that PD patients reported more oral health-related problems than controls (14) and that the oral health impact in PD patients was greater on the "physical disability" and "psychological discomfort" subscales (15). However, studies evaluating self-perception of oral health in PD patients

using the General Oral Health Assessment Index (GOHAI) have not been published yet.

Due to the controversial literature on oral health in PD subjects and their greater oral health complaints, additional studies in this area are required. Therefore, the present study aimed to evaluate the oral health of elders with PD both objectively and subjectively, using oral assessments and the GOHAI, respectively.

Material and Methods

Subjects

This cross-sectional study included 17 elders with PD (mean age 69.41±4.65 years; 8 women and 9 men), members of the Brazilian Parkinson's Association (Piracicaba, SP, Brazil) and 20 elders without PD (mean age 72.00±5.69; 10 women and 10 men), chosen among friends and relatives of the PD volunteers or from elders who sought prosthetic treatment at the dental clinic of the Piracicaba Dental School, Universidade Estadual de Campinas, Brazil. All PD subjects were diagnosed by a neuropsychiatrist using clinical diagnostic criteria (16), were receiving daily levodopa treatment, and had a mean of 6.76±3.80 years since PD diagnosis. Elders with other neurodegenerative disorders or secondary Parkinsonism were excluded from the study. All participants gave written informed consent. The institutional Ethics Committee approved the study (protocol #097/2012). The study was also registered at the Brazilian Registry of Clinical Trials database (#RBR-3czhsf), which is linked to the International Clinical Trials Registration Platform (ICTRP/World Health Organization).

Sociodemographic characteristics including age, educational level and monthly income were collected. Characteristics of the prostheses were verified, including the type of maxillary and mandibular removable dental prosthesis and prosthesis age.

Objective Assessment

To assess oral health, all participants were subjected to clinical examination made using a probe, mouth mirror and flashlight. Each subject's teeth, hygiene and removable dental prosthesis conditions were evaluated as follows:

(1) Number of remaining teeth: the number of teeth present in the mouth was recorded in the partially dentate volunteers.

(2) Decayed, missing and filled teeth (DMFT) index (17): the teeth were categorized as decayed if they were cavitated; missing if they were extracted or extraction was indicated; and filled if they presented amalgam, resin or prosthetic crowns. The sum of the decayed, missing and filled teeth was the DMFT index (17).

(3) Visual Plaque Index (VPI) (18): an adaptation of the VPI was used to assess the oral hygiene. The occurrence of clearly visible plaque on the buccal and lingual surfaces of all remaining teeth was recorded as positive if it was visible beyond doubt by the researcher. The VPI was expressed as a percentage of the positive findings in the total number of examined surfaces.

(4) Salivary flow rate: stimulated salivary flow rate was determined by having participants chew on a piece of parafilm with a 0.02" thickness (Parafilm M®; Bemis Company, Inc., Neenah, WI, USA) for 5 min, expectorating saliva at 30 s intervals into a pre-weighted dish. Salivary flow rate (g/min) was then calculated (19) by subtracting the initial weight from the final weight of the glass; and

(5) Removable prostheses conditions: maxillary and mandibular complete dentures (CD) and/or removable partial dentures (RPD) were evaluated according to Vigild criteria (20). Within the mouth, the maxillary and mandibular prostheses were evaluated for stability, retention, occlusion and vertical height; outside the mouth, they were evaluated for defects, such as wear and/or missing/fractured teeth, broken flanges and loss of pieces of the prosthesis base (20).

Subjective Assessment

Self-perception of oral health was evaluated using the validated GOHAI (10) Portuguese version (11). A single trained examiner administered the GOHAI, asking participants to respond the 12 items in reference to the last three months using a 3-point scoring scale (always, sometimes or never) (11). The final GOHAI score was calculated as previously described by Atchison and Dolan (10) and could range from 12 to 36. Scores of 34 to 36 were classified as high, scores of 31 to 33 as moderate and scores less than 30 as low (21). Higher GOHAI scores indicate more positive perceptions of oral health and lower GOHAI scores are associated with more self-reported oral health problems and poorer oral health conditions (10).

Statistical Analysis

Data were evaluated using SAS 9.3 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA). Exploratory analysis using the Shapiro-Wilk test showed that data were normally distributed. T-tests were used to analyze age, educational level, monthly income and prosthesis age, as well as the number of remaining teeth, DMFT, VPI, salivary flow rate, and subjective data from the GOHAI. Squared chi tests were used to analyze the type and condition of maxillary and mandibular removable dental prostheses. All statistical analyses were carried out at a 5% significance level.

Results

As shown in Table 1, sociodemographic and prosthesis characteristics of PD patients and controls were similar

(p>0.05). Both groups had few remaining teeth, high DMFT, high VPI and normal salivary flow rate (>0.70 g/mL) (p>0.05) (Table 2). Still about DMFT, results showed no differences between groups for the decayed (p=0.876), missing (p=0.422) and filled teeth (p=0.284), with mean number of 0.24±0.75 decayed, 22.18±6.30 missing and 2.41±3.45 filled teeth for PD group; and 0.20±0.62 decayed, 25.40±4.52 missing and 1.25±2.77 filled teeth for controls. GOHAI scores showed a group difference: controls had moderate scores and PD patients had low scores, indicating more self-reported oral health issues in PD subjects (p=0.04) (Table 2). Group differences were also observed in the maxillary prostheses, which had greater defects in the control group (p<0.05), as shown in Table 3. The most common defects observed were worn artificial teeth and missing/fractured teeth.

Table 1. Sociodemographic and removable prostheses characteristics of PD patients and controls

Characteristic	PD (n=17)	Control (n=20)	p
Age (years)	69.41 (±4.65)	72.00 (±5.69)	0.186
Educational level (years)	7.94 (±5.66)	4.48 (±3.50)	0.064
Monthly income (BRL)	2.84 (±1.29)	2.65 (±2.31)	0.839
Edentulous	7 (41.18)	14 (70.00)	0.078
Partially dentate	10 (58.82)	6 (30.00)	0.078
Maxillary prostheses	17 (100.00)	20 (100.00)	
CD	11 (64.70)	18 (90.00)	0.063
RPD	6 (35.30)	2 (10.00)	0.063
Mandibular prostheses	9 (52.94)	17 (85.00)	
CD	6 (66.67)	13 (76.47)	0.072
RPD	3 (33.33)	4 (23.53)	0.855
Prosthesis age (years)			
Maxillary	9.44 (±10.25)	12.71 (±13.84)	0.525
Mandibular	7.94 (±6.52)	11.78 (±11.18)	0.595

Data represent mean (± standard deviation) or frequency (%). BRL: minimum wage in Brazilian reals; PD: Parkinson's disease; CD: complete denture; RPD: removable partial denture.

Table 2. Number of remaining teeth, DMFT, VPI, salivary flow rate, and GOHAI in PD patients and controls

Parameter	PD (n=17)	Control (n=20)	p
Number of teeth	10.00 (±5.23)	8.66 (±3.83)	0.597
DMFT	24.82 (±3.76)	26.85 (±2.18)	0.111
VPI	91.76 (±16.86)	64.10 (±48.91)	0.231
Salivary flow rate (g/min)	0.78 (0.56)	1.00 (0.70)	0.312
GOHAI	27.35 (±4.23)	30.50 (±4.65)	0.040

Data represent mean (±standard deviation). DMFT: Decayed, missing and filled teeth. PD: Parkinson's disease; VPI: Visual Plaque Index; GOHAI: General Oral Health Assessment Index.

Discussion

This cross-sectional study on oral health of elders with PD revealed similar numbers of remaining teeth, DMFT and VPI between the PD and control subjects. Interestingly, PD elders had more negative self-perceptions about their oral health, despite having fewer defects in the maxillary prostheses than the controls.

PD and control subjects had similar age, educational level, monthly income and prosthesis characteristics. Both

Table 3. Removable prosthesis conditions for the upper and lower prosthesis of PD patients and controls

Parameter	PD (n=17)	Control (n=20)	p
Stability of maxillary prostheses			0.054
Satisfactory	15 (88.24)	12 (60.00)	
Unsatisfactory	2 (11.76)	8 (40.00)	
Stability of mandibular prostheses			0.700
Satisfactory	4 (36.36)	5 (29.41)	
Unsatisfactory	7 (63.64)	12 (70.59)	
Retention of maxillary prostheses			0.985
Satisfactory	11 (64.71)	13 (65.00)	
Unsatisfactory	6 (35.29)	7 (35.00)	
Retention of mandibular prostheses			0.463
Satisfactory	4 (36.36)	4 (23.53)	
Unsatisfactory	7 (63.64)	13 (76.47)	
Occlusion			0.911
Satisfactory	2 (33.33)	4 (30.77)	
Unsatisfactory	4 (66.67)	9 (69.23)	
Vertical height			0.252
Acceptable	4 (66.67)	5 (38.46)	
Low	2 (33.33)	8 (61.54)	
Defects of maxillary prostheses			0.037
Absent	10 (58.82)	5 (25.00)	
Present	7 (41.18)	15 (75.00)	
Defects of mandibular prostheses			0.184
Absent	6 (54.55)	5 (29.41)	
Present	5 (45.45)	12 (70.59)	

Data represent frequency (%). PD: Parkinson's disease.

groups had few remaining teeth; no group difference was observed. This result may be influenced by the sample characteristics, which included edentulous and partially edentulous elders in both groups. Previous studies also found similar numbers of teeth between PD subjects and controls (14) and those authors reported that problems such as missing teeth become more marked only in advanced PD stages. In contrast, Nakayama et al. (13) and Hanaoka and Kashihara (22) found few teeth in PD patients than in controls and reported that caries and periodontal disease are frequent complications in this population. Since greater severity of PD predisposes individuals to a poorer state of oral health (5), these contrasting results may be due to inclusion of patients with different degrees of PD severity (13,22), which was not recorded in the present study

As regards DMFT, no difference was observed between groups in the total DMFT, as well as in their components (decayed, missing and filled teeth), demonstrating the same need for caries treatment in PD and control participants. Previous studies also found similar DMFT values for PD and control subjects (23). In contradiction, some authors (6,7) found different total DMFT values in the PD group than in controls. Fukayo et al. (6) verified lower DMFT in PD patients, because they maintained a better routine of oral hygiene than the control ones. Petersen et al. (7) found higher DMFT in PD subjects, probably due to the greater number of missing teeth in their PD subjects, which may explain the difference in results.

In the present study, VPI values were similar between groups and all participants were considered to have high VPI, which represents poor oral hygiene. Fukayo et al. (6) observed more frequent tooth brushing and better oral health in PD outpatients with mild symptoms than in controls. However, they also reported that when some of the caries-associated environments were particularly poor in both PD and control patients, the oral health status between them did not differ (6), which agrees with the present results. On the other hand, Bakke et al. (14) reported that dental plaque, food debris and periodontal health are probably more marked in patients with advanced PD, and Müller et al. (5) reported that younger and hospitalized PD patients had poorer plaque index compared to controls. Those authors (5) did not consider motor fluctuations during evaluations, which may influence their results and support explaining the study's contrasting data.

In addition to the fact that PD subjects were able to perform their own oral hygiene in the current study, the salivary flow rate could also help to explain the similarity of VPI values between groups. Salivary flow rate plays an important role in the buffering capacity of the saliva (23), which is essential to maintain oral health due to its protective functions, including flushing plaque and bacteria from mucosal and dental surfaces in the mouth (5). Although PD participants in the current study were receiving levodopa, which may reduce salivary secretion (6), no difference in salivary flow rate was observed between the PD and control elders. Thus, similar levels of salivary protective functions in PD and control elders could have influenced the VPI observed in both groups in the current study.

Removable prosthesis conditions showed group differences only in defects of the maxillary prostheses, which were greater in the controls. These defects were mainly due to wear of artificial teeth and missing/fractured teeth. Although no previous studies have evaluated prosthesis conditions in PD patients, Bakke et al. (14) reported impaired masticatory performance in PD patients. Thus, the authors of this study hypothesize that the higher frequency of artificial tooth wear and consequently the greater defects of the maxillary prostheses observed in controls of the current study, which was due to their better masticatory ability and greater wear of artificial teeth as consequence.

The GOHAI index showed that PD participants had a more negative self-perception of their oral health than controls, indicating more self-reported oral health issues. This finding supports previous reports (9,15), despite the use of different methodologies for this subjective evaluation. Since the PD and control participants in this study had the same need for dental treatment, as observed in the DMFT results, the PD symptoms may contribute for the GOHAI results. PD tremors and rigidity can affect the orofacial musculature, and they may also induce orofacial pain, cracked teeth dental attrition (24) and could probably create difficulties in controlling and retaining dentures (25). Thus, the motor symptoms of PD may explain the more negative self-perceptions of oral health in these patients.

The GOHAI usually requires a larger sample size than the current study, which could be considered a limitation. However, standardizing by age, educational level and monthly income improved the study's confidence levels. Another potential limitation is that oral health parameters deteriorate as PD progresses (5) and PD patients in the current study were not stratified by disease severity (2). However, the PD volunteers had a mean of 6.76 years since PD diagnosis and all of them were able to attend clinical care sessions and perform their own oral hygiene. This suggests that the PD subjects in the present study were not in the advanced PD stage.

In conclusion, the present study showed that elderly individuals with PD have similar oral health as elderly individuals without the disease. Although all elders showed few remaining teeth, high DMFT and high VPI, those with PD had more negative self-perceptions of their oral health.

Resumo

Este estudo teve como objetivo avaliar objetiva e subjetivamente a saúde bucal em idosos com doença de Parkinson (DP), usando avaliações clínicas bucais e do General Oral Health Assessment Index (GOHAI). Os participantes foram 37 indivíduos usuários de prótese removível, 17 com DP (idade média 69,59±5,09 anos) e 20 sem DP (idade média 72,00±5,69 anos). A avaliação objetiva incluiu avaliação de características bucais,incluindo número de dentes remanescentes; dentes cariados, perdidos e obturados (CPOD); índice de placa visível (IPV), a taxa de fluxo salivar e as condições das próteses removíveis. A avaliação subjetiva incluiu autopercepção da saúde bucal, coletada usando o índice GOHAI. O número de dentes remanescentes, CPOD, IPV, fluxo salivar e os dados GOHAI foram comparadas entre os grupos utilizando o teste *t*. As condições das próteses removíveis foram analisadas utilizando o teste χ^2 ($p<0,05$). Não houve diferenças entre os grupos no número de dentes remanescentes, CPOD, IPV ou fluxo salivar ($p>0,05$). Maiores defeitos na prótese superior foi observada no grupo controle ($p=0,037$). As pontuações do GOHAI foram baixa para o grupo DP e moderada para os controles, com diferença entre os grupos ($p=0,04$). Como conclusão, os idosos com doença de Parkinson tem saúde bucal semelhante aos controles. Embora todos os idosos tenham poucos dentes remanescentes, alto CPOD e alto IPV, os idosos com DP apresentaram autopercepção mais negativa da sua saúde bucal em relação aos controles.

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ANEXO 10 – TOBACCO USE, ORAL HEALTH, AND RISK OF PARKINSON´S DISEASE

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Original Contribution

Tobacco Use, Oral Health, and Risk of Parkinson's Disease

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Few studies have investigated the associations between use of Swedish moist snuff (snus), associated poor oral health, and risk of Parkinson's disease (PD). We followed 20,175 participants who were free of PD in 1973–1974 in Uppsala, Sweden, until the end of 2012. We used Cox proportional hazards regression models to estimate hazard ratios and corresponding 95% confidence intervals for the associations between tobacco use, oral health indicators, and PD risk. We found that tobacco use was associated with a lower risk of PD in males. Compared with males who never used any tobacco daily, pure ever tobacco smokers, pure ever snus users, and combined users had adjusted hazard ratios of 0.68 (95% confidence interval (CI): 0.49, 0.93; $n = 83$), 0.51 (95% CI: 0.27, 0.95; $n = 11$), and 0.21 (95% CI: 0.07, 0.67; $n = 3$), respectively. No association was observed for number of teeth, dental plaque, or detectable oral mucosal lesions and PD risk, although there was a suggestive association with *Candida*-related oral mucosal lesions in males (hazard ratio = 1.56, 95% CI: 0.92, 2.65; $P = 0.098$). Use of snus is associated with a lower risk of PD in males, while poor oral health seems not to be associated with PD occurrence.

cohort studies; oral health; Parkinson's disease; smoking; snus; tobacco

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; PD, Parkinson's disease.

Although the underlying mechanisms remain the subject of debate (1, 2), an inverse association between risk of Parkinson's disease (PD) and tobacco smoking is well documented (2–5). A strong inverse association between tobacco chewing and the risk of PD has also been reported in a nested case-control study (6). Given that nicotine is one of the chemicals most likely to explain the observed inverse association (7), it is plausible to hypothesize that use of Swedish moist snuff (snus), a tobacco product containing constituents of nicotine (8), may also be inversely associated with the risk of PD. To the best of our knowledge, only 2 epidemiologic studies have investigated the association between snus use and risk of PD (9, 10); both showed that snus use is inversely associated with PD incidence and mortality. However, the case-control study (9) was limited by the concerns of recall bias and potential reverse causation. The cohort study (10) identified PD cases from death certificates, which may be problematic due to the low quality or underreporting of PD as the underlying cause of death (11–13).

Systemically elevated levels of inflammatory markers have been observed in PD patients (14–18), and an animal experiment suggested that inflammation may precede neurodegeneration (19). Habitual users of snus almost invariably develop typical lesions in the mucosa corresponding to the location of the quid (20, 21), and poor oral health can cause chronic inflammation (22–24), which is associated with an increased risk of some neurodegenerative diseases (25, 26). Therefore, it is plausible that poor oral health is related to an elevated risk of PD. However, little is known about whether the inflammatory response can lead to PD occurrence. To test the hypotheses, we conducted a population-based cohort study in Uppsala, Sweden, to investigate snus use and associated poor oral health conditions (namely fewer teeth, detectable dental plaque, and presence of oral mucosal lesions) in relation to the risk of PD.

METHODS

Study population

The background of the present study has been described in detail previously (27–29). Briefly, in 1973–1974,

a population-based survey of the prevalence of oral mucosal lesions was conducted among all residents of Uppsala County, central Sweden, aged 15 years or older. Among 30,118 invited residents, 20,333 (68%) participated in an oral health examination after 2 rounds of enrollment. One of the coauthors (T.A.) performed an oral health examination of all participants. We excluded 121 participants for the following reasons: inconsistent personal identification number ($n = 98$), duplicate examinations ($n = 15$), and no readable data ($n = 8$); this left a total of 20,212 participants for the present study.

This study was first approved by the ethics committee of the medical faculty at Uppsala University. Further linkages for the present study were approved by the Regional Ethical Vetting Board in Stockholm, Sweden.

Exposure assessment

Information on sociodemographic factors, tobacco smoking, snus use, and alcohol drinking was obtained through interviews in 1973–1974. Information on tobacco smoking and snus use among participants was comprehensively ascertained, including status (never, ever, former, or current use), age (years) at initiation of use, duration of use (years), and intensity of use (g/day). Only persons who reported daily use of any tobacco (cigarette smoking or snus use) were categorized as ever tobacco users.

Baseline number of existing teeth and level of dental plaque were estimated on the basis of 6 selected teeth (teeth 16, 21, 24, 36, 41, 44) (30). The dental plaque status of each tooth was scored from 0 to 3. A score of 0 represented no detected dental plaque; 1 represented dental plaque covering not more than one-third of the tooth surface; 2 represented dental plaque covering more than one-third of the tooth surface and not more than two-thirds of the tooth surface; and 3 represented dental plaque covering more than two-thirds of the tooth surface. A dental plaque index equal to the total score divided by the number of examined teeth was calculated. The presence of oral mucosal lesions was defined as any abnormal alteration in color or surface aspect or any swelling or loss of integrity of the oral mucosa surface. Based on the previously defined criteria (27, 29), we further grouped oral mucosal lesions into 3 categories that are strongly associated with poor oral hygiene: *Candida*-related oral mucosal lesions, including the presence of pseudomembranous candidiasis, chronic candidosis, angular cheilitis, atrophic and nodular leukoplakia, the median type of atrophy of tongue papillae, or unspecified glossitis; denture-related oral mucosal lesions, comprising the presence of denture stomatitis (localized, generalized, and papillomatous), denture hyperplasia, traumatic ulcer, or flabby ridges; and tongue lesions, comprising the presence of lingua fissurata, plicated tongue, atrophy of tongue papillae, hairy tongue, coated tongue, median rhomboid glossitis, or unspecified glossitis.

Follow-up and case identification

Using each individual's unique national personal identification number (31), we followed all participants through record linkages with the National Patient Register, the Cause-of-Death Register, and the Emigration Register. All of these registers contain essentially complete data on all Swedes. Participants with PD cases were defined as those who had had 1 or more hospital contacts for PD as a primary or secondary diagnosis (11). For PD patients with more than 1 hospital contact, we defined the date of first discharge or outpatient contact for PD as the diagnosis date. After cross-linkages, we further excluded 28 participants who had had a PD diagnosis recorded before the date of enrollment and 9 participants with missing data on snus use or alcohol drinking, leaving a total of 20,175 persons (9,956 males and 10,219 females) for the final analysis.

Person-years of follow-up for each cohort member were counted from the date of enrollment onward and were censored at the date PD diagnosis, death, emigration out of Sweden, moving into a county without Inpatient Register coverage (or with incomplete coverage), or December 31, 2012, whichever occurred first. (See the Web Appendix, available at http://aje.oxfordjournals.org/, for further information.)

Statistical analyses

Age-adjusted incidence rates of PD according to baseline covariates were standardized to the distribution of person-years in the entire cohort (5-year age groups). We used Cox proportional hazards regression models with attained age as the time scale (years; continuous) to estimate hazard ratios and corresponding 95% confidence intervals for PD in association with exposure variables.

To evaluate the overall association with smoking, we initially categorized tobacco smoking status as never, former, or current daily smoking, according to the baseline questionnaire. All multivariate models included area of residence (town, rural area, or small community), marital status (married, single, divorced, or widowed), and alcohol consumption (<once a week or ≥once a week). Analyses were stratified by sex due to the low prevalence of ever daily snus use among women (only 8 women) in 1973–1974. We fitted models in which the hazard ratios associated with tobacco smoking were adjusted for snus use (never daily snus user vs. ever daily snus user) and in which hazard ratios linked to snus use were adjusted for tobacco smoking (never, former, or current daily tobacco smoker). Further, we categorized tobacco habits according to combinations of tobacco smoking and snus use. We also restricted the analysis to never smokers to exclude residual confounding by tobacco smoking. Snus use status was further categorized by duration (categorized as ≤10 years or >10 years) and intensity (categorized as ≤10 g/day or >10 g/day). We tested for linear trends with continuous variables in the models.

Because of the strong association between oral health and age, analyses of baseline oral health conditions were additionally adjusted for age at study entry and tobacco use status (never daily user of any tobacco, pure daily tobacco user, pure daily snus user, or combined user; for females, only smoking status was adjusted) (32). Number of existing teeth at baseline was estimated on the basis of number of available teeth among the 6 teeth selected for examination and was categorized as 0–1, 2–3, 4–5, or 6 of the selected teeth examined. Because evaluation of dental plaque status

is reliable only when people have at least 2 existing teeth out of the 6 teeth selected for examination, we restricted our analyses of dental plaque to those who had at least 2 existing teeth (7,963 males and 7,565 females). Unacceptable dental plaque, acceptable dental plaque, and no dental plaque were defined as an average plaque index of >1, >0–≤1, and 0, respectively. Participants without any diagnosis of *Candida*-related, denture-related, and tongue lesions were included in the reference group when examining oral lesions and PD risk. The combination group included persons with at least 2 of the above-mentioned lesions. To exclude residual confounding by tobacco use, we also performed a subgroup analysis focusing on tobacco abstainers (for females, never daily smokers). Nonproportionality of hazards was investigated using the Grambsch and Therneau test based on Schoenfeld residuals (33), and no violations were observed.

We conducted a number of sensitivity analyses. First, because there is a long preclinical period before PD diagnosis (34, 35), we reanalyzed the data by starting follow-up 8 years after the date of enrollment. Second, we limited the study cohort to participants who were aged 40 years or more at baseline to reduce misclassification of the exposures and covariate measurements. Third, because tobacco use could be affected by tremor, we conducted an analysis by setting the diagnosis date of PD 5 years before the date of discharge or outpatient contact. Fourth, given the potential uncertainty of case ascertainment for persons with only 1 diagnosis of PD recorded in the Patient Register, alternatively we defined PD cases as participants with at least 2 entries in the Patient Register or a primary diagnosis of PD.

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All statistical tests were 2-sided, and P values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics are shown in Table 1. The median age at interview for PD cases was 54.1 years (interquartile range (IQR), 44.5–67.3) in males and 56.7 years (IQR, 45.7–66.9) in females; for non-PD subjects, it was 41.6 years (IQR, 28.8–57.6) in males and 40.8 years (IQR, 28.1–57.4) in females. During an average of 27.9 years (standard deviation, 13.7) of follow-up, we identified 307 incident PD cases. The crude incidence rate of PD was 54.6 per 100,000 person-years.

Tobacco use

For males, we confirmed that current tobacco smoking was inversely associated with PD risk (Table 2). The adjusted hazard ratios for PD in former smokers and current smokers were 0.70 (95% confidence interval (CI): 0.47, 1.04) and 0.62 (95% CI: 0.44, 0.90), respectively, as compared with never daily tobacco smoking. In analyses of snus use, we found that the adjusted hazard ratio for PD among ever daily snus users versus never users was 0.45 (95% CI: 0.26, 0.77), based on 14 observed cases. In addition, we examined the joint contribution of tobacco smoking and snus use to PD risk. Compared with never daily use of any tobacco, pure current tobacco smokers had a lower risk of PD (hazard ratio (HR) = 0.64, 95% CI: 0.44, 0.93). The relative risk was even lower for pure snus users (n = 11; HR = 0.51, 95% CI: 0.27, 0.95) and was lowest among combined users (n = 3; HR = 0.21, 95% CI: 0.07, 0.67). In analyses restricted to never daily tobacco smokers (n = 3,968), there was no obvious dose-response relationship with increasing duration (HR = 0.54 (95% CI: 0.20, 1.49) and HR = 0.50 (95% CI: 0.23, 1.10) for ≤10 years and >10 years, respectively; P_{trend} = 0.11) or intensity (HR = 0.33 (95% CI: 0.12, 0.91) and HR = 0.76 (95% CI: 0.35, 1.66) for ≤10 g/day and >10 g/day, respectively; P_{trend} = 0.16) of snus use.

Ever smoking was not significantly associated with PD risk in females. Compared with females who never smoked daily, the adjusted hazard ratios for PD in former smokers and current smokers were 1.42 (95% CI: 0.81, 2.48) and 0.77 (95% CI: 0.46, 1.30), respectively. Snus use in females was too uncommon (only 8 users, with no PD cases) for us to estimate the association between snus use and PD risk among females.

Oral hygiene

Overall, we observed no associations between fewer teeth or more dental plaque and PD risk (Table 3). For specific types of oral mucosal lesions, we observed a marginally significant excess risk of PD associated with *Candida*-related lesion in males (HR = 1.56, 95% CI: 0.92, 2.65; P = 0.098), compared with persons without any of the 3 types of oral mucosa lesions at baseline. Analysis limited to persons who were never daily users of any tobacco revealed similar results, except that the magnitude of the associations with number of teeth was stronger among males. Compared with those with 6 existing teeth, the hazard ratios for persons with 4–5, 2–3, and 0–1 existing teeth (out of the 6 selected teeth examined) were 1.79 (95% CI: 1.00, 3.20), 1.89 (95% CI: 0.93, 3.84), and 1.35 (95% CI: 0.60, 3.01), respectively (Web Table 1). No significant association was detected between dental plaque or detectable oral mucosal lesions and PD risk in either males or females.

Sensitivity analysis

Results from sensitivity analyses are presented in Web Tables 2–6, including analyses excluding the first 8 years of follow-up, analyses limiting the study cohort to participants aged 40 years or more at baseline, analyses setting the diagnosis date of PD 5 years before the discharge or outpatient contact date, and analyses using definitions of PD cases as those with at least 2 entries in the Patient Register or a primary diagnosis of PD. Different sensitivity analyses showed results comparable to those of the main analyses in both males and females.

DISCUSSION

To our knowledge, this is the first prospective cohort study to have investigated the associations between snus

Table 1. Baseline Characteristics of Participants in a Study of Tobacco Use and Associated Poor Oral Health and the Risk of Parkinson's Disease, Uppsala, Sweden, 1973–2012

	Males						Females					
	PD Cases		Non-PD Subjects		Total		PD Cases		Non-PD Subjects		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at study entry, years[a]	54.7 (14.1)		43.6 (18.0)		43.8 (18.0)		56.5 (13.6)		43.3 (18.2)		43.5 (18.2)	
Duration of follow-up, years[a]	21.3 (11.5)		27.1 (13.9)		27.0 (13.9)		19.4 (11.6)		28.8 (13.4)		28.7 (13.4)	
Age at study exit, years[a]	75.9 (8.2)		70.7 (15.4)		70.8 (15.3)		75.9 (7.8)		72.1 (16.6)		72.2 (16.5)	
Age group at study entry, years												
14–24	1	0.6	1,430	14.6	1,431	14.4	1	0.8	1,555	15.4	1,556	15.2
25–34	15	8.6	2,207	22.6	2,222	22.3	4	3.0	2,311	22.9	2,315	22.6
35–44	24	13.7	1,634	16.7	1,658	16.6	22	16.7	1,658	16.4	1,680	16.4
45–54	47	26.9	1,512	15.5	1,559	15.7	30	22.7	1,537	15.2	1,567	15.3
55–64	37	21.1	1,464	15.0	1,501	15.1	34	25.8	1,367	13.6	1,401	13.7
65–74	36	20.6	986	10.1	1,022	10.3	26	19.7	1,048	10.4	1,074	10.5
≥75	15	8.6	548	5.6	563	5.6	15	11.4	611	6.1	626	6.1
Area of residence												
Town	22	12.6	1,480	15.1	1,502	15.1	13	9.8	1,595	15.8	1,608	15.7
Rural area	71	40.6	3,494	35.7	3,565	35.8	53	40.2	3,338	33.1	3,391	33.2
Small community	82	46.8	4,807	49.2	4,889	49.1	66	50.0	5,154	51.1	5,220	51.1
Marital status												
Single	29	16.6	2,752	28.1	2,781	27.9	13	9.8	2,176	21.6	2,189	21.4
Married	134	76.6	6,469	66.1	6,603	66.3	95	72.0	6,691	66.3	6,786	66.4
Divorced	4	2.3	236	2.4	240	2.4	8	6.1	355	3.5	363	3.6
Widowed	8	4.6	324	3.3	332	3.3	16	12.1	865	8.6	881	8.6
Alcohol consumption, times/week												
<1	37	21.1	1,432	14.6	1,469	14.7	49	37.1	3,029	30.0	3,078	30.1
≥1	138	78.6	8,349	85.4	8,487	85.3	83	62.9	7,058	70.0	7,141	69.9

Abbreviation: PD, Parkinson's disease.
[a] Values are expressed as mean (standard deviation).

use, associated oral health conditions, and the risk of PD incidence. We found that both tobacco smoking and snus use were associated with a lower risk of PD in males; the inverse associations tended to be stronger for the latter. Poor oral health did not appear to be associated with an increased risk of PD, although we observed a suggestive association with *Candida*-related mucosal lesions in males.

The inverse association between snus use and the risk of PD is consistent with the findings of 2 previous studies. Benedetti et al. (9) reported that the odds ratio for PD in association with ever tobacco chewing or snus use was 0.18 (95% CI: 0.04, 0.82). O'Reilly et al. (10) reported that current snus use was associated with a decreased risk of PD mortality (HR = 0.24, 95% CI: 0.08, 0.75) among never-smoking males. The association is biologically plausible. Nicotine and hydroquinone, compounds of cigarette smoke, can stabilize soluble oligomeric forms of α-synuclein (7). In the present study, snus users were even less likely to develop PD than tobacco smokers, which supports the notion that nicotine is one of the chemicals most likely to explain the observed reduced risk of PD. Experimental data showed that snus can cause the same peak nicotine concentrations in blood as tobacco smoke does, and that the high nicotine levels tend to persist and to decline more slowly than those from tobacco smoking (8, 36). This hypothesis, unfortunately, could not be directly tested in the present study. Chen et al. (37) and Kenborg et al. (38) reported that longer duration of tobacco smoking is more likely to be associated with a lower risk of PD. The lack of a positive dose-response trend with duration of snus use could be due to a small number of cases in each group; alternatively, it could be explained by exposure misclassification resulting from a lack of updated information during follow-up or a lack of detailed information on persons who had used snus less often than daily. Because we also lacked information on smoking intensity for participants who smoked but did not smoke daily, we could not examine the association with smoking in detail when studying the dose-response trend with snus use.

It has been argued that the inverse association between smoking and PD risk may be explained by various types of

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	Males						Females					
	PD Cases		Non-PD Subjects		Total		PD Cases		Non-PD Subjects		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at study entry, years[a]	54.7 (14.1)		43.6 (18.0)		43.8 (18.0)		56.5 (13.6)		43.3 (18.2)		43.5 (18.2)	
Duration of follow-up, years[a]	21.3 (11.5)		27.1 (13.9)		27.0 (13.9)		19.4 (11.6)		28.8 (13.4)		28.7 (13.4)	
Age at study exit, years[a]	75.9 (8.2)		70.7 (15.4)		70.8 (15.3)		75.9 (7.8)		72.1 (16.6)		72.2 (16.5)	
Age group at study entry, years												
14–24	1	0.6	1,430	14.6	1,431	14.4	1	0.8	1,555	15.4	1,556	15.2
25–34	15	8.6	2,207	22.6	2,222	22.3	4	3.0	2,311	22.9	2,315	22.6
35–44	24	13.7	1,634	16.7	1,658	16.6	22	16.7	1,658	16.4	1,680	16.4
45–54	47	26.9	1,512	15.5	1,559	15.7	30	22.7	1,537	15.2	1,567	15.3
55–64	37	21.1	1,464	15.0	1,501	15.1	34	25.8	1,367	13.6	1,401	13.7
65–74	36	20.6	986	10.1	1,022	10.3	26	19.7	1,048	10.4	1,074	10.5
≥75	15	8.6	548	5.6	563	5.6	15	11.4	611	6.1	626	6.1
Area of residence												
Town	22	12.6	1,480	15.1	1,502	15.1	13	9.8	1,595	15.8	1,608	15.7
Rural area	71	40.6	3,494	35.7	3,565	35.8	53	40.2	3,338	33.1	3,391	33.2
Small community	82	46.8	4,807	49.2	4,889	49.1	66	50.0	5,154	51.1	5,220	51.1
Marital status												
Single	29	16.6	2,752	28.1	2,781	27.9	13	9.8	2,176	21.6	2,189	21.4
Married	134	76.6	6,469	66.1	6,603	66.3	95	72.0	6,691	66.3	6,786	66.4
Divorced	4	2.3	236	2.4	240	2.4	8	6.1	355	3.5	363	3.6
Widowed	8	4.6	324	3.3	332	3.3	16	12.1	865	8.6	881	8.6
Alcohol consumption, times/week												
<1	37	21.1	1,432	14.6	1,469	14.7	49	37.1	3,029	30.0	3,078	30.1
≥1	138	78.6	8,349	85.4	8,487	85.3	83	62.9	7,058	70.0	7,141	69.9

Abbreviation: PD, Parkinson's disease.
[a] Values are expressed as mean (standard deviation).

use, associated oral health conditions, and the risk of PD incidence. We found that both tobacco smoking and snus use were associated with a lower risk of PD in males; the inverse associations tended to be stronger for the latter. Poor oral health did not appear to be associated with an increased risk of PD, although we observed a suggestive association with *Candida*-related mucosal lesions in males.

The inverse association between snus use and the risk of PD is consistent with the findings of 2 previous studies. Benedetti et al. (9) reported that the odds ratio for PD in association with ever tobacco chewing or snus use was 0.18 (95% CI: 0.04, 0.82). O'Reilly et al. (10) reported that current snus use was associated with a decreased risk of PD mortality (HR = 0.24, 95% CI: 0.08, 0.75) among never-smoking males. The association is biologically plausible. Nicotine and hydroquinone, compounds of cigarette smoke, can stabilize soluble oligomeric forms of α-synuclein (7). In the present study, snus users were even less likely to develop PD than tobacco smokers, which supports the notion that nicotine is one of the chemicals most likely to explain the observed reduced risk of PD. Experimental data showed that snus can cause the same peak nicotine concentrations in blood as tobacco smoke does, and that the high nicotine levels tend to persist and to decline more slowly than those from tobacco smoking (8, 36). This hypothesis, unfortunately, could not be directly tested in the present study. Chen et al. (37) and Kenborg et al. (38) reported that longer duration of tobacco smoking is more likely to be associated with a lower risk of PD. The lack of a positive dose-response trend with duration of snus use could be due to a small number of cases in each group; alternatively, it could be explained by exposure misclassification resulting from a lack of updated information during follow-up or a lack of detailed information on persons who had used snus less often than daily. Because we also lacked information on smoking intensity for participants who smoked but did not smoke daily, we could not examine the association with smoking in detail when studying the dose-response trend with snus use.

It has been argued that the inverse association between smoking and PD risk may be explained by various types of

Table 2. Association Between Tobacco Use Status and Risk of Parkinson's Disease Among Males, Uppsala, Sweden, 1973–2012[a]

Smoking Status	No. of Participants	%	No. of PD Cases	IR[b]	HR	95% CI
Smoking[c]						
Never daily smoker	3,968	39.9	89	85.4	1.00	Referent
Ever daily smoker						
Former smoker	1,763	17.7	37	61.8	0.70	0.47, 1.04
Current smoker	4,225	42.4	49	55.0	0.62	0.44, 0.90
Snus use[c]						
Never daily use	8,401	84.4	161	75.0	1.00	Referent
Ever daily use	1,555	15.6	14	36.9	0.45	0.26, 0.77
Tobacco use status						
Never daily user of any tobacco	3,103	31.2	78	95.5	1.00	Referent
Ever daily user of any tobacco	6,853	68.8	97	56.9	0.61	0.45, 0.83
Pure ever smoker	5,298	53.2	83	62.5	0.68	0.49, 0.93
Former smoker	1,635	16.4	37	64.9	0.73	0.49, 1.09
Current smoker	3,663	36.8	46	59.3	0.64	0.44, 0.93
Pure snus user	865	8.7	11	48.7	0.51	0.27, 0.95
Combined user	690	6.9	3	21.7	0.21	0.07, 0.67

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PD, Parkinson's disease.

[a] HRs and 95% CIs were estimated from Cox proportional hazards regression models with attained age as the time scale and were adjusted for baseline variables, including area of residence, marital status, and alcohol consumption.

[b] Incidence rate per 100,000 person-years, standardized to the age distribution of person-years experienced by all participants using 5-year age categories.

[c] We fitted models in which the HRs associated with smoking were adjusted for snus use (ever vs. never) and in which the HRs associated with snus use were adjusted for smoking (former vs. never, current vs. never).

bias (39–44). First, smoking might only delay age at onset of PD. However, our results showed that the hazard ratios associated with tobacco use were consistent by attained age during follow-up. Second, the prospective study design precluded the possibility of reverse causation in which PD patients might be less prone to smoking or more prone to quit smoking, and it also precluded the possibility that this association was only related to higher mortality among smoking PD patients than among nonsmoking PD patients. Third, twin studies (45) and studies focusing on exposure to passive smoking (46) have also confirmed an inverse association between smoking and the risk of PD, which suggests that the association is unlikely to be confounded by genetic factors.

Our results did not support any associations between indicators of poor oral health—namely fewer teeth, higher levels of dental plaque, and the presence of oral mucosal lesions—and the risk of PD in either males or females. Poor oral health is associated with systematic inflammation (22–24) and an increased risk of several other neurodegenerative diseases (25, 26). Poor oral health thus might also be associated with a higher risk of PD. However, we did not verify that hypothesis in the present study. To evaluate the association with poor oral health more precisely and comprehensively, information on other indicators such as the presence of periodontal diseases and dental caries would also need to be collected. In addition, tobacco use is associated with poor oral health. Therefore, tobacco use may negatively confound the association between poor oral health and PD. Although we found no changes in the hazard ratio estimates before and after adjusting crudely for tobacco use status, we observed a stronger magnitude of association with number of teeth among persons who never used any tobacco daily. This suggests that some associations may have been attenuated by residual confounding by tobacco use history, and the association with oral health, if any, may be complex. Misclassification bias cannot be ruled out, because we only had information on participants' oral health in 1973–1974, which was up to 39 years prior to the PD occurrence. This misclassification of oral health conditions is likely to have been nondifferential and hence may have biased our findings towards the null. Further, we only used oral health as an indirect indicator, rather than direct serological evidence of systematic inflammation and infection.

Strengths of the present study include its prospective population-based design and the use of high-quality Swedish health and demographic registers for outcome ascertainment and censoring of follow-up. Information on oral health conditions was collected by 1 professional dentist; therefore, misclassification of exposure information at baseline has been largely excluded. However, our results should be interpreted in light of several methodological limitations. First, tobacco use habits might change over time, but the

Table 3. Association Between Oral Health Indicators and Risk of Parkinson's Disease in Uppsala, Sweden, 1973–2012[a]

Oral Health Indicator	Males						Females					
	No. of Participants	%	No. of Cases	IR[b]	HR	95% CI	No. of Participants	%	No. of Cases	IR[b]	HR	95% CI
No. of existing teeth (out of 6 selected teeth examined at baseline)												
6	4,936	49.6	50	66.0	1.00	Referent	4,593	44.9	24	31.5	1.00	Referent
4–5	1,883	18.9	42	67.2	1.10	0.71, 1.69	1,874	18.3	32	44.4	1.10	0.63, 1.91
2–3	1,144	11.5	34	77.0	1.29	0.80, 2.08	1,098	10.7	24	49.2	1.05	0.57, 1.96
0–1	1,993	20.0	49	72.8	1.23	0.75, 2.00	2,654	26.0	52	49.6	0.90	0.49, 1.65
Dental plaque status[c]												
No dental plaque	1,080	13.5	15	58.2	1.00	Referent	2,143	28.3	26	45.4	1.00	Referent
Acceptable	4,959	62.3	78	71.4	1.21	0.70, 2.11	4,697	62.1	47	41.3	0.90	0.55, 1.45
Unacceptable	1,924	24.2	33	69.6	1.25	0.67, 2.33	725	9.6	7	34.9	0.74	0.31, 1.73
Oral mucosal lesions[d]												
None	6,928	69.6	110	69.8	1.00	Referent	6,654	65.1	68	40.9	1.00	Referent
Candida-related	538	5.4	17	105.7	1.56	0.92, 2.65	650	6.4	13	58.9	1.18	0.63, 2.22
Denture-related	1,755	17.6	41	65.8	0.96	0.66, 1.41	2,521	24.7	51	48.5	1.04	0.70, 1.55
Tongue	1,578	15.9	31	68.5	0.96	0.64, 1.43	1,490	14.6	24	47.4	1.05	0.65, 1.70
Combination	707	7.1	19	79.7	1.19	0.71, 1.97	901	8.8	18	61.1	1.13	0.64, 1.97

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

[a] HRs and 95% CIs were estimated from Cox proportional hazards regression models with attained age as the time scale and were adjusted for baseline variables, including age at study entry, area of residence, marital status, tobacco use status (for females, only smoking status was adjusted), and alcohol consumption.

[b] Incidence rate per 100,000 person-years, standardized to the age distribution of person-years experienced by all participants using 5-year age categories.

[c] Only among participants who had at least 2 existing teeth out of the 6 selected teeth examined (7,963 males, 7,565 females).

[d] The reference group included persons without any evidence of *Candida*-related, denture-related, or tongue lesions. The combination group included subjects with at least 2 of the above lesions.

information was not updated after baseline. It is possible that the inverse association between snus use and PD risk was due to changed habits from snus use to tobacco smoking. However, several Swedish studies showed that snus use is a habit which tends to be stable over time (47–49). Estimates of the hazard ratios were very similar to those from the analysis using the full cohort when we restricted analysis to persons aged 40 years or more at study entry. Our previous results in a subcohort comprising 252 males with retrievable information on tobacco use habits in 1973–1974 and 1993–1995 showed that none of 60 exclusively snus users in 1973–1974 had changed to tobacco smoking and only 1 man out of 22 who were never users of any tobacco in 1973–1974 had taken up daily snus use. Taken together, it is unlikely that the observed reduced risk among snus users would be explained by changed habits to tobacco smoking. Second, PD is a slowly progressing disease with symptoms arising several years prior to diagnosis (50); therefore, we cannot entirely rule out the possibility that the observed association was from reverse causation due to preclinical PD at baseline. However, the inverse association between snus use and PD risk was consistent in a number of sensitivity analyses, such as analyses excluding the first 8 years of follow-up and analyses using a diagnosis date set to 5 years before the discharge date, which showed the robustness of our findings. Third, misclassification of PD might have occurred because we identified PD cases from the Swedish Patient Register (11). It might be possible that snus-using PD patients are more likely to be recorded in the Patient Register than snus-abstaining PD patients; however, we observed an inverse association between snus use and PD risk. Differential misclassification of PD outcome, again, could have led to underestimation of a true inverse association. In addition, the majority of PD patients are not hospitalized, and outpatient register data were not available before 2001. Therefore, this may have led to both uncertainty regarding true age at PD onset and underdiagnosis of PD cases. It is difficult to predict exactly how misdiagnosis might have affected the results, but most likely, risk estimates would have been attenuated due to nondifferential misclassification. Fourth, we lacked information on other potential confounders such as body mass index, dietary pattern, and physical activity. The estimated associations may have been confounded by socioeconomic status. Although we controlled for residential area and marital status, residual confounding by socioeconomic status may still have occurred. Last, although we had enough statistical power to detect a significant inverse association between snus use

and PD risk, interpretation of these findings should be cautious given the small number of exposed cases observed. A chance finding cannot be ruled out.

In conclusion, tobacco use, including use of Scandinavian moist snuff, was associated with a reduced risk of PD in males, while poor oral health, as indicated by fewer teeth, more dental plaque, and the presence of oral mucosal lesions, was not associated with the risk of PD. Further studies with larger sample sizes, comprehensive oral health examination, and measurement of biomarkers of systemic inflammation are needed to more deeply investigate the question of whether snus use and poor oral health are associated with the risk of PD.

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ANEXO 11 – HYPOSALIVATION AND XEROSTOMIA AMONG PARKINSON´S DISEASE PATIENTS AND ITS IMPACT ON QUALITY OF LIFE

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Hyposalivation and xerostomia among Parkinson's disease patients and its impact on quality of life

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Running title: Dry mouth in Parkinson's disease

Keywords: dry mouth, neurodegenerative disorder, OHIPG-14, OH-related QoL

Abstract

Objective. Parkinson's disease (PD) adversely affects oral health (OH). However, the informative value of xerostomia compared to objective parameters and its impact on quality of life (QoL) is still unclear. This study aimed to explore whether xerostomia correlates with hyposalivation and to define its impact on OH-related QoL.

Materials and methods. Whole stimulated saliva (WSS) was collected from 30 PD patients and 30 matched healthy controls. Objective parameters (Community Periodontal Index of Treatment Needs, plaque/ gingivitis index, mucosa situation and cheilitis angularis), and questionnaires (German Oral Health Impact Profile [OHIPG]-14, visual analogue scale [VAS], xerostomia [yes/no], and the Unified Parkinson's Disease Rating Scale-II) were assessed.

Results. 87% PD patients showed hyposalivation versus 50% of controls (p=0.001). 50% of PD patients reported xerostomia, none of controls (p<0.001). The OHIPG-14 was impaired in PD patients compared to controls (p<0.001), PD patients with xerostomia reported mean VAS values of 4.1 (SD 2.2). WSS did not correlate with VAS values.

Conclusions. Half of PD patients reported xerostomia and underestimated their xerostomic status, with higher probability than healthy controls. WSS did not reflect the grade of xerostomia. PD patients suffered from impaired OH-related QoL. Dental teams should not overlook these oral health risks.

Introduction

Idiopathic Parkinson's disease (PD) is a common and progressive neurodegenerative disease that affects around 250,000–400,000 people in Germany alone, increasing by 12,500 people every year (Dorsey et al., 2007)]. Worldwide, around 1% of adults over the age of 60 years are affected, making it one of the most common movement disorders in the world (Samli A et al., 2004)]. PD is characterised by nigrostriatal cell loss and the presence of the so-called Lewy bodies. Recent evidence suggests that PD is a multi-system brain disease in which non-dopaminergic transmitter systems might be affected at motor onset and become more prominent in later disease stages (Perry et al., 1991). Braak and coworkers introduced a staging procedure from stage 1 to 6 (Braak et al., 2005). This procedure suggests a premotor period, with typical pathological changes spreading from the olfactory bulb and vagus nerve to lower brainstem regions, followed by a symptomatic period when changes involve the midbrain, including the substantia nigra, mesocortex and neocortex. Whether the premotor period is long-lasting is not yet fully solved (Hilker et al., 2005). When PD becomes clinically overt, tremor, rigidity, bradykinesia, and postural instability are considered the cardinal disease symptoms. The disease is chronic and progressive and may be complicated by a wide range of motor and non-motor features contributing to increased disability and diminished quality of life (Schrag et al., 2000). These points are of importance to dentists, as PD has a detrimental impact on oral health (OH) such that difficulties in performing daily oral hygiene manoeuvres (Bakke et al., 2011)], especially in later disease stages, lead to an increased risk of developing caries, periodontitis and tooth loss (Hanaoka & Kashihara, 2009)].

Xerostomia (abnormal subjective dryness of the mouth due to insufficient secretions) – either as a side effect of dopaminergic or anticholinergic medication or due to hyposalivation in line with an autonomic dysfunction in PD patients (Cersosimo et al., 2011)] – might even increase these risks via an imbalance of the microflora. It is important to differentiate between the terms 'hyposalivation' and 'xerostomia' (Turner, 2016). Hyposalivation is defined as the objective finding of decreased salivary production, while xerostomia represents the subjective feeling of dry mouth (Furness et al., 2011). If salivary flow is decreased by 50%, there is evidence that this will result in xerostomia, but it may also occur in patients with normal salivary flow rates (de Almeida Pdel et al., 2008). In the literature, a rate of whole stimulated saliva (as an objective parameter) under 0.5-0.7 ml/min is defined as hyposalivation (Pedersen et al., 2002, Heintze et al., 1983), and PD patients in earlier studies have shown rates below these cut off values (Proulx et al., 2005). Due to the diverse therapy regimens used in PD (i.e. L-dopa, dopamine agonists or dopamine-reuptake-inhibitors), it is not yet fully understood what factor influences the salivation rate the most, and to what extent. Additionally, dysphagia or hypomimia as further symptoms of the disease might also influence the xerostomic burden. Another described symptom of PD patients is anosognosia (Pietracupa et al., 2013), defined as a lack of awareness or denial of deficits and symptoms of dementia. Additionally, the underreporting of non-motor symptoms among PD patients has been reported in a recent series (Chaudhuri et al., 2010). These findings support our own data that PD patients rarely report dry mouth symptoms to their dentists and are therefore poorly informed regarding possible treatment options (Barbe et al., 2016)].

In the literature, there is data regarding objectively explored saliva amounts in PD patients (Proulx et al., 2005)], but only limited data is available regarding if and how PD patients perceive their xerostomia. Additionally, it is not yet clear if PD patients suffer from an impaired OH-related quality of life (QoL) and what impact their dry mouth conditions have on it.

Therefore, we conducted a clinical comparison between a group of well characterised PD patients and a group of healthy controls to explore xerostomia and its informative value regarding the objective salivation rate of PD patients. Based on previous data, we hypothesised that PD patients suffer more often from xerostomia compared to healthy controls, underestimate their dry mouth symptoms, and show an impaired OH-related QoL influenced by their dry mouth conditions when compared to healthy controls.

Materials/Methods

Ethics

The University of Cologne local ethics review board (Study number: 15-026, date of issue: 08.06.2015) granted approval for the study.

Participants

Thirty PD patients and 30 healthy controls were included in the study. PD patients were recruited from the outpatient clinic of the Department of Operative Dentistry and Periodontology and from the Parkinson's outpatient clinic of the Department of Neurology, University of Cologne, Germany. Controls (matched by age [max. +/- 2 years] and sex) were also recruited from the outpatient clinic of the Department of Operative Dentistry and Periodontology, where they received regular prophylactic control appointments. Participants were age and sex matched because of the well described influence of age and gender on salivary secretion rate. All patients and healthy controls

that were eligible and willing to participate were included in the study starting from 09/2015. Controls were eligible to participate if they did not suffer from xerostomia, did not have any diagnosed diseases and did not take any daily medications. PD patients that agreed to participate were checked for inclusion and exclusion criteria and written informed consent was obtained before study participation. Inclusion criteria were: a minimum of 18 years of age, diagnosis of PD diagnosed by a neurologist, being able to self-complete the questionnaires, and provision of written informed consent. Exclusion criteria were: evidence of a persisting or recurrent malignant disease in the head and neck region or radiation/chemotherapy in the medical history, diagnosis of diabetes, Sjögren's syndrome or other direct medical causes of xerostomia, significant medical dental problems with pain or inflammation within the last three months, planned extensive dental treatment, deep brain stimulation, and pregnancy or planned pregnancy during the study. The intake of prescribed medications of PD participants was documented.

Parameters assessed

Clinical characteristics. The community periodontal index of treatment needs (CPITN), the plaque index (PI) and gingival index (GI) were obtained as described in detail elsewhere (Baelum et al., 1995, Loe & Silness, 1963)] among the PD participants and served as characterisation of the study population. Additionally, the oral dryness situation was assessed via four dichotomous "yes/no" questions, "Is there a lake of saliva on the mouth floor?", "Does the mucosal surface appears shiny?", "Are lips strongly reddened or cracked?" and "Is there a cheilitis angularis?".

Questionnaires. All questionnaires were completed in a quiet room without help or interference. Participants could take as much time as they needed. The questionnaires were finalised and collected before the clinical examinations. The questionnaires consisted of four sections: (i) clinical characteristics of PD, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part II (MDS-UPDRS)-II (self-assessment of disease progression), (ii) OH-related QoL (German version of the Oral Health Impact Profile, OHIPG-14) (John et al., 2006)], (iii) self-assessment of xerostomia (yes/no), and (iv) a 10 cm visual analogue scale (VAS) ("completely normal saliva" to "no saliva at all") (Dirix et al., 2008)]. PD participants with subjective dry mouth completed sections (i-iv), PD participants without subjective xerostomia completed sections (i-iii), and healthy controls completed sections (ii-iii). Since none of the healthy controls showed subjective xerostomia, none of them completed section (iv).

Levodopa equivalent daily dose (LEDD). To address the problem of the different drug regimens of PD, conversion factors were calculated for anti-parkinsonian drugs, to yield a total levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010)].

MDS-UPDRS-II. Parkinson's disease severity was assessed using the MDS-UPDRS scale (Rodriguez-Blazquez et al., 2013)]. Part II of this scale contains self-evaluation of activities of daily life, including speech, swallowing, handwriting, and dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food.

Xerostomia. Self-assessed xerostomia could be classified by answering "yes" or "no". Additionally, a VAS score (0-10) was obtained from the participants, where they rated their subjective burden from 0 (completely normal saliva) to 10 (no saliva at all).

German version of the OHIP-14. Oral health was measured with the OHIP-G-14 questionnaire (John et al., 2006)]. The questions of the OHIPG-14 monitor pain, physical, psychological and social limitations and disabilities on a five-level scale ranging from never (score 0), hardly ever (1), occasionally (2), fairly often (3), always (4). The results are expressed as the sum of the scores for the 14 questions (maximum 56).

Stimulated salivation rate. All saliva collections took place between 9 and 11 am in a quiet room in the Department of Operative Dentistry and Periodontology and were performed by the same examiner (AH). The participants did not consume any food or drinks two hours prior to the examination and did not brush their teeth during this time. The clinical collection of chewing-stimulated whole saliva samples has been outlined in detail elsewhere (Kongstad et al., 2013, Bardow et al., 2014)]. In brief, stimulated saliva sampling was started by flushing in tap water followed by chewing on paraffin wax (Ivodent Vivodent AG, Liechtenstein) (1 g) for 30 seconds. Subsequently, participants were instructed to spit continuously for five minutes in a sterile plastic cup to obtain the rate (ml/min), and during the last few seconds of the five minutes the resting amount of saliva also was collected. Ml amounts were determined using luer slip syringes (BD Discardit II, Becton, Dickinson and Company, Europe). Saliva produced at a rate <0.7 ml/min was defined as objective hyposalivation (Sreebny LM et al., 1992)] .

Sample size calculation

In order to detect a standardised effect of 0.6 with 80% at two-sided significance level 5%, the paired *t*-test requires 24 data pairs (Dupont & Plummer, 1990)]. To account for any missing values and possibly reduced efficiency of non-parametric methods, 30 PD patients and 30 matched healthy controls were included.

Statistical analysis

Continuous variables are summarised by mean±standard deviation (SD) or median (interquartile range, IQR), contingent on distributional characteristics. Qualitative variables are described by count and percentage. The correlation of age, years since first diagnosis of PD, total number of medications, LEDD and MDS-UPDRS-II scores with VAS values, OHIP-14 total scores and objective saliva amounts was calculated according to Pearson (linear relation); only coefficients >0.4 are reported. Distributions of paired and unpaired data were compared by rank based methods, i.e. Wilcoxon signed-rank test and Mann-Whitney *U*-test, respectively. Moreover, the association of any two binary variables was evaluated by exact McNemar's test (paired data) and Fisher's exact test (unpaired data). All calculations were done with SPSS Statistics 24 (IBM Corp., Armonk, NY, USA). Data were entered twice and reconciled in case of inconsistencies. *P* values < 0.05 were considered to indicate statistical significance (comparison-wise type I error control).

Results

Clinical characteristics

Thirty PD patients and thirty healthy controls provided written informed consent and participated in and finished the study. Of the PD participants, 43% were female, the mean age was 69 (SD: 8.0) years, and the mean disease duration was 8 (SD: 4.3) years. All participants had regular medical and dental health insurance. The mean self-reported MDS-UPDRS-II score was 12 (SD: 8.8). The mean LEDD was 661.2 (SD: 376.7) mg/d (Table 1). Participants used a mean of 5 (SD: 2.6) prescribed medications (Table 2). All used medications are described in Supplementary material table 1.

Regarding the results of the clinical examination, PD patients had a mean PI of 1.6 (SD: 0.9) and a mean GI of 1.8 (SD: 0.8), 70% (21/30) showed a lake of saliva on the mouth floor, 87% (26/30) showed shiny mucosal surfaces, 37% (11/30) had reddened or cracked lips, and 17% (5/30) showed cheilitis angularis.

Xerostomia

In total, half of PD participants exhibited xerostomia (54% of females and 47% of males), and the mean VAS score was 4.1 (SD: 2.2), with higher VAS values in women. None of the healthy controls reported xerostomia and the difference was significant ($p<0.001$) (Table 2). The values reported on the VAS did not correlate with increasing age ($p=0.138$) or disease duration ($p=0.098$) but showed a statistical trend when correlated with the OHIPG-14 total scores ($p= 0.060$).

Hyposalivation

There was difference in the mean WSS between PD participants (0.4 ml/min) versus controls (0.8 ml/min) ($p<0.001$). Therefore, 87% of PD participants showed hyposalivation compared to 50% of controls ($p=0.001$), with women generally showing less WSS amounts compared to men. When PD patients were divided into PD patients with and without xerostomia, the mean WSS rate was lower among PD patients with xerostomia ($p=0.024$) (Table 2). All PD participants with xerostomia had hyposalivation, as did 73% (11/15) of PD participants without xerostomia. Therefore, PD patients underestimated their dry mouth symptoms relative to their objective saliva measurements. The WSS rates of PD participants correlated with the total number of medications (Pearson's $r=-0.4$, $p=0.015$) and the LEDD (Pearson's $r=-0.4$, $p=0.001$) (Figure 1A and B). None of the healthy controls reported xerostomia, but 50% (13/26) showed hyposalivation (Table 2) (i.e. they also underestimated their dry mouth symptoms). When the two sets of participants were compared regarding "wrong negative self-estimation", 73% (11/15) of PD participants versus 50% (13/26) of healthy controls underestimated their xerostomic symptoms ($p=0.049$*, McNemar's test).

OHIPG-14

The mean OHIPG-14 total score was 11.6 (SD: 9.3) in participating PD patients versus 3.1 (SD: 4.4) in controls ($p<0.001$) without a difference between PD patients with and without xerostomia ($p=0.601$) (Table 2). Also, all OHIPG-14 sub-items were lower in PD patients compared to controls, 11 of them significantly lower ($p<0.05$). Answers to the OHIPG-14 sub-items did not differ depending on the presence of xerostomia among PD participants. The years since first diagnosis (Pearson's $r=0.5$, $p=0.006$) and the total number of medications (Pearson's $r=0.4$, $p=0.049$) correlated with the OHIPG-14 total scores (Figure 1C and D).

Discussion

Our results show that every second of PD patients suffer from xerostomia, which is consistent with earlier reports (Cersosimo et al., 2011)]. We also confirmed that the amount of saliva collected objectively in PD patients was significantly reduced compared to healthy controls, which supports previous evidence of hyposalivation in PD (Cersosimo et al., 2011)].

We were able to show that PD patients underestimate their dry mouth symptoms; almost all of the PD patients in our study showed hyposalivation, but only half of these patients reported xerostomia. There might be several reasons for this finding: it has been described elsewhere that PD patients underreport their non-motor symptoms (Chaudhuri et al., 2010)], and xerostomia might be counted as such. Since PD patients perceive their xerostomia as rather mild, it might take a back seat in the perception of patients relative to symptoms of the disease that have a greater impair on quality of life (Li et al., 2010)]. Furthermore, contrary salivary symptoms of PD patients as xerostomia may offset the paradoxic hypersalivation with saliva drooling that results from dysphagia and which might have a greater impact on PD patients. Critically, underestimation of hyposalivation (i.e. a secretion rate <0.7 ml/min) seems to be greater among PD patients than controls. Whether it is disease dependent or reflects the complicated interaction between medications in PD patients cannot yet be clarified. However, it should be noted that healthy controls also underestimated their xerostomic diagnosis when subjective burden was correlated with the objective cut-off points (0.7 ml/min). Therefore, this problem does not seem to be a specific to PD. Yet since the prevalence of xerostomia seems to be higher among PD patients, underestimation in this special population might have a greater impact, as xerostomia needs to be treated before it impairs oral health. However, Cersosimo et al (Cersosimo et al., 2011)] reported that only 12% of PD patients with xerostomia reported the symptoms to their physicians, while we could show that PD patients with xerostomia rarely receive advice regarding the management of their symptoms (Barbe et al., 2016)]. Therefore, dentists should be highly aware of their need to specifically discuss these symptoms with their PD patients.

PD patients with xerostomia reported a burden of 4.1 on the VAS (0-10), which may be regarded as mild; other populations have reported higher values. The subjective xerostomic burden of head and neck cancer patients was 53 mm on a 100 mm VAS more than 6 months after radiotherapy (Dirix et al., 2008)]. Therefore, xerostomia in PD patients might be less of a burden than in cancer patients. Further research with more patients regarding the differences between the xerostomic impact in different populations is required. Since our population represents PD patients in earlier stages of the disease, our results may not be applicable to all PD patients. The subjective burden might increase in later stages of the disease and the objective salivation rate may decrease.

We confirmed our hypothesis that PD patients suffer from an impaired OH-related QoL compared to healthy controls. Regarding our hypothesis that the subjective burden of xerostomia would negatively influence QoL, we could not show a difference between PD patients with and without xerostomia. This might also underline the findings that the burden of xerostomia in PD patients seems to be mild and might therefore easily be overlooked in daily clinical routine.

From a clinical point of view, these findings raise some concerns regarding diagnostics in the daily clinical routine. If objective measurements do not represent xerostomia and PD patients underestimate their symptoms, it is of high importance to dentists and their teams to explore this symptom via subjective measurements very proactively, i.e. regularly distributed questionnaires such as that proposed by Thomson et al (Thomson, 2007)] and – since first appearance of xerostomia should determine the starting point of a symptomatic therapy – to focus the patient's awareness on these symptoms and therefore be able to start early treatment regimens (Villa et al., 2015)]. All participants in this study were offered treatment possibilities according to the daily clinical routine when treating dry mouth patients in our department – after talking to the patient's

neurologist to see if medication dose reduction or dosing changes could be achieved. Additionally, all patients were offered symptom-relieving product systems, such as gels, sprays, mouth rinses, gums or sugar-free candies, as well as soft tooth brushes or frequent fluoride applications, if necessary. Other treatment possibilities included combination agents of xylitol, beatine, and oils or sialologues such as pilocarpine (Felix et al., 2012). All treatment options have to be adapted very individually depending on the medical cause for the dry mouth problems. The patients received recall appointments, with recall intervals between 3 and 4 months, according to Muller et al (Muller et al., 2011), to establish the best possible oral hygiene. The exact cut-off point regarding the rate of salivation that really determines impaired dental health has not yet been clarified and further research should focus on this question in order to be able to determine the start of therapeutic regimens on the basis of objective parameters. Until now, the objective signs and symptoms as surrogates for dry mouth, such as tooth decay, mucosal pathologies or caries at untypical locations, appear late after a possible diagnosis of xerostomia if patients underestimate their symptoms. These late symptoms might be prevented by an early diagnosis.

Regarding the objective whole saliva measurements, one limitation of this study might be that there are many factors that are known to influence the salivation rate including, for example, gender, age, mucosal fluid absorption, evaporation, circadian rhythms (Dawes, 2004), patient habits regarding oral hygiene or eating, medication dosing, actual stress levels, or the differentiation between areas in the mouth, such as the latter site and anterior dorsum of the tongue, where xerostomic symptoms might be more perceptible than at other sites (Dawes & Odlum, 2004)]. Unfortunately, it is impossible to fade out these factors. We have tried to consider some relevant factors by presenting exemplary descriptive values of gender and correlations of absolute number of medications, age and PD disease duration, but they may simply be counted as helping to characterise the study population in the best possible way. Additionally, we have tried to standardise saliva sampling in our study design by including saliva sampling in the morning and keeping the same basic conditions for the participants to make the results as specific as possible.

Another limitation of our study might be the reduced classification of the disease severity via MDS-UPDRS II. According to the piloting character of our study and the study setting in a dental department, we only collected self-evaluated MDS-UPDRS-II values that could be easily completed in an outpatient setting. Nevertheless, we believe that the MDS-UPDRS-II is a good approximation of disease severity in our study setting and has been shown elsewhere to be a good parameter in dental studies (Barbe et al., 2016)]. We have not investigated the DMFT (decayed missing filled teeth) index or use of a prosthesis among our study participants, although this information might have had valuable impact on the quality of life. With this information, we might have been able to even better determine the consequences of the factors ‘xerostomia’ and ‘hyposalivation’ on the quality of life. Since the focus of our study was strongly directed towards dry mouth issues and its impact on quality of life parameters, and since we had to keep the examination time for the population of PD patients as short as possible, we had decided in advance not to include these parameters in our study protocol. Finally, the presented correlations might not be strong enough when interpreted as a warning sign defined as a hard threshold or limit value. Such cut-off values could not be defined based on our data. But because of the well-known high variability and large variety of influences regarding the stimulation rate, even low correlations paired with our descriptive results, and taking into account the well-known evidence of non-PD patients regarding

hyposalivation and xerostomia and its impact on quality of life, provide enough evidence to show a significant clinical trend and therefore a warning sign for professionals that treat PD patients.

Conclusions

A great proportion of PD patients underestimate their dry mouth status. This is of relevance because half of them suffer from xerostomia. The objective rate of whole stimulated saliva does not reflect the grade of xerostomia, which is perceived to be mild. PD patients suffer from an impaired OH-related QoL. Dental teams should specifically investigate PD patients' xerostomia, hyposalivation and oral health situation to initiate need-related intervention plans and thus reduce the risk of developing caries, periodontitis and tooth loss.

Conflicts of interest: none to declare

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Table 1. Clinical characteristics.

	PD, n (%)	Controls, n (%)
Gender		
Male	17 (56.7)	17 (56.7)
Female	13 (43.3)	13 (43.3)
Periodontitis (CPITN)	18 (62.1)	20 (66.7)
	Mean (SD)	Mean (SD)
Age (years)	69.3 (8.0)	69.3 (7.9)
Disease duration (years)	8.0 (4.3)	N.a.
MDS-UPDRS-II total score	12.0 (8.8)	N.a.
LEDD (mg/d)	661.2 (376.7)	N.a.

LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; SD, standard deviation; CPITN, community periodontal index of treatment needs; N.a., not applicable for non-PD patients.

Table 2. Xerostomia, WSS, Hyposalivation, VAS and mean OHIPG-14 total scores in PD patients (with and without xerostomia) compared to age and sex matched healthy controls and exemplary descriptive values after gender-separation.

	Xerostomia, % (n)	WSS (ml/min), mean (SD)	Hyposalivation [a] % (n)	VAS, mean (SD)	OHIPG-14 total score, mean (SD)
PD (N=30)	50 (15/30)	0.4 (0.4)	86.7 (26/30)	4.1 (2.2)	11.6 (9.3)
female (N=13)	*54 (7/13)*	*0.2 (0.2)*	*100 (13/13)*	*5.1 (2.2)*	*11.9 (11.9)*
male (N=17)	*47 (8/17)*	*0.5 (0.5)*	*76 (13/17)*	*3.2 (1.9)*	*11.4 (8.0)*
Controls (N=30)	0 (0/30)	0.8 (0.5)	50.0 (13/26)	-	3.1 (4.4)
female (N=13)	-	*0.6 (0.6)*	*69.2 (9/13)*	-	*3.5 (4.9)*
male (N=17)	-	*0.9 (0.4)*	*30.8 (4/13)*	-	*2.9 (4.2)*
p value	<0.001*	<0.001*	0.001*		<0.001*
PD xeros+ (N=15/30)		0.2 (0.1)	100 (15/15)		12.7 (10.2)
PD xeros- (N=15/30)		0.5 (0.5)	73.3 (11/15)		10.4 (9.3)
p-value		0.024*	0.100		0.601

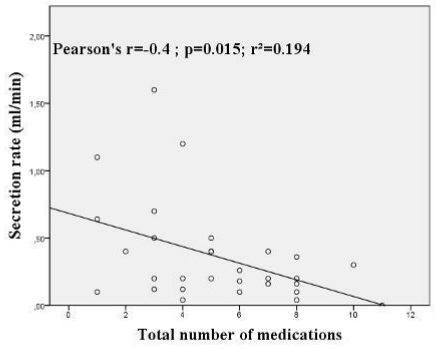
[a] Hyposalivation defined as WSS amount <0.7 ml/min; * p<0.05; WSS, whole stimulated saliva; VAS, visual analogue scale; Xerost+, with xerostomia; Xeros-, without xerostomia.

Figure 1.

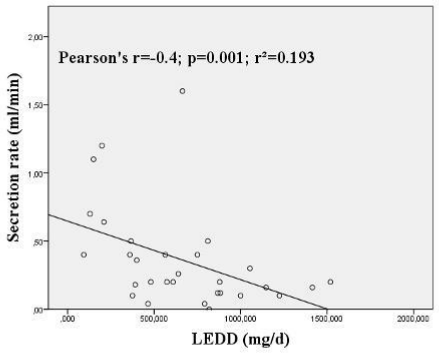
A and B: Correlation of the WSS rate (ml/min) with the total number of medications (Pearson's r=-0.4, p=0.015) and the LEDD (Pearson's r=-0.4, p=0.001) (n=30 PD participants).

C and D: Correlation of the OHIPG-14 total scores with years since first diagnosis (Pearson's r=0.5, p=0.006) and the total number of medications (Pearson's r=0.4, p=0.049).

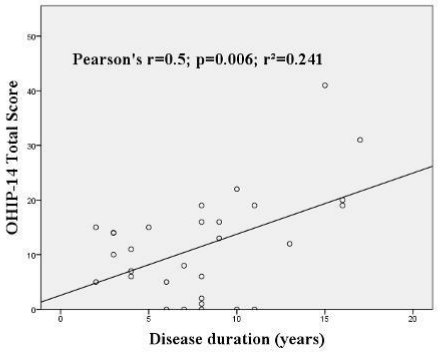
1A.



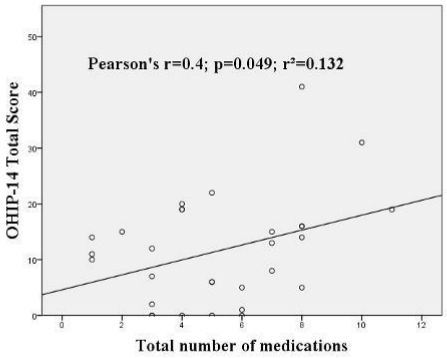
1B.



1C.



1D.



ANEXO 12 – CHARACTERIZATION OF BURNING MOUTH SYNDROME IN PATIENTS WITH PARKINSON´S DISEASE

Characterization of Burning Mouth Syndrome in Patients with Parkinson's Disease

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Aims: To determine the prevalence and characteristics of burning mouth syndrome (BMS) in a Parkinson's disease (PD) population through a self-administered, custom-made survey. **Methods:** A total of 218 surveys were collected during regular outpatient visits at two Movement Disorders Clinics in Montreal (Canada) and Toulouse (France) to gather information about pain experience, PD-related symptoms, and oral and general health. A neurologist confirmed the diagnosis of PD, drug treatment, Hoehn-Yahr stage, and Schwab & England Activity of Daily Living score. Data between groups were compared using the independent samples Mann-Whitney U test and two-sided exact Fisher test. **Results:** Data from 203 surveys were analyzed. BMS was reported by eight subjects (seven females and one male), resulting in a prevalence of 4.0% (95% confidence interval [CI] = 2.1–7.8). Five participants with chronic nonburning oral pain were excluded. PD severity and levodopa equivalent daily dose did not differ between non-BMS and BMS participants. Mean poor oral health index was higher in BMS compared to non-BMS subjects (49.0 vs 32.2 points, $P < .05$). BMS manifested after PD onset in seven patients, did not occur on a daily basis in four, and always coexisted with restless legs syndrome. **Conclusion:** This survey yielded a low prevalence of BMS in PD patients, indicating no strong link between the two conditions. An augmenting effect such as that resulting from drug treatment in restless legs syndrome or sensory neuropathy cannot be excluded.
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Keywords: *burning mouth syndrome, oral pain, Parkinson's disease*

The majority of patients living with Parkinson's disease (PD) experience chronic pain, whether the pain is related to PD or not.[1] Different classification schemes for diagnosing pain have been proposed; for instance, to distinguish dystonic from nondystonic pain.[2,3] Convincing evidence suggests that pain perception is altered in PD, with the demonstration of a lowered pain threshold[4] and activation of central nociceptive pathways[5] as examined by positron emission tomography (PET) in the off-drug condition and normalized following levodopa administration. Body localization has focused on the neck, shoulder, back, and extremities, with little data regarding the orofacial area.

Among the sources of chronic orofacial pain, stomatodynia, or burning mouth syndrome (BMS), is a condition typically described as a chronic painful burning sensation without any clinical alterations in the oral mucosa, present continuously for at least 4 to 6 months. The pain primarily involves the tongue but may extend to soft and hard tissues of the mouth.[6] BMS is classified as secondary when local, nutritional, or systemic factors are identified. In the absence of any identifiable cause, BMS is classified as primary or idiopathic. Depending on the underlying cause, the pain intensity may increase throughout the day (type 1), be continuous (type 2), or be intermittent (type 3). Idiopathic BMS most often affects postmenopausal women (it is up to 7-fold more common in women than in men) with a prevalence varying between 0.7% to 7% or more.[7]

A few reports have suggested a link between BMS, central dopamine deficiency, and PD. The prevalence of BMS in a PD population was examined by administering a mail survey to individuals registered to the

Parkinson's Disease Society of Northern Ireland; the survey yielded a prevalence rate of 24%,[8] a figure possibly up to 34-fold higher than in the general population. A case study reported a PD patient who experienced relief of BMS with pramipexole after showing aggravation of symptoms with carbidopa/levodopa[9]; another case of idiopathic BMS was also improved with pramipexole.[10] Decreased dopamine-mediated central inhibition has been suggested as a potential mechanism in BMS, supported by positron emission tomography (PET) scan results showing reduced fluorodopa uptake capacity and increased dopamine D2 receptor binding levels in the putamen.[11,12] Furthermore, both BMS and PD share autonomic nervous system dysfunction.[13] Several aspects related to the relationship between BMS and PD, its characterization as a nonmotor or premotor feature of PD, and its possible augmentation with antiparkinsonian drug therapy need further investigation. Therefore, the goal of this study was to determine the prevalence and characteristics of BMS in a PD population through a self-administered, custom-made survey. There is no standard or ideal tool to screen for BMS. Different neuropathic pain questionnaires have been used previously, such as the PainDETECT and the Douleur Neuropathique 4 questionnaire and its abbreviated version (DN4, DN4i), with variable sensitivity and specificity values to detect BMS.[14] In order to keep the self-administered questionnaire brief and to collect information about BMS, PD-related symptoms, and oral and general health issues, BMS is characterized in the patient population by using a survey developed by the investigators.

Materials and Methods

Participants

The study was conducted in Movement Disorders Clinics of university hospitals in Montreal and Toulouse and was approved by the local ethics committees. Between December 2013 and June 2014, all patients with idiopathic PD who had a follow-up outpatient clinic appointment were solicited upon arrival at the reception desk to fill out a survey on the premises, without pressure or obligation to do so. No other preselection criteria were applied. Filled surveys were given to the neurologist by the patients at the time of their routine examination in order to confirm the diagnosis of PD based on the conventional definition of the UK Parkinson's Disease Society Brain Bank and to ensure the medication profile was properly listed. The neurologist also indicated the Hoehn-Yahr stage of severity and the Schwab & England Activities of Daily Living Scale score. Surveys from those with an alternative diagnosis such as drug-induced parkinsonism or atypical parkinsonism were rejected.

Survey

The anonymous survey was developed by the investigators and consisted of 42 multiple-choice questions. This survey took 20 minutes to complete. The cover page provided a comprehensive description of the research project. Completion of the questionnaire was considered as consent to take part in the study. Participants could get help from a caregiver or a neurologist for clarifications. A general query inclusive of different abnormal chronic oral sensations was first proposed, excluding known sources of oral (eg, dental) pain: "Do you suffer from unexplained chronic oral pain or burning affecting parts of your mouth (tongue, lips, palate, cheek) without any infection, injury, or apparent relation to a dental problem?" Those answering positively needed to address 16 more questions related to the localization, description, intensity, daily profile, and duration of the oral pain condition, as well as its relation with the onset of PD, antiparkinsonian drug intake, or presence of motor fluctuations. All participants provided basic information on their experience with PD and the presence or absence of fluctuations, dyskinesias, restless legs syndrome (RLS), and chronic craniofacial, back, and limb pain. These features were drafted in layman's terms to enhance the participant's understanding. RLS is typically difficult to describe and was broadly defined as the presence of pins and needles, itching, pulling sensations, or discomfort predominating in the legs while sitting or lying down, typically during the evening/nighttime, with an urge to move. Visceral pain and dysautonomia were not addressed. Specific queries pertaining to the orodental condition included the number of natural teeth, wearing of prostheses, presence of xerostomia and excessive thirst sensation, taste abnormality, and purposeless oral behaviors (eg, bruxism, tongue movements, sucking, chewing habits).

Statistical Analyses

The number of surveys collected at each site was based on a previous study.[8] In order to raise specificity, participants reporting chronic oral pain of a nonburning quality were excluded. Answers to the survey questions were transcribed to an Excel database to compare BMS and non-BMS groups. The investigators also developed a poor oral health index (POHI) and an oral habits score (OHS), considering that oral health is compromised in PD by increased prevalence of caries and periodontal disease causing tooth loss, xerostomia, and taste impairment, among other problems.[15] The calculations of these indices were based on weighing factors in proportion to their perceived importance in relation to pain. The POHI (0–104 points) was calculated using the formula: 64 – (2 × number of natural teeth) – denture subscore (32 points for two dentures, 16 for one denture, 6 for two bridges, 3 for

Table 1 Demographic and Basic Parkinson's Disease Data of Participants With and Without BMS

Data	BMS (n = 8)	Non-BMS (n = 190)
Women (%)	87.5	41.1*
Postmenopausal (%)	85.7	93.5
Mean age (± SD)	69.0 (10.3)	68.2 (9.6)
Median PD duration interval (y)	6–10	6–10
Motor fluctuations (%)	66.7	64.4
Dyskinesias (%)	50.0	52.7
Median Hoehn & Yahr stage	3	2.5
Median Schwab & England scale score	60	80
Autonomy for drug self-administration (%)	87.5	79.5
Levodopa replacement therapy (%)	87.5	87.9
Dopamine agonist therapy (%)[a]	25.0	39.5
Mean LEDD (mg)	630.1	653.9

SD = standard deviation; LEDD = levodopa equivalent daily dose.
[a]Dopamine agonists = pramipexole, ropinirole, rotigotine, piribedil, apomorphine.
*Statistically significant difference between groups ($P < .05$).

Table 2 Comparison Between Participants With and Without BMS

	Entire cohort (n = 198)	BMS (n = 8)	Non-BMS (n = 190)
Oral condition			
Edentulism (%)	11.6	0	12.1
Mean Poor Oral Health Index	32.9	49.0	32.2*
Oral Habits Score	4.8	14.3	4.4*
General health condition			
Chronic extraoral pain (%)	74.2	100	73.2
TMJ	9.5	62.5	6.5*
Masticatory muscles	3.4	37.5	1.4*
Neck	6.8	37.5	5.0*
Low back	53.7	62.5	53.2
Limbs	46.9	75.0	45.3
History of depression (%)	28.4	62.5	27.0*
Current use of antidepressants (%)	23.9	25.0	23.8
Diabetes (%)	5.6	25.0	4.8
Restless legs (%)	52.2	100	50.0*

*Statistically significant difference between groups ($P < .05$).

one bridge) + mouth subscore (18 points for xerostomia, 12 points for excessive thirst sensation, 3 points for abnormal or bitter taste).

The OHS (0–51 points) was generated as follows: 15 points for jaw clenching or grinding, 6 points for rubbing or pushing tongue against teeth, and 3 points for sucking or chewing lip, mucosa, or tongue. The levodopa equivalent daily dose (LEDD) was calculated as previously described[16]: levodopa dose + levodopa dose × 1/3 if on entacapone + levodopa dose × 0.67 if on long-acting preparation + pramipexole (mg) × 67 + ropinirole or rotigotine (mg) × 20 + piribedil (mg) + apomorphine (mg) × 8. Ordinal data from BMS and non-BMS participants were compared using the independent samples Mann-Whitney U test, and nominal data compared with the two-sided exact Fisher test (SPSS 23 software). Missing or "I don't know" answers were excluded.

Results

A log was not kept of all the PD outpatients who declined to complete the survey. Since no preselection criteria other than a diagnosis of PD were used, there is no reason to believe that there was a bias against subjects with BMS. A total of 218 surveys were collected and 15 were discarded due to alternative underlying diagnoses (ie, atypical parkinsonism and drug-induced parkinsonism). The answers from 203 participants (87 females and 116 males), half from each clinic, were analyzed. Only five answers were missing. Overall, 13 individuals (6.4%) reported chronic nondental oral pain, with a proportion three-fold higher in women than in men (10.3% vs 3.4%). Five of the individuals (38.5%) reported oral pain of a nonburning quality and were excluded from further analysis. Thus, eight subjects were included in the BMS group, representing a prevalence of BMS of 4.0% (95% confidence intervals [CI]: 2.1–7.8).

Apart from a marked female predominance (seven females and one male) in the BMS group, demographics and basic PD data and treatment were comparable between the BMS and non-BMS groups (Table 1). Oral and general health conditions differed between groups (Table 2). The mean POHI (49.0 vs 32.2 points, $P < .05$) and mean OHS (14.3 vs 4.4 points, $P < .05$) values were higher in the BMS group compared to the non-BMS group. Purposeless oral habits were reported by 75% of the BMS subjects. Xerostomia (87.5% in BMS, 54.7% in non-BMS; $P = .081$) and dysgeusia (37.5% in BMS, 29.1% in non-BMS; $P = .0695$) were common complaints in both groups. In contrast to the low prevalence of BMS, chronic extraoral pain was experienced by nearly three quarters of the participants and by all BMS subjects. Low back pain and limb pain (small or large joints) were reported by 45% to 75% of participants without significant differences between groups. Of note, BMS coexisted with

RLS (100%) and with pain localized to the temporomandibular joint (TMJ) (62.5%), masticatory muscles (37.5%), and neck (37.5%). The BMS group included a greater proportion of subjects with a past history of depression compared to the non-BMS group (62.5% vs 27.0%, $P < .05$), but current antidepressant drug use was similar between groups.

The chronic burning in the BMS group (n = 8) was at least moderate in intensity and not necessarily present every day (Table 3). It variably affected the tongue, floor of the mouth, jaw, anterior palate, and oral mucosa, and was bilateral in six subjects. It had been present for 1 to 5 years in four subjects. BMS occurred after PD onset in seven subjects and fluctuated with other PD symptoms during the day in three subjects. It was not relieved with antiparkinsonian drug intake during the day, but was relieved with ongoing oral activity in four subjects.

Table 3 Characteristics of Oral Pain in the BMS Group (n = 8)

Pain feature	Descriptors (no.)
Pattern during the day	Not everyday (4), persistent (3), increasing (1), night only (1)
Intensity	Moderate (6), very strong (2)
Localization	Entire tongue (5), anterior palate (3), inferior and superior gingiva (3), jaw (3), floor of mouth (4), teeth (1), interior of cheek (1), tip of tongue (1)
Affected side	Always bilateral (6), left only (2)
Duration	1–5 y (4)
Oral health	Wearing of prosthesis or bridge (7), purposeless oral habits (6), xerostomia (7), dysgeusia (3)
Onset in relation to PD	Pain not present before PD (7), variation of pain with PD symptoms (3)
Response to PD medications	Relief (0), no response (3), unsure (2), increased (2)
Relief with oral activity	While eating (4), drinking (4), talking (1)
Restless legs syndrome	Present (8)
Chronic extraoral pain	Present (8)

Discussion

Little data are available about oral pain in PD. Chronic oral pain may be burning in quality or not, as the present findings illustrate. Nonburning pain may be related to atypical odontalgia, chronic myofascial pain, neuropathic pain, and stomatitis. Thus, participants reporting nonburning pain were excluded in the present study. In contrast to the common occurrence of chronic extraoral pain, BMS was found only in a small fraction (4.0%) of PD patients in this PD population. This represents one-sixth of the prevalence value obtained previously in a smaller PD cohort surveyed by mail in Northern Ireland.[8] This low prevalence and clear female predominance do not indicate BMS as a somatosensory feature of PD. However, the occurrence of BMS after PD onset is in agreement with the Northern Ireland mail survey. The present findings are also consistent with the conclusion of Clifford et al[8] regarding the possibility that BMS may be influenced by medication intake, resulting for instance from an augmentation effect such as that seen in RLS or from levodopa-associated sensory neuropathy with vitamin B12 deficiency, as documented recently.[17] However, the latter hypothesis would hardly explain the gender predominance found in the BMS group in the present study. Nonetheless, the constant coexistence of BMS with RLS is of potential importance and could suggest a link with the dopamine system. The presence of purposeless oral habits in 75% of the BMS subjects in the present study is consistent with the proportion of 61% found in another study on BMS conducted in 84 patients (85% female).[18] The higher mean OHS value in BMS subjects found in the present study would also support a common substrate with RLS, as suggested previously.[10]

The diagnosis of BMS requires a detailed examination to exclude oral (eg, dental, prosthetic, mucosal) pathology, a critical step that was not undertaken in this outpatient survey. In contrast to typical idiopathic BMS, daily and continuous (or nearly continuous) burning was not a universal feature in the BMS group of the present study. BMS in PD was associated with a higher mean POHI value compared to non-BMS patients, calling for a formal examination of the oral cavity and dentures necessary to identify potential sources for secondary BMS. No apparent relation was found between the proportion of edentulism or denture wearing and BMS, as observed previously,[8] but other possible relevant features such as denture design, retention, condition, and microbial colonization were not addressed. Xerostomia and dysgeusia are often described in idiopathic BMS and were common in the present study as well, somewhat more in the BMS participants. Trigeminal small-fiber sensory neuropathy has been suggested as a BMS mechanism in a tongue biopsy study of 12 subjects with BMS,[19] perhaps in relation to herpes virus reactivation.[20] It could also occur in some PD patients, but one would reasonably expect the resulting pain to manifest daily and persistently, unlike in four of the BMS patients in the present study. Since the study participants were not queried specifically about dysautonomia, such features cannot be used as supportive evidence for a neuropathic process.

Some relevant general health issues were raised in the present study's survey. A history of depression was more commonly reported in the BMS group. Interestingly, BMS has been attributed to serotonin-selective reuptake inhibitor intake in a woman without apparent glossitis.[21] Thus, even though the current use of antidepressants in the present study was similar between BMS and non-BMS groups, a possible drug-induced origin beyond antiparkinsonian medication cannot be overlooked. Chronic extraoral pain was common in both groups alike and a constant feature in the BMS participants, in agreement with other studies and with the activation of central nociceptive pathways previously documented in PD.[5] The relatively high prevalence of craniocervical pain (temporomandibular joint, masticatory muscles, and neck) found in the BMS group is intriguing, but its significance remains undetermined. The coexistence of BMS with visceral pain is unclear since this aspect was not addressed in the survey. Further analysis of the relations between BMS and PD is limited by the self-reporting study design, nonvalidated pain survey, small cohort size, and lack of oral examination and laboratory results.

Conclusions

In contrast to previous findings, the custom-made survey administered to nonselected outpatient PD subjects yielded a low prevalence of BMS. BMS was almost exclusively in women and nearly always manifested after PD onset, not always in a daily or continuous fashion, and always coexisted with RLS. Although a diagnosis of idiopathic BMS cannot be excluded in these patients, a possible link with antiparkinsonian drug therapy cannot be rejected, as suggested previously.[8,9] Since BMS subjects showed a higher mean POHI value relative to non-BMS subjects, they should be consistently referred to a dentist to rule out oral or denture problems.

Acknowledgments

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Survey on a subtype of chronic oral pain called burning mouth syndrome in Parkinson's disease

Madam, Sir,

At least one-half of patients literally suffer from Parkinson's disease. Pain may be present at any stage of the illness. This survey is about « burning mouth syndrome », a special type of chronic oral pain which is not of dental origin (on a tooth abscess for example), causing an unexplained burning sensation in the mouth without any obvious lesion (the mouth looks healthy otherwise). Your answers will allow researchers to better understand the significance of this subtype of chronic pain in the context of Parkinson's disease.

ALL patients living with the typical or conventional form of Parkinson's disease are invited to participate, not only those who do experience chronic oral pain. Your answers will reflect your consent to the study. This survey is anonymous, your name will not appear anywhere. Your participation is voluntary, you can refuse to participate without any justification or loss in your privileges and rights. We ask you not to complete the survey if you are uncertain about the diagnosis of Parkinson's disease, or if you have obvious mouth lesions such as thrush or ulcers.

This survey is conducted in partnership with the University Hospitals of Montreal (CHUM) and Toulouse. All answers will be transferred to a computer databank and kept in Montreal for 10 years.

We thank you for your collaboration.

With best regards,

Pierre Blanchet, MD, FRCPC, PhD
Neurologist, CHU Montreal

Olivier Rascol, MD
Neurologist, CHU Toulouse

1. You are:

- ❑ WOMAN
- ❑ MAN

2. How old are you?_____

3. If you are a woman, are you postmenopausal?

- ❑ YES
- ❑ NO

4. Do you suffer from unexplained **chronic oral pain or burning** affecting parts of your mouth (tongue, lips, palate, cheek) without any infection, injury, or apparent relation to a dental problem?

- ❑ YES – Go to the next question
- ❑ NO – Go to question #21

5. Your chronic oral pain not of dental origin (please check all that apply):

- ❑ is absent (or minor) upon awakening and worsens throughout the day to peak in intensity in the evening
- ❑ is already present upon awakening and persists throughout the day
- ❑ is not present everyday
- ❑ is absent overnight
- ❑ is present at night enough to wake me up

6. Which structure is painful in your mouth (please check all that apply)?

- ❑ tip of the tongue only
- ❑ entire tongue or so
- ❑ front part of the palate
- ❑ lower lip
- ❑ upper lip
- ❑ upper gingiva
- ❑ lower gingiva
- ❑ inside of the cheek

- ❑ jaw
- ❑ one tooth or more
- ❑ floor of the mouth (under the tongue)

7. Your chronic oral pain is present (check one only):

   - ❑ always on the same side (right ❑ left ❑)
   - ❑ sometimes on the right, sometimes on the left
   - ❑ always on both sides

8. Which of the following descriptive word best describes your chronic oral pain (check the choice that fits best your pain experience)?

   - ❑ burning
   - ❑ scalding
   - ❑ numb feeling
   - ❑ tingling
   - ❑ discomfort
   - ❑ like a toothache
   - ❑ tearing
   - ❑ crushing
   - ❑ pulling
   - ❑ other

9. How would you generally rate the intensity of your chronic oral pain (check the choice that fits best your pain experience)?

   - ❑ minimal
   - ❑ slight
   - ❑ moderate
   - ❑ severe
   - ❑ very severe

What is the average intensity of your chronic oral pain at different periods of the day? Provide a value between 0 [no pain] and 10 [extreme, unbearable pain] according to the pain experienced at specific times:

	Hour	Pain intensity (scale from 0 to 10)					
10	At 9 o'clock in morning?	O0 O6	O1 O7	O2 O8	O3 O9	O4 O10	O5
11	At 3 o'clock in afternoon?	O0 O6	O1 O7	O2 O8	O3 O9	O4 O10	O5
12	At 9 o'clock in evening?	O0 O6	O1 O7	O2 O8	O3 O9	O4 O10	O5
13	At 3 o'clock at night?	O0 O6	O1 O7	O2 O8	O3 O9	O4 O10	O5

14. How long have you experienced chronic oral pain (check the choice that fits best your pain experience)?

- ❑ less than 3 months
- ❑ between 3 to 6 months
- ❑ between 7 to 12 months
- ❑ between 1 to 5 years
- ❑ between 6 to 10 years
- ❑ over 10 years

Please answer YES or NO to the following questions (check the corresponding circle):

	Question	Yes	No
15	Is your oral pain relieved (or absent) while eating?	O1	O2
16	Is your oral pain relieved (or absent) while drinking cold water?	O1	O2
17	Is your oral pain relieved (or absent) while talking?	O1	O2

18. Have you ever been treated with a specific approach in order to relieve your chronic oral pain?

- ❑ yes, with the following agents (check all that apply)?
  ○Lipoic acid ○Clonazepam (Rivotril, Klonopin) ○Amitryptiline (Elavil, Laroxyl) ○Gabapentin (Neurontin) ○ Pregabalin (Lyrica) ○Capsaïcin ○Anti-inflammatory (aspirin, ibuprofen, naproxen) ○Minor analgesics (acetaminophen, paracetamol) ○Strong analgesics (codein, morphine, hydromorphone, oxycodone, Tramadol) ○Marijuana
- ❑ yes, by replacing my denture(s)
- ❑ no, I do not recall

19. If you have been treated for chronic oral pain not of dental origin, were you relieved of that pain?

- ❑ yes, clearly
- ❑ no, not at all
- ❑ partially

20. Is your chronic oral pain at least partly relieved by the intake of your Parkinson's pills during the day?

- ❑ yes
- ❑ no
- ❑ uncertain
- ❑ on the opposite, oral pain is worsened with those pills

GENERAL HEALTH CONDITION

21. How long ago were you diagnosed with Parkinson's disease?

- ❑ under 6 years
- ❑ 6 to 10 years
- ❑ 11 to 15 years
- ❑ 16 to 20 years
- ❑ over 20 years

22. Which side of your body is most affected by Parkinson's disease?

- ❑ right
- ❑ left
- ❑ uncertain

23. Were you experiencing chronic oral pain even BEFORE the first signs of Parkinson's disease became apparent?

- ❑ yes; if so, how many years before?_____ years
- ❑ no
- ❑ uncertain
- ❑ I have no chronic oral pain

24. Do you experience periods in which your Parkinson's symptoms reappear during the day (for instance when it is time to take your pills)?

- ❑ yes clearly
- ❑ no
- ❑ I do not know

25. Do you experience **dyskinesia** during the day, with abnormal involuntary movements involving your head, arms, legs, or trunk, occurring against your self-control and will? (Please note that such movements are distinct from tremor activity.)

- ❑ yes
- ❑ no
- ❑ uncertain

26. Did you ever notice that the intensity of your chronic oral pain varies or fluctuates with the level of control of your Parkinson's symptoms, whereby your oral pain is more severe when your Parkinson's tremor, stiffness, slowness, and gait difficulty, reappear during the day?

- ❑ yes clearly

- ❑ no
- ❑ I do not know
- ❑ I have no chronic oral pain

27. How many natural teeth do you have in your mouth?_____

28. Concerning your dental condition (check all that apply):

- ❑ I am edentulous (no natural teeth) at the upper jaw
- ❑ I am edentulous (no natural teeth) at the lower jaw
- ❑ I wear one removable partial denture
- ❑ I wear two removable partial dentures
- ❑ I wear one fixed bridge (permanent restauration replacing missing teeth)
- ❑ I regularly wear one full denture
- ❑ I regularly wear two full dentures

29. Do you **often** have the habit of moving or contracting one part of your mouth during the day (check all that apply)?

- ❑ I press my tongue against the front teeth
- ❑ I push my tongue between two teeth
- ❑ I clench my jaw
- ❑ I grind my teeth during the day
- ❑ I suck a tooth or my denture
- ❑ I chew my tongue, my lips, or my cheek
- ❑ no, I have no habits of that kind

Reflecting upon your general health condition (check the corresponding circle):

	Condition	**Yes**	**No**
30	Is your mouth often dry?	O1	O2
31	Do you often have a bitter or metallic taste in your mouth?	O1	O2
32	Are you often thirsty?	O1	O2
33	Do you find difficult tasting the foods and drinks you take?	O1	O2

34	Do you have diabetes?	O1	O2
35	Have you ever suffered from a depression?	O1	O2
36	Do you currently take an antidepressant drug?	O1	O2
37	Are you treated for anemia?	O1	O2

38. Do you experience **restless legs**, with tingling, ants-crawling, or pulling sensations, or an unpleasant discomfort, predominating in your legs while sitting quiet or lying in bed, with an urge to move them in order to find relief, particularly during the evening and nighttime?

- ❑ yes
- ❑ no
- ❑ uncertain

39. Do you <u>regularly</u> (meaning everyday or several days a week) suffer from pain outside the mouth area?

- ❑ yes; if so, check all that apply:
  - ❑ head
  - ❑ jaw joint in front of the ear
  - ❑ jaw muscles
  - ❑ front of the neck
  - ❑ back of the neck
  - ❑ arm
  - ❑ low-back area
  - ❑ legs
  - ❑ large limb joints (shoulder, hip, knee)
  - ❑ small limb joints (wrist, hand, ankle, toes)
  - ❑ genital area
- ❑ no (go to question #41)

40. Is your body pain worsening in intensity when your Parkinson's symptoms reappear during the day?

- ❑ yes
- ❑ no
- ❑ uncertain

41. Do you self-manage your drug administration during the day?

❑ YES ❑ NO

42. Using the table below, please check **ALL** the pills you take to manage your Parkinson's disease.

NAME	DOSE	DAILY INTAKE (number of pills/day)				
Levodopa/carbidopa	100/25	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
		O_{11}	O_{12}	O_{13}	O_{14}	O_{15}
		O_{16}	O_{17}	O_{18}	O_{19}	O_{20}
		O_{21}	O_{22}	O_{23}	O_{24}	O_{25}
Levodopa/benserazide (Prolopa, Madopar)	50/12.5	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
		O_{11}	O_{12}	O_{13}	O_{14}	O_{15}
		O_{16}	O_{17}	O_{18}	O_{19}	O_{20}
Levodopa/benserazide (Prolopa, Madopar)	100/25	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
		O_{11}	O_{12}	O_{13}	O_{14}	O_{15}
		O_{16}	O_{17}	O_{18}	O_{19}	O_{20}
		O_{21}	O_{22}	O_{23}	O_{24}	O_{25}
Levodopa/benserazide (Madopar)	200/50	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
Levocarb-CR (Sinemet-CR)	100/25	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
		O_{11}	O_{12}	O_{13}	O_{14}	O_{15}
		O_{16}	O_{17}	O_{18}	O_{19}	O_{20}
Levocarb-CR (Sinemet-CR)	200/50	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
Stalevo	50/12.5/200	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
Stalevo	75/18.75/200	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
Stalevo	100/25/200	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}
Stalevo	125/31.25/200	O_1	O_2	O_3	O_4	O_5
		O_6	O_7	O_8	O_9	O_{10}

Stalevo	150/37.5/200	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
Entacapone (COMTAN)	200 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
Pramipexole (Mirapex, Mirapexin)	0.25 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
		O11	O12	O13	O14	O15
		O16	O17	O18	O19	O20
Pramipexole	0.5 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
Pramipexole	0.75 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
Pramipexole	1 mg	O1	O2	O3	O4	O5
Pramipexole	1.5 mg	O1	O2	O3	O4	O5
Ropinirole (ReQuip)	0.25 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
		O11	O12	O13	O14	O15
		O16	O17	O18	O19	O20
Ropinirole	1 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
		O11	O12	O13	O14	O15
		O16	O17	O18	O19	O20
Ropinirole	2 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
		O11	O12	O13	O14	O15
Ropinirole	5 mg	O1	O2	O3	O4	O5
Amantadine (Symmetrel)	100 mg	O1	O2	O3	O4	O5
Rasagiline (Azilect)	0.5 mg	O½	O1	O2		
Rasagiline	1 mg	O½	O1	O2		
Selegiline (Eldepryl)	5 mg	O½	O1	O2		
Trihexiphenidyl	2 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
Procyclidine (Kemadrin)	2.5 mg	O1	O2	O3	O4	O5
		O6	O7	O8	O9	O10
Procyclidine	5 mg	O1	O2	O3	O4	O5
Benztropine (Cogentin)	1 mg	O1	O2	O3	O4	O5
Benztropine	2 mg	O1	O2	O3	O4	O5

Thank you very much for participating in this survey.

SECTION TO BE COMPLETED BY YOUR NEUROLOGIST:

MODIFIED HOEHN & YAHR STAGING

- ❑ Stade 0 : No signs of disease.
- ❑ Stade 1 : Unilateral disease.
- ❑ Stade 1,5 : Unilateral plus axial involvement.
- ❑ Stade 2 : Bilateral disease, without impairment of balance.
- ❑ Stade 2,5 : Mild bilateral disease, with recovery on pull test.
- ❑ Stade 3 : Mild to moderate bilateral disease; some postural instability; physically independent.
- ❑ Stade 4 : Severe disability; still able to walk or stand unassisted.
- ❑ Stade 5 : Wheelchair bound or bedridden unless aided.

SCHWAB & ENGLAND ACTIVITIES OF DAILY LIVING SCALE

- ❑ 100% : Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
- ❑ 90% : Completely independent. Able to do all chores with some degree of slowness, difficulty or impairment. Might take twice as long. Beginning to be aware of difficulty.
- ❑ 80% : Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
- ❑ 70% : Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
- ❑ 60% : Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
- ❑ 50% : More dependent. Help with half of chores, slower, etc. Difficulty with everything.
- ❑ 40% : Very dependent. Can assist with all chores, but few alone.
- ❑ 30% : With effort, now and then does a few chores alone or begins alone. Much help needed.
- ❑ 20% : Nothing alone. Can be a slight help with some chores. Severe invalid.
- ❑ 10% : Totally dependent, helpless. Complete invalid.
- ❑ 0% : Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

ANEXO 13 – CLINICAL EVALUATION OF THE PERIODONTAL HEALTH CONDITION AND ORAL HEALTH AWARENESS IN PARKINSON´S IN DISEASE PATIENTS

Gerodontology

Original article

Clinical evaluation of the periodontal health condition and oral health awareness in Parkinson's disease patients

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Clinical evaluation of the periodontal health condition and oral health awareness in Parkinson's disease patients

Objective and background: The objectives were to compare periodontal status between subjects with and without Parkinson's disease (PKD) to determine the influence of PKD on periodontal disease. This study was conducted to evaluate the relationship of periodontal status with severity of PKD.
Materials and methods: This study was conducted on 45 subjects with PKD (subjects with PKD were divided into 5 groups from group 2 to group 6 according to Hoehn and Yahr stages) and 46 control subjects (group 1). Probing depth (PD), clinical attachment level (CAL), gingival index (GI), plaque index (PI) and percentage of bleeding sites (%BoP) were evaluated. All subjects were interviewed regarding their practice of oral hygiene and access to professional dental care.
Results: There were statistically significant differences in PD, CAL, GI, PI and %BoP in subjects with PKD and controls ($p < 0.001$). All the evaluated periodontal clinical parameters and indices deteriorate with increase in severity of PKD. The mean PD value increased from 2.75 mm for group 1 to 6.17 mm for group 6, and mean CAL value increased from 3.14 mm for group 1 to 6.74 mm for group 6. The mean GI, PI and %BoP values increased from 0.55, 1.35 and 20.37 to 2.66, 3.80 and 70.86, respectively with increasing severity of PKD.
Conclusion: There is a need for dental care and encouragement to use plaque control methods for subjects with PKD as periodontal pathology presented a high prevalence even in the early stages of PKD.

Keywords: Parkinson's disease, oral hygiene, oral health, periodontal disease.

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Introduction

Parkinson's disease (PKD) is a chronically progressive, disabling neurodegenerative disorder caused by a loss of dopaminergic neurons in the substantia nigra, as well as other dopaminergic and non-dopaminergic areas of the brain and characterised by tremors, slowness of movement (bradykinesia), muscle rigidity, postural instability and gait disturbance[1–3].

PKD is one of the most common neurological diseases (incidence: 120 per 100,000) and affects men more commonly than women. In about 5% of the patients, the disease is hereditary[4]. The age of onset is usually after 40 years, and the prevalence increases, with age, to 1–5% after 65 years[5].

Patients with PKD suffer from disabilities of walking, eating, chewing, swallowing, using the toilet, movement, communicating, respiration and autonomic nervous system disorders[6,7].

Disturbance in fine hand movements is one of the features of PKD[8,9]. These movements play a major role in oral hygiene maintenance, and inability in performing good oral hygiene is among the early signs of this disorder. Disturbance in oral health may cause caries and periodontal disorders, eventually leading to loss of teeth. Physical and mental deterioration may be produced by this diseased dental condition, leads

to impairment of one's quality of life (QOL) and results in higher mortality[10,11].

There are not many studies on the oral and dental health status of the patients with PKD[12]. Some of the studies among them have reported increased incidence of patients with PKD with deteriorating dental condition[12–14], whereas other studies have reported less chance of patients with PKD developing caries and tooth loss[15,16]. Some of the previous studies have reported increased periodontal pathology in subjects with PKD[14,17,18]. In these studies, subjects with PKD showed increase in mean Community Periodontal Index for Treatment Needs (CPITN)[14], mean pocket depth[17] and frequency of periodontal pockets[18] when compared to controls.

To the best of our knowledge, only a few studies have evaluated the periodontal clinical parameters in subjects with PKD and association of these parameters with severity of PKD. The objectives of this study were to compare periodontal disease status between subjects with and without PKD to determine the influence of PKD on periodontal disease.

Material and Methods

Selection criteria

This cross-sectional study was conducted between February 2012 and May 2012. The study was approved by Institutional Ethical Committee and Review Board, Government Dental College and Research Institute, Bangalore. The subjects for this study were selected from the outpatient section, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. On certain weekday mornings, subjects with an appointment offered a 30-min dental examination and counselling. Periodontal clinical parameters were recorded in 45 consecutive 50- to 79-year-old subjects with PKD who had no diabetes mellitus or other disease affecting oral health, motor or cognitive status. The diagnosis of provable-PKD was based on the United Kingdom Brain Bank criteria[19] and Hoehn and Yahr scale[20]. All subjects with PKD who agreed to participate were in their 'on' state (i.e. the best level of motor functioning). The subjects with PKD were asked to come with their partner or other close family member who would act as a comparison/control. 46 age-matched control subjects were examined in the same way.

All the subjects were divided into six groups. Group 1 included 46 subjects as control. 45 subjects with PKD were divided into five groups from group 2 to group 6 according to Hoehn and Yahr stages[20].

These stages are mild/early disease (Stage 1: only one side of the body is affected, usually with minimal or no functional impairment and Stage 2: both sides of the body are affected, but posture and balance remain normal); moderate disease (Stage 3: both sides of the body are affected, and there is mild imbalance when standing or walking); and advanced disease (Stage 4: both sides of the body are affected, and there is disabling instability while standing or walking, that is, the person requires substantial help and cannot live alone and Stage 5: severe, fully developed disease is present, that is, the person is often cachectic and restricted to bed or a wheelchair unless aided)[20].

All subjects participating in the study received written information beforehand about the aims of the study and the methods used during the examination. All subjects gave their written informed consent to participate in the study.

Inclusion and exclusion criteria

The inclusion criteria for subjects with PKD were confirmed diagnosis of PKD[19,20], age 50–79 year old and a minimum of 10 teeth present.

The exclusion criteria were any medical conditions known to affect periodontal status (e.g. diabetes mellitus, obesity, metabolic syndrome, etc.)[21], antibiotic treatment in the past 3 months prior to entry in the study, history of tobacco use in any form. Study inclusion and exclusion criteria for the control subjects were also similar except for the absence of PKD.

Clinical evaluations and dental interview

All subjects received a comprehensive oral/periodontal evaluation including probing measurements. Two experienced examiners (SPS and SSM) blinded to the objectives of the study performed all of the dental examinations under the supervision of chief investigator ARP. The examiners were calibrated and standardised in the use of the clinical evaluation measures employed in the study. Several calibration exercises were conducted before the start of the study and throughout the study period to control and minimise examiner drift. The examiners were calibrated on all periodontal measures used. Examiners calculated absolute agreement, relative agreement and converted the continuous probing measures into categorical entities to calculate the kappa statistic. For categorical probing measures, intraexaminer

agreement (*k*-statistic ranged from 0.78 to 0.93) was higher than interexaminer agreement (*k*-statistic ranged from 0.63 to 0.81). Standardisation sessions were performed periodically to recalibrate examiners throughout the study period.

The clinical parameters to be recorded included plaque index (PI)[22,23], gingival index (GI)[24], bleeding on probing sites percentage (%BoP), probing depth (PD) and clinical attachment level (CAL).

CAL measured to the nearest mm from the cement–enamel junction to the deepest probeable point[25] using a standardised periodontal probe (UNC 15 periodontal probe, Hu-Friedy, IL, USA), and PD taken from the gingival margin to the bottom of the pocket. BoP was scored positive if a site bled immediately after pocket probing or if a site bled at completion of the probing of a jaw quadrant. All subjects were interviewed regarding their practice of oral hygiene, frequency of brush change and access to professional dental care.

Statistical analysis

Statistical analysis was performed with statistical software (SPSS version 10.5, SPSS, Chicago, IL).

Table 1 Demographic and dental care measures by group.

	Control group (n = 46)	*Parkinson's disease (n = 45)*
Age (years), mean (SD)	63.9 ± 13.1	64.5 ± 9.1
Males (%)	60.9	66.7
Females (%)	39.1	33.3
Tooth brushing >once/day	76.1	75.6
Brush change (months), mean (SD)	6 ± 2.3	6.3 ± 2.6
Flossing ever (%)	19.5	13.3
Mouthwash ever (%)	39.1	35.6
Dental visits > once/year	32.6	28.8

The values of different parameters collected are expressed as mean ± standard deviation (SD). Mann–Whitney *U*-test and single factor ANOVA were performed to explore associations; conventional *p* values <0.05 were regarded as statistically significant.

Results

Table 1 summarises the demographic and dental care characteristics of control group and group of patients with PKD. Subjects in both the groups were of 50–79 years of age. Majority of subjects in both the groups brushed their teeth at least once a day. All subjects reported brushing with toothpaste and changed their brush approximately in 6 months. The use of over the counter mouthwash and dental floss was not common in both the groups. Tendency to use mouthwash was little higher than flossing. Frequency to visit the professional dental clinic was not common in all subjects in both the groups.

Table 2 summarises the clinical dental/periodontal measures for the six groups. Table 3, 4 and 5 shows the intergroup comparisons of all the parameters.

PD and CAL

The mean PD and CAL values of different groups were given in Table 2. There was statistically significant difference found in mean PD and CAL values in all groups. The mean value of PD and CAL was higher in patients with PKD than control subjects. PD and CAL also increased with severity of PKD. The mean PD value increased from 2.75 mm for group 1–6.17 mm for group 6, and mean CAL value increased from 3.14 mm for group 1–6.74 mm for group 6.

Table 2 Mean ± standard deviation (SD) and *p* values of Clinical Parameters.

Parameters	*Group 1*	*Group 2*	*Group 3*	*Group 4*	*Group 5*	*Group 6*	*p Value*
Probing depth	2.75 ± 0.92	3.26 ± 0.73	3.54 ± 0.53	4.41 ± 0.81	5.80 ± 0.76	6.17 ± 1.04	<0.001*
Clinical attachment level	3.14 ± 0.96	3.87 ± 0.69	4.05 ± 0.62	4.78 ± 0.87	6.27 ± 0.81	6.74 ± 1.09	<0.001*
Gingival index	0.55 ± 0.48	1.24 ± 0.47	1.34 ± 0.36	1.92 ± 0.46	2.62 ± 0.29	2.66 ± 0.35	<0.001*
PI	1.35 ± 0.61	2.17 ± 0.46	2.31 ± 0.79	2.77 ± 0.74	3.66 ± 0.46	3.80 ± 0.57	<0.001*
%BoP	20.37 ± 6.40	33.36 ± 6.68	37.50 ± 4.38	48.60 ± 5.78	69.33 ± 11.14	70.86 ± 13.30	<0.001*

*Statistically significant at 5% level of significance ($p < 0.05$).

Table 5 Intergroup comparison of mean difference ± standard error (SE) of %BoP.

	Group 1 %BoP	*Group 2 %BoP*	*Group 3 %BoP*	*Group 4 %BoP*	*Group 5 %BoP*
Group 1	–	12.99 ± 2.22*	17.13 ± 1.81*	28.23 ± 2.06*	48.96 ± 3.83*
Group 2	12.99 ± 2.22*	–	4.14 ± 2.54	15.24 ± 2.72*	35.97 ± 4.22*
Group 3	17.13 ± 1.81*	4.14 ± 2.54	–	11.10 ± 2.39*	31.83 ± 4.02*
Group 4	28.23 ± 2.06*	15.24 ± 2.72*	11.10 ± 2.39*	–	20.73 ± 4.24*
Group 5	48.96 ± 3.83*	35.97 ± 4.22*	31.83 ± 4.02*	20.73 ± 4.24*	–
Group 6	50.49 ± 5.11*	37.49 ± 5.41*	33.36 ± 5.26*	22.26 ± 5.35*	1.52 ± 6.25

*Statistically significant at 5% level of significance ($p < 0.05$).

There was statistically significant difference in intergroup comparison of mean PD and CAL values between all the groups except between group 2 and group 3, and group 5 and group 6 as shown in Table 3.

GI, PI and %BoP

The mean GI value increased from 0.55 for group 1–2.66 for group 6 (Table 2). The mean value of PI was 3.80 for group 6, which was quite high as compared to 1.35 for group 1 (Table 2). There was statistically significant difference exist in mean GI and PI values for all groups. Except between group 2 and 3, and group 5 and 6, there was statistically significant difference found in intergroup comparison of all the groups (Table 4).

As shown in Table 2, %BoP mean value was very high for group 5 and 6 (69.33 and 70.86) as in comparison with group 1, 2 and 3 (20.37, 33.36 and 37.50). The mean value of %BoP was found statistically significant in all groups. The difference in mean %BoP values of group 2 and 3, and group 5 and 6 was not significant (Table 5). All the other groups showed statistically significant difference.

Discussion

Although patients with PKD have several risk factors for dental and periodontal pathology, less is known about their actual periodontal status, practice of oral hygiene measures or dental treatment requirements. However, the increasing prevalence of neurodegenerative disorders in our ageing society will also necessitate to give more attention on the special dental care needs of these patients and to increase the awareness of these patients regarding oral health. Previous epidemiological investigations with PKD patients have remained controversial. Oral health of patients with PKD has also been studied with contradictory results. A case control study in Japan showed that patients with PKD have fewer teeth and also did not clean their dentures as regularly as controls[12]. Accordingly, severe dental problems were reported in all participants of a Greek survey by Anastassiadou *et al.*[26] Similar results were found by Clifford and Finnerty[13] in a study on the dental awareness and needs of a population with PKD by means of postal questionnaires sent to members of PKD societies of Belfast and London.

On the other hand, studies by Persson *et al.*[15] and Fukayo *et al.*[16] found contradictory results from these studies. Persson *et al.*[15] checked the influence of PKD on oral health, and their results revealed that patients with PKD had significantly more teeth and less caries than a control group of corresponding age. In a study on 31 outpatients with PKD and 104 control subjects, similar to Persson *et al.*[15], Fukayo *et al.*[16] also found that patients with PKD had more teeth than controls[16].

Results of our study are contrary to that of Persson *et al.*[15] and Fukayo *et al.*[16] Our results indicate towards deteriorating dental condition in subjects with PKD as compare to controls. Periodontal condition worsens with increase in severity of PKD as all the periodontal clinical parameters and indices evaluated were found significantly increased.

Studies of the periodontal health status of the subjects with PKD are not numerous. Increased periodontal pathology in subjects with PKD has been reported by Schwarz *et al.*[14], Einarsdóttir *et al.*[17] and Hanaoka *et al.*[18].

Schwarz *et al.*[14] reported the CPITN data in 70 subjects with PKD and 85 age-matched control subjects,and results of this study showed that there was a significant difference of mean CPITN indices of subjects with PKD and controls. In a study on Iceland population, Einarsdóttir *et al.*[17] reported more missing teeth, caries, dental plaque and poorer periodontal health in subjects with PKD than controls. Patients with PKD had fewer remaining teeth, more caries and a higher inci-

dence of deep periodontal pockets as showed by Hanaoka *et al.*[18]

The results of our studies showed an increase in mean PD and CAL values in subjects with PKD than control subjects. These values increased significantly with increase in severity of PKD. In subjects with severe PKD, mean PD and CAL values were very high, 6.17 ± 1.04 and 6.74 ± 1.09, respectively. GI and PI values were also significantly increased as early as stage 1 of Hoehn and Yahr scale. %BoP was increased from 20.4% in control group to 70.9% in Hoehn and Yahr stage 5.

Our results showed that periodontal health of subjects with PKD starts deteriorating in very early stages. Even in the Hoehn and Yahr stage 1, all the evaluated parameters showed significant difference with subjects without PKD.

The periodontal condition appears to worsen with the progression of Hoehn and Yahr stages, which indicates that the periodontal pathology in subjects with PKD increases as motor impairment progresses. Brushing is reported to be crucial for preventing the progression of periodontal disease[27]. Although in our study, majority of subjects brushed their teeth at least once a day, the periodontal pathology was significantly less in control subjects. This may be because of decreased ability of subjects with PKD to clean their teeth effectively due to disturbance in fine hand movements[8,9]. Routine regular cleaning of teeth in patients with PKD may be affected by motor and cognitive dysfunction including tremor, akinesia, muscle rigidity, and dementia. In our study, periodontal pathology was found to develop from an early Hoehn and Yahr stage. Therefore, motor and cognitive impairment may not account for all the factors that lead to poor oral hygiene in subjects with PKD. Additional factors need to be clarified in future studies.

Dysphagia, difficulty in chewing, oral dyskinesia, hypersialorrhea, and xerostomia caused by autonomic dysfunction and/or anti-Parkinsonian medications also may affect oral hygiene by disturbing the mouth's self-cleaning mechanism[28]. Due to dysphagia and poor oral hygiene, patients with PKD have a high risk of aspiration pneumonia which may sometime leads to death[29–31]. Poor oral and periodontal health may be a risk factor for progression of diabetes mellitus, cardiovascular diseases, ischaemic stroke, atherosclerosis and pulmonary diseases[32–35]. Apathy and depression, as well as dementia, may affect patient's ability to notice dental problems, and gait disturbance, due to akinesia and postural instability, for example, may prevent visits to the dentist to obtain and/or maintain good oral health.

Therefore, there was a need to reinforce oral hygiene in subjects with PKD. Regular follow-up by a dentist to ensure that patients are able to maintain reasonable oral hygiene would appear to be a sensible adjunct to treatment. PKD also should be included in the list of risk factors that disturb the oral hygiene and related with increased periodontal pathology.

Conclusion

Our study has shown a need for dental care for subjects with PKD as periodontal pathology presented a high prevalence even in the early stage of PKD, with no functional deficits. The disturbance in fine hand movements, tremor and decreased movement make it difficult for the patient to perform daily oral hygiene care properly even though patients brush their teeth regularly and attempt to improve their oral hygiene. Motor and cognitive impairments may be facilitating factors that lead to poor periodontal health in subjects with PKD. Future longitudinal studies with larger sample size are required to evaluate patients with PKD to better assess the effect of PKD on periodontal health and to clarify the role of additional factors such as saliva condition, mental status and medications, so that the cause of poor periodontal health in subjects with PKD could be better identified. Also, there is need of studies that will aim to provide special preventive measures to preserve and improve the periodontal status in subjects with PKD. Our study has clearly demonstrated the need of careful attention towards oral health of subjects with PKD from early stages. Furthermore, both subjects with PKD and their caregivers require dental hygiene education in early PKD to achieve better oral hygiene and good periodontal condition to maintain a good QOL.

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ANEXO 14 – PERIODONTAL HEALTH AND CARIES PREVALENCE EVALUATION IN PATIENTS AFFECTED BY PARKINSON´S DISEASE

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Clinical Study

Periodontal Health and Caries Prevalence Evaluation in Patients Affected by Parkinson's Disease

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Parkinson's disease (PD) is a progressive neurodegenerative disorder related to the loss or absence of dopaminergic neurons in the brain. These deficits result in slowness of movement, tremor, rigidity, and dysfunction of behaviour. These symptoms negatively influence the patient's capability to carry out the daily oral hygiene manoeuvres. The aim of this work is to record the oral health condition of PD patients evaluated at the IRCSS Bonino-Puleio in Messina. The oral health of 45 consecutive PD patients (study group) with neurologic diagnosis based on United Kingdom Brain Bank Criteria has been compared with that of another 45 no PD patients of the same age (control group). The evaluation of the general oral condition was recorded underlining tooth loss, active periodontal disease, and presence of untreated caries. The frequency of untreated caries, periodontal diseases, and missing teeth of the study group was significantly higher than in control group. Based on the data results, clinicians should direct high attention to the oral hygiene of patients with PD, above all at the early stages of the caries or periodontal disease, in order to prevent serious evolution of those pathologic dental conditions that may finally result in the tooth extraction event.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder typically characterized by motor symptoms such as bradykinesia, rigidity, and postural instability with resting tremor. In addition, cognitive impairments are present, even in early disease stages, and predominantly affect executive functions such as planning abilities. Moreover, regarding a high risk for clinical dementia and clinical depression nondemented and nondepressed PD patients manifest themselves subtle cognitive problems, even in the earliest disease stages, which reflect incident pathological dementia and quality of life [1–6].

The motility impairment in PD patients is related with the damage and loss of about 60 to 70% of the neurons that memory and release dopamine in the substantia nigra. This disability results on the deletion of the neurotransmitter in the striatum area of the basal ganglia, basic to produce smooth and coordinated body movement [7–9]. Therefore, a large spectrum of no motor signs like hypotension, cardiac dysrhythmias, sweating bladder constipation, and sex dysfunction is typical of the PD Patients [10].

Parkinson tremors usually begin in a hand and then inducing alteration of the movements. Through the disease development, tremor involves the legs, face, tongue, and mandible [2, 11, 12].

In patients with Parkinson's disease (PD), chronic levodopa treatment may be related with several dyskinetic movements (levodopa induced dyskinesias (LID)), which are classified according to the type of movement and also in relation with the effect of levodopa.

The association between levodopa and the induction of dyskinesias was recognized soon after the introduction of levodopa [13, 14]. In the past, levodopa therapy was associated with the development of motor complications in about 80% of patients within 5 years of treatment [15, 16]. In patients with young onset PD, the incidence of LID was higher and ensued more rapidly [14, 17]. Currently, with the introduction and widespread use of dopaminergic agonists, the overall treatment exposure to levodopa is decreasing,

especially in the first years of treatment; nevertheless, progression of the nigrostriatal deficit will facilitate the onset of LID at a later point in time. Thus, LID continues to be a common and important cause of disability in PD and one of the main reasons for recommending surgical treatment.

The diagnosis of PD is based on patient's anamnesis and medical history. However, the clinical evaluation of the signs by physical examination and in some cases, a positive sustained response to dopaminergic medications are parameters that clinicians should be considered for performing a correct diagnosis. Therefore, instrumental investigation like laboratory tests and imaging studies are not routinely used [6, 8, 18].

Parkinson patient's disability can be classified accordingly to neurological graveness of the diseases. Hoehn and Yahr firstly proposed a scale based on the type of motor symptoms, assist clinicians in staging the disorder [19, 20]. Due to the tremors, the PD patients may reveal difficulty for performing oral hygiene daily maneuvers. Numerous cofactors like motor impairment, dysphagia, apathy, depression, dementia, hypersialorrhea, xerostomia can involve to this disability. In addition, patients also have a progressive relative inability to start voluntary and involuntary movements [6, 8, 11]. The facial expression initiates to be reduced, blinking and swallowing may be associated too. Other clear signs are the incapability of getting dressed, bathing, arising from a sitting position, and the overall sense of weakness. Body muscles motility is not usual and uncontrollable related to an increased muscular tone developed. Autonomic dysfunction of PD patients manifests itself as variations in blood pressure causing cardiac dysrhythmias, excessive sweating, and consequently sexual dysfunction. Insomnia, sleep apnoea, and sleep fragmentation with resultant daytime drowsiness are disability conditions of PD patients [19–21].

Poor dental and periodontal health, conversely, may be a risk factor for progression of associated disease like diabetes mellitus, pulmonary disease, atherosclerosis, cardiovascular disease, and stroke [21–24].

The damaging effects related with this progressive disease can significantly influence life and especially the oral health of those patients. Oral hygiene of PD patients can often be neglected as a result of the disease's evolution. For this reason, the clinicians through the complete knowledge of the disease should perform accurate dental control manoeuvres. Moreover, the general dentists should perform an overview of the patient's PD clinical features, and pharmacological drugs administration in order to increase the patients' PD oral health. The purpose of this investigation is to evaluate the frequencies of periodontal disease and caries, tooth loss in PD patients in relation to oral hygiene condition guiding early intervention and developing new therapies necessary to give PD patients high life quality.

2. Patients and Methods

Between May 2012 and August 2012 the oral condition of periodontal health and caries prevalence were recorded in 45 consecutive 65 to 78 years old patients affected by Parkinson's disease of a mild type in stages 1-2 of Hoehn and Yahr scale [20] (study group). PD Patients were consecutively recruited from IRCSS Neurolesi Bonino-Puleio.

One other 45 patient's group of the same ages was recorded (control). Those consecutive patients were recruited at the Odontostomatolgy Department of Messina Policlinic, where they came for routine dental visit.

The institutional ethical committee board of IRCCS Centro Neurolesi "Bonino-Pulejo" Messina approved protocol, and all subjects and their proxies provided written informed consent.

One of the investigators clinically inspected the oral cavity by dental probe using for periodontal deep socket investigation. Clinical investigation was completed by mouth mirror investigation for evaluating the presence of dental caries and the number of missed teeth was recorded for each patient. The teeth involved in previous conservative, endodontic, or prosthetic treatment were not included in the one caries affected. For further investigation all patients underwent X-ray ortopanoramic investigation in order to record also the presence of interproximal caries. All the periodontal pockets deeper than 4 mm were considered pathologic accordingly with the International Periodontal Index [25].

Patients with at least three pathological pockets on two different teeth were classified to have periodontal disease. Clinical pictures of the patients were recorded and included on the study for comparing the two groups. The study PD patients' cognitive functions were assessed by the minimental state examination (MMSE) and the motor impairment severity was assessed by the Persson et al. stage [24]. The decayed, missing and filled test (DMFT) was done for all the patients in both groups.

3. Results

A total of 90 patients have been examined. The study group involved patients affected by Parkinson's disease (28 women, 17 men) and the control group (10 women, 35 men) recorded no PD patients. The mean ages of PD patients were comparable and similar to the control group.

3.1. Number of Missed Tooth. (The complete dentature accordingly to the International Consensus about the presence of 28 teeth in upper and lower jaw avoiding the presence of the wisdom teeth) [25].

(i) The number of missed teeth per patient ranged from 10 to 22 in the PD group with a media of 13 missed teeth for person (a total of 330 teeth has been clinically recorded).

(ii) The number of missed teeth per patient ranged from 8 to 23 in the control group with a media of 9 missed teeth for person (a total of 418 teeth has been clinically recorded).

3.2. Untreated Caries

(i) The number of untreated caries per patient ranged from 3 to 18 in the PD group (lesions were recorded on 190 of 330 teeth).

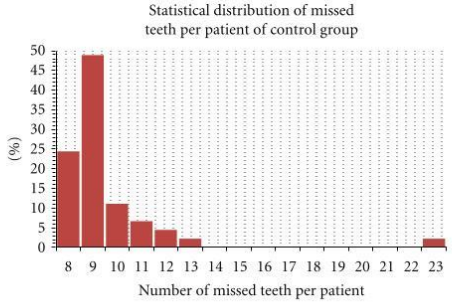

Figure 1: Student's *t*-test performed for number of missed teeth on control Parkinson's patient group.

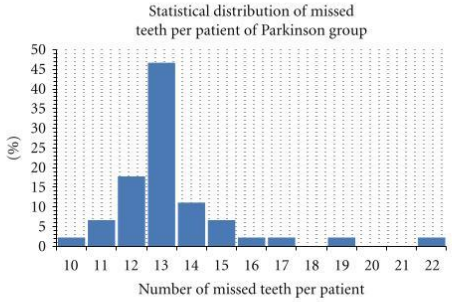

Figure 2: Student's *t*-test performed for number of missed teeth on control group patient.

(ii) The number of untreated caries per patient ranged from 6 to 14 in the control group (lesions were recorded on 203 of 418 teeth).

3.3. Incidence of Periodontal Disease. Baseline periodontal scores. PPD: probing pocket depth, SBI: sulcus bleeding index, Mob: tooth mobility (accordingly with Loe and Sillness Gingival index (1963) Muhlemann and Son's Sulcus; Bleeding index; and Plaque index) [26, 27].

(i) A total of the 250 on 330 teeth investigated in the PD study group revealed periodontal pockets ranged from 5 to 8 with a bleeding score positive on pocket probing (92 of 250 teeth with periodontal disease). Severe tooth mobility (Miller class II-III) 23 was recorded on 74 of 250 teeth with periodontal disease.

(ii) A total of 188 of 418 teeth recorded in the control group revealed periodontal pockets ranged from 4 to 6 with negative bleeding score. No severe tooth mobility (Miller class II-III) 23 was recorded in the Control group. (Figures 1, 2, 3, 4, 5, 6 and 7).

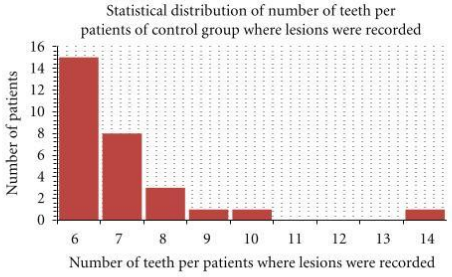

Figure 3: Number of caries recorded in control group.

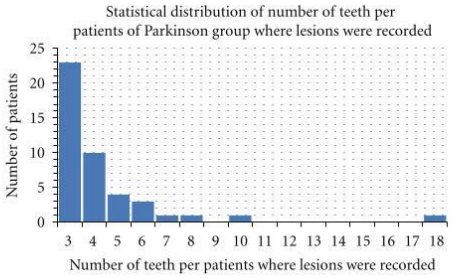

Figure 4: Number of caries recorded in PD group.

4. Discussion

Data results clearly showed how the frequencies of missed teeth and periodontal disease were significantly higher in the PD patients group while there was no significant difference between the percentages of untreated caries teeth on both group. Therefore, specifically about the periodontal disease, no marked bleeding and no gingival inflammation signs were observed in the control group. The results of the present study may be principally connected to the clinical patients' oral conditions of the two investigated groups. The similar condition of untreated caries and the same frequency of this pathology in both groups can be related to the sugar diet that older people prefer to assume [28, 29].

Nutrition is an important determinant of health in elderly patients. Over the past decade, the importance of nutritional condition has been increasingly evaluated in numerous morbid conditions including cancer, heart disease, and dementia in persons over the age of sixty-fives; therefore, frequent meals and snacks are suggested by physicians and dieticians. In many cases, the snacks are high in sugar, soft and sticky, favouring plaque formation. Sugar diet will also significantly increase the risk of caries and periodontal disease [29–32]. Moreover, vitamin drinks as substitute of snacks may help maintain proper nutrition and eliminate the caries and periodontal disease predisposing factors.

This study highlights that the maintenance of high oral hygiene is fundamental for patients affected by neurological

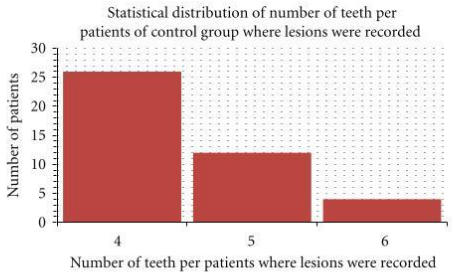

Figure 5: Deep of the sockets recorded in control group.

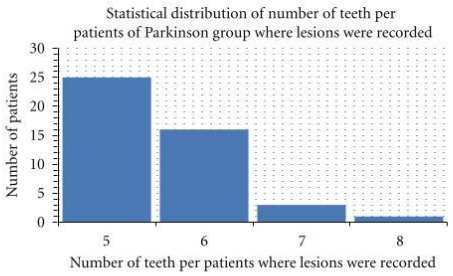

Figure 6: Deep of the sockets recorded in PD group.

disease like PD. Results demonstrated that periodontal disease is frequent in patients with PD and regarding the difficulty in plaque removing, it is related to motor and cognitive impairment. Merchant et al. pointed out that the increasing of physical activity and diminished the risk of periodontal disease [33].

The altered ability to have regular oral self-care is connected with impaired manual dexterity, as well as cognitive problems, apathy, depression, and changed motor behaviour and fluctuations. Absent-mindedness associated with dementia may also influence negatively oral hygiene habitude in many individuals with PD [4, 6, 33].

Clinicians should give to the patients with no cognitive impairments instructions in proper tooth brushing and flossing methods that maximize removal of dental plaque.

The opportunity of this study involving PD patients underlined how there are behavioural changes that may negatively impact dental care. Apathy, depression, and forgetfulness are factors that may influence patients' ability to notice dental problems [12, 22, 24, 32].

Moreover, PD patients seemed to have a decreased appetite. This status, associated with the poor dental hygiene, often increase the tendency to not assume nutrient chewing rich foods like vegetables or meat [31–33].

People with Parkinson's may be strongly influenced by dentist prescriptions and suggestions. This group of patients reflects a large load for the health care system because of its occurrence among the increasing proportion of elderly people in Italy. The results of the investigation clearly underlined how the PD patients' age is increasing. For this reason, dentistry and medicine have much to offer patients with this disease, in order to prevent and control caries or periodontal diseases. Topical fluoride gel treatments are commonly used for the plaque control and a daily application may be useful for having better home hygiene in the between of dental visits. Patients of the study seem to accept this kind of treatment cause of easy application and pleasant on tasting. However the interdisciplinary treatment represents the better choice. Moreover to have safe therapeutic strategies, the dentist should consult with the patient's physician to identify any need for modifications of typical treatment practices [34, 35].

Figure 7: Clinical investigation is performed by periodontal probe in order to evaluate the socket deep.

After recording oral health status in both groups, patient's requests and problems about dental hygiene were underlined and recorded. All the patients were uncomfortable with the mouthwashes, maybe for the fear of choking. Our goal was to have the patient PD total trust and confidence in the dental visits and in the prescription.

Accordingly to the literature and with our experience, there are numerous procedures in which people with Parkinson's can increase the value of their visits to the dentist, beginning with timing them strategically [29, 33–35]. All the dental visits recorded in the study were performed in the early morning, when the attention grade is higher and the patient cooperation is at its best.

By the investigations results, the oral health of PD patients can be considered generally worse than the comparable general population. This suggests that PD patients should follow a preferential routinely check dental care visit. Those procedures are fundamental for preventing the increasing of caries and periodontal diseases in those patients.

Parkinson's disease is a progressive central nervous system disorder characterized by tremors, rigidity, and impaired motor function. Oral involvement is significant and affects the oral health status of the patient. According to this study, the frequencies of caries and periodontal disease are high in PD patients. Clinicians should routinely check those patients' oral health in order to maintain high quality of life of those patients. We suggest short and frequent dental visits for having high range attention of the PD patients. Moreover a strong dental hygiene education should be led on the PD

patients in order to avoid the increase of invasive caries and to control active periodontal disease.

Disclosure

M. Cicciù, DDS Ph.D., Head of the Project visited the patients of each group. He was involved in organization and execution of the research project; design and execution of statistical analysis; writing of the first draft and review and critique of paper. G. Risitano, Ph.D., M.Sc., was responsible of the collection data and the graphics. E. Bramanti, DDS, Ph.D., was responsible for the patient collection. He made the direct relationship with the IRCSS "Neurolesi Bonino Puleio Center" Parkinson's patients. The authors intend to submit an article entitled "*Periodontal health and caries prevalence evaluation in patients affected by Parkinson's disease*" as an Original Research. This study has been performed by the cooperation of the IRCSS Neurolesi Center Bonino Pulejo and the Messina University. The authors hope that the important results of the study may be interesting for the numerous readers in order to help Parkinson's disease patient's management. They hereby transfer, assign, or otherwise convey all copyright ownership, including any and all rights incidental thereto, exclusively to the journal, in the event that such work is published by the journal. As corresponding author M. Cicciù confirms that the paper in its submitted form has been read and approved by all authors. Moreover, in case of acceptance the authors hereby guarantee the publishing expenses covering. All the authors confirm that there is no conflict of interests with the published materials. Authors document that there are no funding sources, regardless of relationship to the current research in the paper. All the works and investigations have been performed privately just for doing research in this very actual topic.

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ANEXO 15 – CARIES AND PERIODONTAL DISEASE IN PATIENTS WITH PARKINSON´S DISEASE

ARTICLE

ABSTRACT

Parkinson's disease (PD) has been associated with aging, reduced fine motor skills, and malnutrition caused by eating soft sticky foods and a decreased liquid intake, which may contribute to the onset of caries, periodontal disease, and tooth loss. The objective of this study was to investigate the oral health of 101 patients with PD (mean age: 66.2 ± 10.5 years) and compare them to 75 control subjects (CO) (mean age 71 ± 10.53). Patients with PD had poorer oral health than the control group (papilla bleeding index: PD 6.97 ± 8.34; CO 2.12 ± 2.73). Lower frequencies of daily toothbrushing (PD: 1.69 ± 0.83; CO: 2.08 ± 0.80), longer time since the last dentist visit (PD: 1.94 ± 1.49; CO: 1.21 ± 0.60 years), and reduced salivary flow (PD: 2.69 ± 0.94; CO: 3.53 ± 1.11 ml). All of these factors may be related to the gingival recession and tooth mobility found in our patients with PD. Individuals with PD, their caregivers, and their physicians need to focus more on their oral health and quality of oral hygiene.

KEY WORDS: oral hygiene, Parkinson's disease

Caries and periodontal disease in patients with Parkinson's disease

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Introduction

When combined with various medical conditions, such as osteoporosis and malnutrition, age may lead to caries, periodontal disease, and tooth loss.[1] Oral health is contingent upon oral hygiene, which requires a series of simple and complex hand movements.[2] Reduced fine motor skills, malnutrition, and osteoporosis are characteristics of Parkinson's disease (PD).[1–3]

Several investigators[1,3] have reported poor oral health in subjects with PD. Schwarz *et al.*[2] found female patients with PD in particular to be at a greater risk of developing periodontal disease. However, Schwarz *et al.*'s study[2] included more male than female patients with PD, and no relationships concerning gender and severity of the disease were investigated. Nevertheless, impaired fine motor performance, which limits toothbrushing abilities, was considered a primary risk factor for the deteriorated oral health found in the patients with PD.[2] Cognitive disturbances, such as dementia or apathy, altered motor behavior (e.g., tremor), and particularly motor fluctuations may influence the quality and frequency of daily oral hygiene care by patients with PD. Alterations in the amount of saliva produced may represent a further risk factor for poor oral health.[1–3] Swallowing dysfunctions and changes in salivary flow rates may also affect the oral self-cleaning mechanisms in patients with PD.[1,2]

As the literature has presented contradictory outcomes regarding the oral health of patients with PD,[1] we carried out a pilot investigation. We hypothesized that the onset of caries, periodontal disease, and tooth loss was higher in patients with PD than in control subjects. The objectives of this study were to evaluate the state of oral health in patients with PD and compare them to a control cohort.

Methods

Subjects

For this study, 101 patients with PD were recruited from the Department of Neurology of the St. Josef Hospital, Bochum, Germany, where they resided as in-patients for diagnosis or optimization of their PD drug therapy. The study subjects' mean age was 66.2 ± 10.5 years; there were 55 men (mean age 63.9 ± 10.7 years) and 46 women (mean age 69.1 ± 9.6 years). Using the Hoehn and Yahr scale,[4] subjects' disease progression ranged from stages 1 through 4, with the mean stage of 2.72 ± 0.84. Using the Unified Parkinson's Disease Rating Scale

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Table 1. Comparison between patients with PD and controls.

		PD	CO	*P*
Dental status	Missing teeth	19.09 ± 10.64	19.45 ± 8.71	ns
	Replaced teeth	13.41 ± 11.28	15.27 ± 9.01	ns
	Dental crown	3.47 ± 4.32	6.64 ± 5.76	*
	Filled teeth	6.83 ± 9.87	5.69 ± 7.54	ns
	Decayed teeth	2.90 ± 6.64	0.67 ± 2.04	**
Periodontal disease	PBI	6.97 ± 8.34	2.12 ± 2.73	*
	API	20.38 ± 30.58	7.25 ± 7.41	*
	OHI	17.38 ± 31.06	3.65 ± 4.96	*
Periodontal pockets	Pocket depth	19.70 ± 36.32	2.23 ± 1.12	*
	Loss of gingival attachment	20.01 ± 36.21	2.82 ± 1.54	*
Mobility	I°	19.06 ± 36.98	1.89 ± 3.47	*
	II°	17.67 ± 37.32	0.28 ± 0.99	*
	III°	16.92 ± 37.57	0.05 ± 0.23	*
Gingival recession	I°	20.08 ± 36.65	2.00 ± 3.41	*
	II°	20.69 ± 36.34	1.25 ± 3.00	*
	III°	18.79 ± 36.99	0.15 ± 0.59	*
	IV°	16.99 ± 37.54	0 ± 0	*
Oral care	Frequency of toothbrushing	1.69 ± 0.83	2.08 ± 0.80	**
	Last dentist visit (years)	1.94 ± 1.49	1.21 ± 0.60	*
	Salivary flow (ml)	2.69 ± 0.94	3.53 ± 1.11	*

PD = patients with Parkinson's disease; CO = controls; ns = not significant; PBI = papilla bleeding index; API = approximate plaque index; OHI = oral hygiene index. All data are given as mean ± standard deviation.
*$p < .001$; **$p < .01$.

(UPDRS),[5] on Part I (mental behavior), subjects had a mean score of 6.48 ± 3.65; for Part II (activities of daily living), it was 15.87 ± 5.78; for Part III (motor examination), it was 30.64 ± 13.78; and for Part IV (complications of therapy), it was 3.57 ± 2.81.

A convenience sample of 75 control subjects was recruited from a private practice, where they had sought general dental care; none had a history of or current symptoms of a neurological disease. The control group's mean age was 71 ± 10.53 years; there were 35 men (age: 71.6 ± 11.6 years), and 40 women (age: 70.5 ± 9.6 years). The study subjects were younger than the controls ($p = .004$); this age difference was due to the men ($p = .002$) but not the women ($p = .5$).

Evaluation of dental health

One of the researchers (RP, a dental hygienist) was blinded to the clinical data. He asked the subjects how many times per day they usually brushed their teeth. He examined the whole oral cavity with a mouth mirror and a periodontal probe (PCP11.5/WHO) and identified the number of remaining teeth, dental caries status, and periodontal disease status. The number of carious and remaining teeth was based on detection of untreated decayed and missing teeth. Filled teeth were excluded, in order to account for recent caries only. A periodontal pocket more than 4 mm deep was considered a pathologic periodontal pocket, according to the Community Periodontal Index of Treatment Needs.[6] Subjects with at least one such pathologic pocket were considered to have periodontal disease. Nonstimulated whole, parotid, and submandibular/sublingual resting saliva samples were collected from each subject. All oral examinations were carried out three hours after their mid-day meal.

Rating

The severity of PD for study subjects was scored using the UPDRS, which is a rating scale used to follow the longitudinal course of patients with PD. This scale is subdivided into four domains and gains information by investigation and interview. Motor behavior was rated in the "ON" state, when patients showed good movement behavior.[5] A rough global assessment of the severity of subjects with PD was based on clinical findings and functional disability and was additionally done using the Hoehn and Yahr scale,[4] which grades PD into five stages. Patients with PD were excluded from the study if they had intense involuntary movements, so-called dyskinesia, which would impair their ability to maintain daily oral hygiene independently.

Statistics

Data showed a normal distribution according to the Kolmogorov-Smirnov test. As a result, we only carried out parametric tests. We applied the *t*-test for independent samples for comparisons between the study and control groups.

Ethics

All participants gave written informed consent. The study was approved by the local ethics committee of the Ruhr University of Bochum, Germany.

Results

Comparisons between the study and control groups

In general, subjects with PD had a poorer state of oral health when compared with the control subjects (Table 1). We found lower frequencies of toothbrushing and dental visits as well as impaired oral self-cleaning mechanisms, which was reflected by reduced salivary flow in subjects with PD. We also observed more

Table 2. Comparison between male and female subjects in both cohorts.

		PD		I	CO		II	III	IV
		Male	Female	*p*	Male	Female	*p*	Male	Female
Dental status	Missing teeth	20.15 ± 10.22	17.83 ± 11.11	ns	18.37 ± 8.77	20.40 ± 8.66	ns	ns	ns
	Replaced teeth	14.42 ± 11.50	12.20 ± 11.01	ns	14.09 ± 9.22	16.30 ± 8.81	ns	ns	ns
	Dental crown	2.51 ± 3.15	4.61 ± 5.21	*	6.40 ± 5.17	6.85 ± 6.28	ns	***	ns
	Filled teeth	6.84 ± 10.32	6.83 ± 9.41	ns	5.51 ± 7.42	5.85 ± 7.73	ns	ns	ns
	Decayed teeth	4.20 ± 8.39	1.35 ± 3.01	*	0.86 ± 2.6	0.50 ± 1.40	ns	*	ns
Periodontal disease	PBI	6.89 ± 8.15	7.07 ± 8.65	ns	2.46 ± 3.35	1.83 ± 2.02	ns	**	***
	API	19.56 ± 29.58	21.35 ± 32.04	ns	6.34 ±7.67	8.05 ± 7.16	ns	*	*
	OHI	16.47 ± 30.14	18.46 ± 32.43	ns	4.29 ± 6.61	3.10 ± 2.80	ns	*	**
Periodontal pockets	Pocket depth	21.03 ± 37.58	18.11 ± 35.09	ns	2.42 ± 1.15	2.06 ± 1.07	ns	**	**
	Loss of gingival attachment	21.59 ± 37.33	18.11 ± 35.14	ns	2.40 ± 1.52	3.17 ± 1.60	ns	***	***
Mobility	I°	20.09 ± 38.13	17.80 ± 35.92	ns	2.00 ± 4.09	1.80 ± 2.88	ns	**	**
	II°	18.45 ± 38.81	16.74 ± 35.88	ns	0.14 ± 0.36	0.40 ± 1.32	ns	**	**
	III°	18.20 ± 38.92	15.39 ± 36.25	ns	0.06 ± 0.24	0.05 ± 0.22	ns	**	**
Gingival recession	I°	21.22 ± 37.88	18.72 ± 35.48	ns	2.06 ± 3.72	1.95 ± 3.15	ns	**	**
	II°	22.84 ± 37.29	18.13 ± 35.41	ns	0.94 ± 1.83	1.53 ± 3.75	ns	***	**
	III°	19.27 ± 38.47	18.22 ± 35.54	ns	0.20 ± 0.76	0.10 ± 0.38	ns	**	**
	IV°	18.29 ± 38.88	15.43 ± 36.23	ns	0 ± 0	0 ± 0	ns	**	**
	HYS	2.91 ± 0.72	2.50 ± 0.92	*					
	UPDRS I	7.48 ± 3.56	5.26 ± 3.41	**					
	UPDRS II	16.98 ± 5.10	14.53 ± 6.32	ns					
	UPDRS III	32.72 ± 12.92	28.13 ± 14.53	ns					
	UPDRS IV	4.20 ± 2.75	2.82 ± 2.72	*					

PD = patients with Parkinson's disease, CO = controls; ns = not significant; PBI = papilla bleeding index; API = approximate plaque index; OHI = oral hygiene index; I = comparison between male and female patients with PD, II = comparison between male and female controls, III = comparison between male controls and male patients with PD; IV = comparison between female controls and female patients with PD. All data are given as mean ± standard deviation.
*$p < .05$; **$p < .01$; ***$p < .001$ (*t*-test for independent samples).

pronounced gingival recession and tooth mobility in subjects with PD, compared to the control subjects (Table 1).

Comparisons between male and female subjects

Male subjects with PD had more carious teeth and fewer crowned teeth. However, male subjects with PD were more severely affected by Parkinson's disease than females, according to the scores from the UPDRS I, II, and IV assessment (Comparison I, Table 2). There were no gender differences among the control subjects (Comparison II, Table 2).

Compared to control subjects, both males and females with PD were found to have more severe periodontal disease, and more periodontal pockets, mobility, and gingival recession (Comparison III and IV, Table 2).

Discussion

Several factors put patients with PD at risk for dental and periodontal pathology.[1–3] We confirm that subjects with PD have fewer teeth and clean them less often, compared with control subjects.[1,3,7,8] Earlier studies[1–3] included fewer patients and controls. In general, Schwarz *et al.*[2] found better periodontal health among females in the control group. The higher frequency of carious teeth and lower number of crowned teeth found in the male cohort with PD may be related to the fact that male patients had higher UPDRS I, II, and IV and Hoehn-Yahr scores than the females. Since the severity of PD predisposes to a poorer state of oral health, we assumed that gender had no impact on the oral health of patients with PD. Generally, our study suggested that dental care might be an underestimated problem in persons with PD. We found

that the onset of PD contributed to the occurrence of many dental, oral, and maxillofacial problems. Periodontal disease and coronal and root surface caries may increase during the progression of PD. Since saliva is essential to maintain oral health owing to its protective functions, including flushing plaque and bacteria from oral mucosal and dental surfaces, patients with diminished salivary flow are more likely to develop periodontal disease and caries.[1,2] In addition, many meals consumed by patients with PD contain food or beverages that increase the risk of oral disease, as it is known that people with PD often develop a craving for sweets.[1,2] Therefore, preventive dentistry may be the most important aspect of dental treatment for patients with PD. We suggest that patients with PD should regularly visit a dentist at least once every four months. Oral status should be examined and should also consider the number of natural teeth, crowns, and dental bridges or the existence of partial or complete dentures, or a combination of these dental therapeutic strategies. Pathologic conditions should be diagnosed and treated as early as possible.[9] Oral health parameters, including salivary flow, gingival health (bleeding, plaque, calculus), periodontal health (pocket depth, recession, loss of attachment), and dental conditions (number of decayed, missed, and filled teeth) should be measured at baseline after diagnosis of PD and then again at each follow-up visit. It is important to recognize the limitations of both patients with PD and their dentists in performing oral care. Patients with PD should receive oral care in the safest manner and most appropriate setting possible. Dentists and their staff members should be encouraged to assume a greater share in the total care of patients with PD in cooperation with neurologists.[9]

There were certain limitations to this cross-sectional investigation. Patients with PD were younger than the controls. During our evaluations, the subjects with PD motor fluctuations were not considered, so there was a one-time recording which consisted of bad ("OFF") and good ("ON") movement behavior and influence of UPDRS III scores.[5] Controls were recruited from a cohort of individuals who had consulted a general practitioner on a check-up visit. They may not be representative of the behavior of the general population. Recruitment of patients with PD was from hospitalized subjects only. Thus, one may assume that we did not include the entire population with PD. In general, discussion of our results in comparison with the literature is difficult, since the quality of healthcare systems and particularly dental treatment differs all over the world.

Conclusion

Our study showed that, in patients with PD, oral health is a problem that may be caused by inadequate dental care. Therefore, the intraoral status of patients with PD needs to be assessed by the patients themselves, their caregivers, and their physicians so that a preventive regimen can be instituted. We propose the implementation of a practice-based research network in order to collect more oral health data on patients with PD so that better oral health care can be delivered.

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ANEXO 16 – OROFACIAL FUNCTION AND ORAL HEALTH IN PATIENTS WITH PARKINSON´S DISEASE

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Orofacial function and oral health in patients with Parkinson's disease

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No comprehensive study has previously been published on orofacial function in patients with well-defined Parkinson's disease (PD). Therefore, the aim of this study was to perform an overall assessment of orofacial function and oral health in patients, and to compare the findings with matched control subjects. Fifteen outpatients (nine women and six men, 61–82 yr of age; Hoehn & Yahr Stages 2–4; and with motor impairment ranging from 17 to 61 according to the Unified Parkinson's Disease Rating Scale, Objective Motor Part III) were examined in their 'on' state together with 15 age- and gender-matched controls. Orofacial function and oral health were assessed using the Nordic Orofacial Test, masticatory ability, performance and efficiency, oral stereognosis, jaw opening, jaw muscle tenderness, the Oral Health Impact Profile-49, number of natural teeth, and oral hygiene. Orofacial dysfunction was more prevalent, mastication and jaw opening poorer, and impact of oral health on daily life more negative, in patients with PD than in controls. The results indicate that mastication and orofacial function are impaired in moderate to advanced PD, and with progression of the disease both orofacial and dental problems become more marked. It is suggested that greater awareness of the special needs in PD patients and frequent dental visits are desirable to prevent dental diseases and decay and to support masticatory function.

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Parkinson's disease (PD) is one of a group of motor system disorders and is an irreversible, slowly progressive, neurodegenerative movement disorder with tremor, rigidity, and bradykinesia as cardinal symptoms (1). They result in a lack of facial expression with a characteristic 'mask-like' face, reduced blinking rate, drooling, a quiet monotone voice, slurring of speech, dysphagia, resting tremor, slow reactions and responses, short shuffling steps, and gait instability (2). Additionally, there is an increased incidence of depression and cognitive impairment related to the disease. Parkinson's disease is one of the most common neurological diseases (incidence: 120 per 100 000) and affects men 1.5 times more frequently than women. In about 5% of the patients the disease is hereditary (3). The onset is usually after the age of 40, and the prevalence increases, with age, to 1–5% after 65 yr (4). The disease is mainly related to the degeneration of dopaminergic neurons in the basal ganglia and substantia nigra of the brain. Increased mortality depends on disease duration and often results from infections.

Parkinson's disease is divided into stages according to Hoehn & Yahr (5). These stages are: mild/early disease (Stage 1: only one side of the body is affected, usually with minimal or no functional impairment; and Stage 2: both sides of the body are affected, but posture and balance remain normal); moderate disease (Stage 3: both sides of the body are affected and there is mild imbalance when standing or walking); and advanced disease (Stage 4: both sides of the body are affected and there is disabling instability while standing or walking, i.e. the person requires substantial help and cannot live alone; and Stage 5: severe, fully developed disease is present, i.e. the person is often cachectic and restricted to bed or a wheelchair unless aided).

Administration of medications is usually initiated when the symptoms interfere with the patient's level of functioning. The standard medication is levodopa, which is taken up by the remaining neurons in the basal ganglia and transformed into dopamine, thereby facilitating synaptic transmission and improving function. However, the effect decreases with time, and after 5–10 yr of treatment at least half of the patients becomes partially unresponsive to the medication. Then, the effect fluctuates during a 24-h cycle with an 'on' period with good motor function where the drug has an effect, and an 'off' period when the medication is ineffective (2). Other drugs are usually used in combination with levodopa, both for PD and the associated symptoms, and several medications that are used have severe side effects. A frequent side effect is development of dyskinesia of the head, face, and tongue, including bruxism, which results in dental attrition and adverse orofacial reactions such as xerostomia (2).

There have been conflicting findings regarding the dental health of patients with PD. However, patients with PD seem to have more missing teeth, caries, dental plaque and food debris, poorer oral clearance and

periodontal health, and more denture problems, which have been ascribed to a lack of orofacial muscular control, hyposalivation, and compromised manual dexterity (2, 6–11). The neuromuscular and cognitive deficits associated with PD enhance the progression of dental disease, impair home care regimens, and encumber in-office dental treatment (2). In addition, both dentists and patients with PD may be reluctant to embark upon complex dental procedures.

The orofacial functions seem to be impaired in PD in several ways. The jaw mobility and the speed of the jaw movements are reduced (12). The rigidity, the reduced mobility, and the tremor complicate the formation and the placement of the food bolus, and the chewing process (6, 13). Moreover, food retention and dysphagia are common. It has also been suggested that the rigidity and involuntary jaw movements may induce orofacial pain (14). In PD, 30–80% of patients have drooling of saliva from the corners of the mouth (15) which is typically caused by a combination of pooling of saliva in the mouth as a result of dysphagia, decreased swallowing frequency, diminished closure of the lips, and antecollis (16).

To our knowledge, no comprehensive study on orofacial function in PD has been published on a well-defined group of patients with matched control subjects. Therefore, the aim of the present study was to perform an overall assessment of the orofacial function and oral health in patients with moderate to advanced PD, and to compare the findings from the patients with those from age- and gender-matched control subjects.

Material and methods

Patients and control subjects

The study was approved by the local scientific, ethical committee in Bispebjerg Hospital. The patients were chosen among the patients treated for moderate to advanced PD corresponding to UK Brain Bank criteria (Table 1) (17) and Hoehn & Yahr Stages 2–4 (5) in the Day Hospital and Outpatient Clinic (Department of Neurology, Bispebjerg University Hospital). On certain weekday mornings during a period of 2½ months, patients with an appointment were offered a 30-min dental examination and counselling. All fifteen patients who were asked agreed to participate. They were in their 'on' state (i.e. the best level of motor functioning) and were classified as having motor impairment ranging from 17 to 61 according to the Unified Parkinson's Disease Rating Scale, Objective Motor Part III (UPDRS) (18) (Table S1), which, in contrast to the Hoehn & Yahr scale, is sensitive to medication. The patients were nine women and six men (age-range, 61–82 yr) (Supporting Table S1). Age- and gender-matched control subjects, mainly chosen from family and friends, were examined in the same way. Informed consent was obtained in all cases.

Table 1

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (17)

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
And at least one of the following
Muscular rigidity
4–6 Hz rest tremor
Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Orofacial function

The Nordic Orofacial Test – Screening (NOT-S) was used to perform a comprehensive screening of orofacial dysfunction (19). It consisted of a structured interview and a clinical examination (20). The interview reflected six domains – sensory function, breathing, habits, chewing and swallowing, drooling, and dryness of the mouth – and the examination included six domains – the face at rest, nose breathing, facial expression, masticatory muscle and jaw function, oral motor function, and speech. One or more 'yes' responses for impairment in one of the 12 domains scored 1 point, and the maximum score for the test was 12 points.

A subjective mastication index modified after Yoshida *et al*. (21)was used to evaluate masticatory ability (22). The subject chose the best-fitting possibility of four: 0, 'normal'; 1,'able to eat anything, but it takes long'; 2, 'able to eat a soft diet only'; 3, 'difficult to eat even a soft diet and it takes long'; or 4, 'only liquid diet'. Masticatory performance was tested using a commercially available stick-type sugar-free chewing gum (mean weight 1.93 g, 3 × 6 × 43 mm; Stimorol Senses Peppermint Twist; Cadbury Stimorol, Gumlink, Vejle, Denmark) using a method modified from Anastassiadou & Heath (23). The masticatory performance was assessed as the total weight loss of substances, such as sweeteners and flavouring, from a preweighed piece of gum chewed for a 2-min period at a fixed chewing cycle of 800 ms (24) (i.e. 75 strokes per minute). After the 2-min chewing period, the chewed gum was rinsed under running tap water and dried gently with tissue. Then, it was placed in a desiccator at room temperature for 3 days, together with a preweighed, unchewed piece of gum from the same gum package. The weight loss was calculated as the difference between the weight of the gum before the chewing test and the weight of the desiccated gum, expressed as a percentage of the weight of the gum before it was chewed and corrected by the eventual percentage weight loss of the unchewed gum. Masticatory efficiency was evaluated by the duration of chewing a standardized slice of crisp apple (11 g of Granny Smith with the rind and core removed) from the first bite to the swallow (22).

Oral stereognosis (i.e. the ability to recognize and discriminate forms in the mouth) (25), was tested with five different test pieces in polished solid steel consisting of a shaped form (a triangle, a circle, a square, a round disc, or a star) on a handle like a lollipop, which were administered in a fixed order. The shapes were 3 mm thick and they ranged in size from 13 × 13 to 19 × 19 mm. No practice trial was held. For each test piece the subject was blindfolded, helped to place the test piece in their mouth, instructed to move it around freely and suck on it, and to indicate when the shape was recognized. Immediately afterwards, the subject, now without the blindfold, was asked to identify the test piece on a chart that showed eight shapes, including the five shapes used in the test and three shapes not used in the test. The mean response time to recognize the five shapes was

Table 2

Orofacial function, oral health, and dental condition in patients with moderate to advanced Parkinson's disease compared with age- and gender-matched control subjects

	Patients with Parkinson's disease (n = 15)	Age- and gender-matched control group (n = 15)	Mann–Whitney U-test P-value
Orofacial function			
Nordic Orofacial Test – Screening (NOT-S; 0–12)	5.5 ± 2.9 (5.0)	0.7 ± 0.0 (0.9)	0.000005*
Subjective assessment of masticatory ability (index: 0–4)	0.9 ± 1.0 (1.0)	0.0 ± 0.0 (0.0)	0.001*
Masticatory performance			
Weight loss of gum (%)	24.0 ± 11.5 (30.2)	33.5 ± 3.8 (34.4)	0.004*
Masticatory efficiency			
Chewing time of apple slice (s)	67.6 ± 57.8 (46.0)	34.4 ± 4.2 (35.0)	0.1
Oral stereognosis			
Mean response time (s)	8.6 ± 6.5 (6.4)	5.9 ± 3.1 (4.8)	0.1
Identification index (0.0–1.0)	0.6 ± 0.6 (0.3)	0.8 ± 0.2 (1.0)	0.2
Maximum active jaw opening capacity (mm)	44.0 ± 7.1 (45.0)	58.5 ± 4.3 (60.0)	0.000005*
Tenderness of jaw elevator muscles (index: 0–4)	0.2 ± 0.4 (0.0)	0.1 ± 0.3 (0.0)	0.3
Oral health			
Self-administered Oral Health Impact Profile (full OHIP: 0–196)	35.2 ± 21.5 (29.0)	11.9 ± 8.3 (13.0)	0.0001*
Complement of natural teeth (n = 0–32)	19.1 ± 10.7 (24.0)	24.3 ± 7.3 (27.0)	0.1
Oral hygiene (index: 0–3)	0.9 ± 1.0 (1.1)	0.3 ± 0.6 (0.0)	0.06

The data are expressed as mean ± SD (median).
*$P < 0.05$.

calculated, as was the identification index describing the number of correct identifications of the five test pieces (0.0–1.0).

Maximum active jaw-opening capacity was measured (in mm) at the incisors, taking the vertical overlap between the maxillary and mandibular incisor teeth into account. Tenderness of jaw elevator muscles was evaluated by manual palpation of the anterior temporal and masseter muscles on both sides, with firm pressure (1–2 kg) applied with two fingers on the bulk of the relaxed muscles. If no eye blink or avoidance responses were recorded by palpation, the index score was 0, and if responses were elicited by palpation of one, two, three or all four muscles, the scores was 1, 2, 3 or 4, respectively.

Oral health and dental condition

The possible impact of the oral health situation on daily life in the last month was rated in the self-administered questionnaire Oral Health Impact Profile-49 (OHIP) (26). The questionnaire consisted of 49 questions concerning seven domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Responses to the questions, indicating how frequently the problem had been encountered, were scored on a scale of 1–5, as follows: never experienced; 1, hardly ever experienced; 2, occasionally experienced; 3, experienced fairly often; or 4, experienced very often. The total summary score from all questions, and the score for each domain, were calculated. The OHIP has been translated to Scandinavian languages, and the reliability and validity have been evaluated as good (27, 28).

First of all, the number of natural teeth and eventual prostheses and the oral hygiene were recorded. The hygiene was evaluated as follows: 0, good (no visible plaque, or visible plaque in fewer than four dental stagnation areas, i.e. gingival margins, on approximal surfaces, or on unopposed occlusal surfaces); 1, moderate (visible plaque in four or more stagnation areas); 2, poor (visible plaque in both stagnation and non-stagnation areas); and 3, very poor (visible plaque in both stagnation and non-stagnation areas, and debris outside the dental arch). Then, a quick dental examination was performed to see if there were any acute carious lesions or other problems that needed immediate treatment.

Statistical analysis

The data were analyzed using conventional statistical methods (STATISTICA; StatSoft, Tulsa, OK, USA) and reported as mean ± SD and median. Comparisons between data from patients with PD and control subjects were analyzed using the Mann–Whitney U-test. Correlations between the Hoehn & Yahr disease stages and the outcome data on orofacial function and oral health, and between Unified Parkinson's Disease Rating Scale and the outcome data on orofacial function and oral health, were analyzed using Spearman Rank Correlation Analysis. Statistical significance was accepted as $P < 0.05$.

Results

General health and medication

The 15 patients had suffered from PD for 1–14 [6.7 ± 3.8 (median = 7.0)] yr, and as assessed from their information and the prescribed drugs, only two suffered from PD alone (Table S1). In the control group, six of the 15 subjects had no medication or diagnoses and the rest were treated for one, or for combinations of the following conditions (listed according to frequency): hypertension, depression, myxoedema, osteoporosis,

rheumatoid arthritis, osteoarthritis, ulcerative colitis, incompensated morbus cordis and pacemaker, and Sjögren's syndrome. In 14 of the patients and in three of the control subjects, dry mouth could have been a side effect of their medication.

Orofacial function

The total scores in the NOT-S screening test for orofacial dysfunction differed significantly between the group of patients with PD (Table 2) and the age- and gender-matched control group, and the total scores increased significantly with the severity of the PD in terms of Hoehn & Yahr stages and the UPDRS motor impairment scale (Table 3). The patient group and the control group also differed significantly with respect to the single domains 'breathing' ($P = 0.03$), 'chewing and swallowing' ($P = 0.009$), 'drooling' ($P = 0.01$), 'nose breathing' ($P = 0.03$), 'facial expression' ($P = 0.00002$), 'masticatory muscle and jaw function' ($P = 0.01$), 'oral motor function' ($P = 0.001$), and 'speech' ($P = 0.00004$) (Fig. 1A).

The patients with PD described their masticatory ability as significantly poorer than did the control subjects (Table 2), and the masticatory ability decreased significantly with the severity of the PD in terms of Hoehn & Yahr stages and the UPDRS motor impairment scale (Table 3). Likewise, masticatory performance measured as the weight loss of gum during chewing for 2 min differed significantly between the patient group and the control group (Table 2). However, the masticatory efficiency in terms of chewing time of a standardized apple slice did not differ significantly between patients and controls (Table 2), even if it tended to increase with the UPDRS motor impairment scale (Table 3).

There were no significant differences between the groups in the stereogenic perception measures, response time, and identification index, but the recognition decreased significantly with the severity of the PD in terms of Hoehn & Yahr stages (Table 3). The maximum jaw opening capacity was reduced in the patients with PD in comparison with the control subjects (Table 2). However, the opening was not correlated with the severity of motor impairment of PD (Table 3). The tenderness of the jaw elevator muscles in the patients with PD did not differ from those of the control subjects (Table 2), and no correlation was found with the severity or motor impairment of PD (Table 3).

Oral health and dental condition

The patients with PD reported more often (Table 2) oral health-related problems in the OHIP questionnaire than did the age- and gender-matched control subjects, and the problems experienced increased significantly with the UPDRS score on motor impairment (Table 3). The patient group and the control group differed significantly with respect to the domains 'functional limitation' ($P = 0.001$), 'psychological discomfort' ($P = 0.04$), physical disability' ($P = 0.00004$), psychological disability' ($P = 0.02$), and 'social disability' ($P = 0.03$) (Fig. 1B).

The examination identified no statistically significant differences between the number of natural teeth in the patients with PD and the control subjects (Table 2). However, two patients with PD were edentulous and six had fixed or removable prostheses, whereas there were no edentulous persons in the control group and only four had fixed or removable prostheses. In addition, four patients with PD and only one control subject needed treatment for acute carious lesions. The oral hygiene also

Table 3

Correlation between the severity of Parkinson's disease (Hoehn and Yahr stages and motor assessment according to Unified Parkinson's Disease Rating objective motor Scale III) and parameters of orofacial function, oral health, and dental condition in 15 patients

	Spearman Rank Correlation Analysis	
	Hoehn and Yahr stages: 1–4 r_s (*P*-value)	Unified Parkinson's Disease Rating Scale: 0–108 r_s (*P*-value)
Orofacial function		
Nordic Orofacial Test – Screening (NOT-S: 0–12)	0.64 (0.01)*	0.77 (0.0008)*
Subjective assessment of masticatory ability (index: 0–4)	0.60 (0.02)*	0.72 (0.002)*
Masticatory performance		
Weight loss of gum (%)	−0.19 (0.5)	−0.46 (0.09)
Masticatory efficiency		
Chewing time of apple slice (s)	0.38 (0.2)	0.50 (0.06)
Oral stereognosis		
Mean response time (s)	0.13 (0.7)	0.40 (0.1)
Identification index (0.0–1.0)	−0.54 (0.04)*	−0.29 (0.3)
Maximum active jaw opening capacity (mm)	−0.20 (0.5)	−0.12 (0.7)
Tenderness of jaw elevator muscles (index: 0–4)	−0.02 (0.9)	−0.10 (0.7)
Oral health		
Self-administered Oral Health Impact Profile (full OHIP: 0–196)	0.35 (0.2)	0.52 (0.04)*
Complement of natural teeth (n = 0–32)	−0.45 (0.09)	−0.47 (0.08)
Oral hygiene (index: 0–3)	0.73 (0.002)*	0.75 (0.001)*

*$P < 0.05$; r_s Spearman Rank Correlation Coefficient.

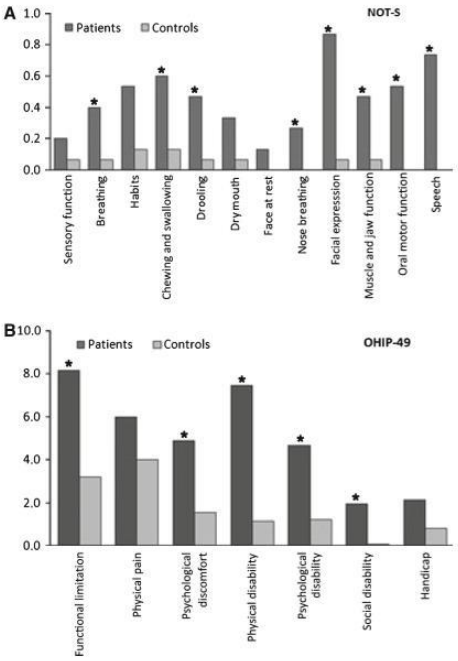

Fig. 1. Median scores for each domain from patients with PD and matched controls. The asterisks indicate domains where data from patients differed significantly from controls ($P < 0.05$). NOT-S, Nordic Orofacial Test – Screening; OHIP-49, Oral Health Impact Profile-49.

tended to be worse in the patient group than in the control group ($P = 0.06$; Table 2), and it increased significantly with the severity of the PD in terms of Hoehn & Yahr stages and the UPDRS motor impairment scale (Table 3).

Discussion

The study included a relatively small number of randomly selected patients with moderate to advanced PD. However, the results were clear: orofacial dysfunction and oral health were generally poorer in the patients than in the age- and gender-matched control subjects, and both orofacial function and oral health decreased with the severity of the disease. The control subjects were well-functioning and representative for their age in the present country, not perfectly healthy, 'supernormal' subjects, and two-thirds had medical conditions and used drugs. Two patients with PD, but no control subjects, were edentulous. This difference seemed to be a consequence of the disease, but might also add to the differences between the two groups.

The total NOT-S scores from the two groups corresponded to the results published previously,of patients with diseases of the nervous system according to the ICD-10 classification (International Statistical Classification of Diseases and Related Health Problems 10th Revision, World Health Organization) and of healthy control subjects (19). Therefore, the impairment of motor function in PD was also present in the jaw and orofacial muscles. Self-assessed measures of chewing ability are often over-rated when compared with functional tests (29). However, in the present study, both subjective and objective analyses showed the patients to have clearly impaired masticatory function. The findings agreed with the published results on jaw movements in PD (12), but were in contrast to the previous suggestions regarding orofacial pain from jaw muscles (14) as little tenderness was recorded by palpation of the masseter and temporalis muscles.

The frequent drooling of saliva, which has been described in PD, was also reported significantly more by the patients than by the controls. Interestingly, fewer patients reported dry mouth (xerostomia) in spite of the possible side effects of their medication (2, 30). No impairment, as a result of PD, could be recorded of the sensory function in the oral cavity, as judged from the NOT-S, but the response time in the stereognostic test increased with the severity of the PD, probably as a result of cognitive impairment. The only other group studying oral stereognosis in PD (31) also failed to find any difference between the patient group and the control group, but their patient group was not well defined.

The scores in the OHIP increased with the progression of the disease, and the tendency to accumulate greater amounts of plaque was probably associated with muscle rigidity, jaw tremor, and impaired motor control caused by PD. Therefore, the previous, rather conflicting, findings regarding the dental health of subjects with PD may be explained by the different degrees of disease severity present in the patients (2, 6–11). Thus, missing teeth, caries, dental plaque and food debris, poorer oral clearance and periodontal health, and denture problems are probably more marked in patients with advanced or fully developed PD. As the maintenance of a reasonable number of healthy natural teeth is of paramount importance to obtain and secure comminution and masticatory efficiency (29, 32), dental disease and decay should be prevented and treated in order to attempt to diminish and compensate for the impairment in the control of masticatory and tongue muscles, and the dysphagia.

In conclusion, the present results indicate that mastication and orofacial function are impaired in moderate and advanced PD, and, with progression of the disease, both the orofacial and the dental problems become more marked. Dentists should be aware of the special needs of patients with PD, and frequent dental visits seem desirable to prevent dental diseases and tooth decay, to support masticatory function and swallowing.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of patients with Parkinson's disease included in the study.

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