INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

PERIODONTAL STATUS IN PARKINSON'S DISEASE PATIENTS: A RETROSPECTIVE STUDY

Trabalho submetido por
Patrícia Soares Lyra
para a obtenção do grau de Mestre em Medicina Dentária

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Trabalho orientado por
Prof. Doutor Luís Francisco Alexandrino Proença

e coorientado por
Prof. Doutora Catarina Afonso Godinho
Prof. Doutor José João Baltazar Mendes

Setembro 2020

Dedicatory

To my beloved parents, Fátima and George

"Without the quest, there can be no epiphany"

Constantine E. Scaros

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Abstract

Background: People with Parkinson's Disease (PD) may be at risk of having bad periodontal status. A consistent periodontal examination is critical to investigate the impact on quality of life and if periodontitis in PD patients potentially causes systemic repercussions.

Aims: Our primary goal was to assess the association of periodontitis and PD, considering patient's self-perceived general quality of life, oral health-related quality of life (OHRQoL) and xerostomia. Secondly, we compared blood and standard biochemistry surrogates of PD patients with periodontitis with PD patients without periodontitis.

Material and Methods: Firstly, 28 individuals from the Portuguese Association of Parkinson's Disease Patients were consecutively enrolled, PD clinical manifestations were assessed, a full-mouth periodontal examination was performed and questionnaires on self-perceived quality of life in PD (PDQ-8), oral health impact profile (OHIP-14) and xerostomia (SXI-5) were applied. Secondly, National Health and Nutrition Examination Survey (NHANES) 2011-2012 dataset was analyzed, with PD participants being identified through specific PD reported medications, from a sample of periodontally assessed individuals, and blood levels and standard chemical laboratory profiles were compared according to the presence of periodontitis.

Results: The prevalence of periodontitis in the Portuguese sample was 75.0% with 46.4% of severe cases. Upper extremities rigidity and hands postural and kinetic tremors were significantly correlated with worse periodontal status. PDQ-8 showed correlation with self-perceived OHRQoL and xerostomia levels. In the American sample, we found an association of periodontitis in PD patients with increased White Blood Cells (WBC), segmented neutrophils and basophils and lower Total Bilirubin levels. Furthermore, WBC, segmented neutrophils, Vitamin D2 and gender presented potential predictive value to infer periodontitis in PD individuals.

Conclusions: People with PD may have high prevalence of periodontitis. Deteriorated levels of the upper extremities in advanced PD stages may influence the periodontal status and hygiene habits. Quality of life in PD appears to be associated with self-perceived OHRQoL and xerostomia. Periodontitis may cause systemic changes with predictive

value in PD patients. Future studies should further assess periodontitis impact on the quality of life of PD patients and its potential systemic inflammatory burden.

Keywords: Parkinson's Disease; Periodontitis; Periodontal Disease; Quality of Life; Hematologic Tests; Vitamin D.

Resumo

Contexto: Indivíduos com doença de Parkinson (PD) podem estar em risco de apresentar um mau estado periodontal. Uma avaliação periodontal consistente é fundamental para investigar o impacto na qualidade de vida dos pacientes, e se a periodontite em pacientes com PD desencadeia potenciais repercussões sistémicas.

Objetivos: O nosso principal objetivo foi a avaliação da associação entre a periodontite e a PD, considerando a autopercepção da qualidade de vida global do paciente, da qualidade de vida relacionada com a saúde oral (OHRQoL) e de xerostomia. Secundariamente, comparámos marcadores sanguíneos e bioquímicos padrão de pacientes com PD com e sem periodontite.

Materiais e Métodos: Primeiramente, após a inclusão consecutiva de 28 indivíduos da Associação Portuguesa de Doentes de Parkinson, avaliaram-se as manifestações clínicas da PD, o estado periodontal e questionários de autopercepção da qualidade de vida na PD (PDQ-8), do perfil de impacto da saúde oral (OHIP-14) e de xerostomia (SXI-5). Posteriormente, mediante análise de dados do National Health and Nutrition Examination Survey (NHANES) 2011-2012, de uma amostra de indivíduos avaliados periodontalmente, selecionaram-se doentes de Parkinson através de medicação específica relatada na PD, e compararam-se níveis sanguíneos e perfis bioquímicos padrão de acordo com a presença ou não de periodontite.

Resultados: A prevalência de periodontite na amostra portuguesa foi de 75,0%, com 46,4% de casos graves. Rigidez das extremidades superiores e tremores posturais e cinéticos das mãos foram significativamente correlacionados com um pior estado periodontal. O PDQ-8 mostrou correlação entre os níveis de autopercepção de OHRQoL e xerostomia. Na amostra Americana, encontrámos uma associação de periodontite com o aumento de glóbulos brancos, neutrófilos segmentados e basófilos, bem como níveis mais baixos de bilirrubina total, em pacientes com PD. Adicionalmente, fatores como a contagem de glóbulos brancos, neutrófilos segmentados, vitamina D2 e género apresentaram potencial valor preditivo para inferir a presença de periodontite em indivíduos com PD.

Conclusões: Indivíduos com PD apresentaram uma elevada prevalência de periodontite. A maior incapacidade motora dos membros superiores em fases avançadas de PD podem influenciar o estado periodontal e os hábitos de higiene. A qualidade de vida na PD parece estar associada com a autopercepção de OHRQoL e xerostomia. A periodontite pode causar alterações sistémicas com valor preditivo em pacientes com PD. Estudos futuros devem explorar o impacto da periodontite na qualidade de vida dos pacientes com PD e na potencial carga inflamatória, a nível sistémico.

Palavras-chave: Doença de Parkinson; Periodontite; Doença Periodontal; Qualidade de Vida; Testes Hematológicos; Vitamina D.

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Abbreviation Index

25OHD2 | 25-Hydroxy D2

BOP | Bleeding on Probing

CD14 | Cluster of Differentiation 14

CNS | Central Nervous System

CT | Computed Tomography

DJ-1 | Deglycase 1

DBS | Deep Brain Stimulation

EDS | Excessive Daytime Sleepiness

eIF4G1 | Eukaryotic Translation Initiation Factor 4 G1

FCGR2A | Fc Fragment of IgG Receptor IIa

GBA | Glucocerebrosidase

H&Y | Hoehn & Yahr

IL1B | Interleukin 1 Beta

IL6 | Interleukin 6

LRRK2 | Leucine-Rich Repeat Kinase 2

MCI | Mild Cognitive Impairment

MDS-UPDRS | Movement Disorder Society – Unified Parkinson's Disease Rating Scale

NHANES | National Health and Nutrition Examination Survey

OHIP-14 | Oral Health Impact Profile

OHRQoL | Oral Health Related Quality of Life

PARK2 | Parkin 2

PD | Parkinson's Disease

PDQ-8 | Parkinson's Disease Questionnaire

PINK-1 | PTEN-induced Kinase 1

PISA | Periodontal Inflamed Surface Area

PET | Positron Emission Tomography

PFC | Prefrontal Cortex

PIGD | Postural Imbalance Gait Disorder

PMNs | Polymorphonuclear Neutrophils

RBD | REM Sleep Behavior Disorder

REM | Rapid Eye Movement

SNc | Substantia Nigra Pars Compacta

SNCA | α-synuclein Encoding Gene

SXI-5 | Shortening the Xerostomia Inventory

TNF | Tumoral Necrosis Factor

US | United States

WNT5A153 | Wnt Family Member 4A 153

WBC | White Blood Cells

I. INTRODUCTION

1. PARKINSON'S DISEASE

Parkinson's Disease (PD) is a chronic and progressive neurodegenerative process, clinically characterized by a variety of motor and nonmotor features which heavily affect patients' quality of life (Obeso et al., 2010).

After Alzheimer's disease, PD is one of the most frequent neurodegenerative conditions that mostly impacts the central nervous system (CNS) (de Lau & Breteler, 2006; Nussbaum & Ellis, 2003).

PD occurrence increases with age, being rare under 50, affecting 1% of individuals over 60 and reaching up to 4% in higher age groups (Tysnes & Storstein, 2017). Therefore, in unselected populations, at any time, PD prevalence varies from 0.1% up to 0.2% (Tysnes & Storstein, 2017). Also, about 0.24% of the portuguese population over 50 years of age has PD (Jesus-Ribeiro et al., 2017). An estimated total of 10 million individuals are suffering from PD today (Ball et al., 2019).

In a globally aged population, PD occurrence seems to be noticeably increasing, and is expected to duplicate in the next couple decades (Johnson et al., 2019; Dorsey et al., 2018). PD has an annual incidence of roughly 15 new cases in a 100 000 universe (it varies from less than 10 to more than 20 – this variation can be the result of PD under-diagnosing) (Tysnes & Storstein, 2017).

Also, PD tends to affect more men than women, since the risk of developing the disease is 1.5 to 2 times higher in the male gender (Alves et al., 2009; Ball et al., 2019; Ferreira et al., 2017; Schrag et al., 2000).

1.1. Clinical Manifestations

PD is considered a heterogeneous disorder due to the broad range of motor and non-motor features (Foltynie et al., 2002).

The classic motor manifestations are resting tremor, muscular rigidity and bradykinesia (lost capability to command movement, which becomes slow), all often targeted by

available levodopa-therapies (Nussbaum & Ellis, 2003; Obeso et al., 2010). An asymmetric onset and resting tremors are typical clinical signs of the sporadic form of this disease (Tysnes & Storstein, 2017).

Other motor and non-motor manifestations – such as loss of balance, gait dysfunction, swallowing and speech impairment, autonomic disturbances and cognitive decline (including hallucinations and delirium) – may be complications of the administration of dopaminergic drugs like levodopa, and end up being responsible for the disability in PD (Figure 1) (Obeso et al., 2010).

These motor and nonmotor features can eventually develop dementia in 30 to 80% of cases, which stands as the ultimate causal factor of disability (Obeso et al., 2010). Therefore, PD progression and treatment may interfere with daily-life activities and ultimately deteriorate patient's overall quality of life (Kalia & Lang, 2015; Poewe et al., 2017).

1.2. Diagnosis

A positive diagnosis of PD is delivered when gradual onset of motor symptoms takes place, especially its three cardinal signs - resting tremor, rigidity and bradykinesia (Figure 1) (Obeso et al., 2010).

To date, PD clinical diagnosis is merely speculative, since an easy and reliable testing process is yet to be developed (Litvan et al., 2003; Nussbaum & Ellis, 2003). The use of single-photon-emission CT or PET is only useful in the diagnosis of isolated PD patients in specialized settings (de Lau & Breteler, 2006). Therefore, a definitive diagnosis only happens via post-mortem evaluation (Kalia & Lang, 2015; Litvan et al., 2003). Discrepancies between PD clinical diagnosis and its histopathological signs at autopsy are frequent, and only approximately 80 to 90% of clinically diagnosed PD are validated at autopsy (de Lau & Breteler, 2006; Tysnes & Storstein, 2017).

There are multiple disorders that present similar clinical manifestations to PD, such as the postencephalitic, drug-induced and arteriosclerotic parkinsonism or the rare autosomal recessive juvenile parkinsonism (Nussbaum & Ellis, 2003). Therefore, an asymmetric symptom onset and clinical responsiveness to the administration of levodopa are

important factors to corroborate PD differential diagnosis (de Lau & Breteler, 2006). An accurate PD clinical diagnosis is less effective at an early stage, and implicates several long-term follow-up reavaluations in the course of the disease (de Lau & Breteler, 2006).

However, several lines of evidence show that there might be a pre-motor phase of PD, usually beginning up to 20 to 30 years prior to diagnosis, with non-motor prodromal signs such as hyposmia (olfactory dysfunction), sleep abnormalities (REM-sleep behavior disorder), cardiac sympathetic denervation, constipation, depression and pain (Figure 1) (Heintz-Buschart et al., 2018; Obeso et al., 2010; Tysnes & Storstein, 2017). Evidence shows that constipated individuals have 2.7 times more risk of developing PD (Figure 1) (Tysnes & Storstein, 2017). Patients with the presence of this wide range of signs, still without any PD motor impairs, might be considered at high-risk of developing PD, and those non-motor prodomal signs might even stand as early biomarkers to PD diagnosis (Nair et al., 2018; Obeso et al., 2010).

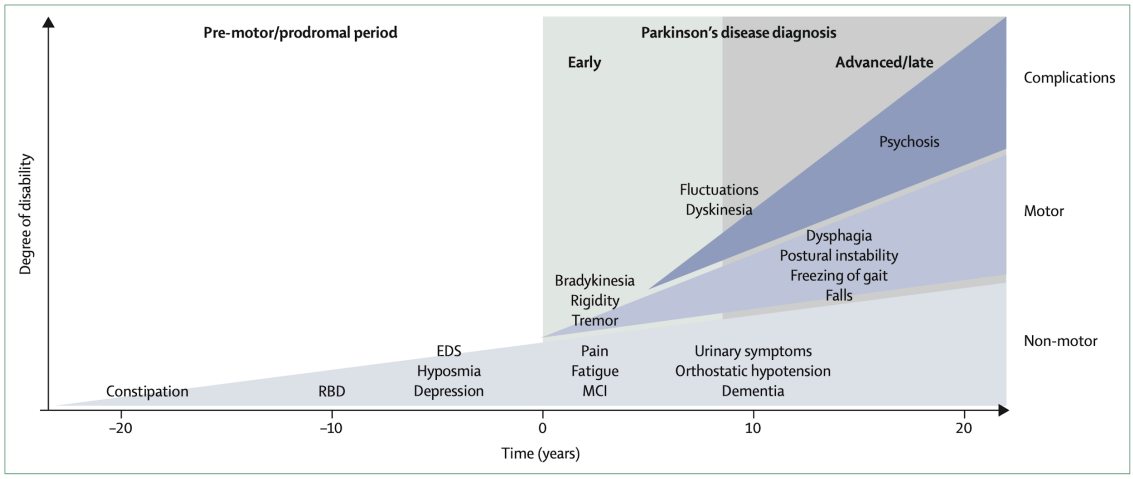

Figure 1 | Schematic representation of PD clinical development.
Prior to PD diagnosis (at 0 year's time mark), which usually occurs upon the establishment of the three cardinal motor symptoms (bradykinesia, rigidity and tremor), there might be a 20 plus year timespan of pre-motor/prodromal signs. Subsequently, further into PD establishment, other non-motor symptoms usually settle alongside the complications of dopaminergic therapy (such as fluctuations, dyskinesia and psychosis), and disability might emerge in advanced PD cases. RBD - REM Sleep Behavior Disorder; EDS - Excessive Daytime Sleepiness; MCI - Mild Cognitive Impairment (Adapted from Kalia & Lang (2015), by permission of corresponding author).

1.3. PD Subtypes, Onset and Progression

Despite being a heterogeneous condition, to this date, PD is known to have two major clinical subtypes based on the onset age, the predominance of clinical features and the rate of progression (Foltynie et al., 2002; Obeso et al., 2010):

- On the one hand, the early-onset form, mostly affecting young people (20 to 40 years of age), is usually a tremor-predominant form (Kalia & Lang, 2015);
- On the other hand, the late-onset form, often observed in the elderly (mostly over 60 to 70 years of age), is typically a non-tremor-predominant form also identified as Postural Imbalance Gait Disorder (PIGD), and akinesia (deterioration of voluntary movement), rigidity and gait and balance impairment are its typical signs (Thenganatt & Jankovic, 2014).

Usually the late-onset form is the most common one, since PD often starts to develop in patients around 65 to 70 years of age and an onset prior to the 4th decade of life happens in less than 5% of cases (Tysnes & Storstein, 2017).

Onset age is considered to be the best predictor for the rate of progression in PD: young patients subtype tend to have a slow decline in motor function, and elderly patients tend to present a quicker long-term progression (Thenganatt & Jankovic, 2014). Also, cognitive impairment tends to start earlier and is more common to appear in patients who are older at the start of clinical manifestations (Obeso et al., 2010).

1.4. Causal and Risk Factors

Currently, the causal factors of PD continue elusive (Ball et al., 2019). Being considered a heterogeneous disorder through its vast clinical phenotypes, the neurodegeneration observed in PD is unlikely to occur solely from a single causal mechanism (Thenganatt & Jankovic, 2014). Therefore, each clinical subtype is the complex conjugation product of different causative factors - mostly idiopathic, but also genetic and environmental (Figure 2) (Kalia & Lang, 2015).

Usually, non-genetic (environmental and idiopathic) factors play a key role in PD, as they are mostly responsible for 90% of PD cases (which are the sporadic late-onset forms of the disease), while genetic factors end up being responsible for the minority of cases (typically in the familial early-onset subtypes) (Tysnes & Storstein, 2017). Nonetheless, the non-genetic factors involved in the etiology of sporadic PD seem to synergically relate to existing susceptibility genes (de Lau & Breteler, 2006; Kalia & Lang, 2015). Further, 5 to 10% of PD total population presents some kind of genetic influence and that the immediate family of a PD patients have a doubled or tripled risk of developing PD (Nussbaum & Ellis, 2003). Since the heterozygous state of PD is considerably more common than the homozygous state, PD is classically a hereditary autosomal dominant neurodegenerative disorder (Nussbaum & Ellis, 2003).

The risk of developing PD - which is particularly aggravated in men - has not only been linked to the generalized ageing of the world's population, but also to several environmental risk factors (Ball et al., 2019; Tysnes & Storstein, 2017).

The occupational exposure to environmental toxins like pesticides and herbicides involved in farming and rural living, as well as to heavy metals in the welding industry (iron, copper, aluminium, zinc, etc.) have been hypothesised to increase the risk of developing PD, although further research is needed (Ball et al., 2019; Jankovic, 2005; Petrovitch et al., 2002; Priyadarshi et al., 2000). As was aforementioned, exposure to heavy metals increases oxidative stress due to free radical formation and heavy metal aggregates accumulation in the SNc (Substantia Nigra Pars Compacta) (de Lau & Breteler, 2006). Moreover, dietary habits like the high intake of satturated fatty acids, non-heme iron and dairy products (especially milk) have also been considered a risk factor in PD (Boulos et al., 2019).

Furthermore, inflammation seems to have a role in PD pathogenesis, since increased cytokine levels have been detected in the CNS of PD patients (brain and cerebrospinal fluid), as well as activated microglia in post-mortem evaluations (de Lau & Breteler, 2006). Actually, infectious and inflammatory agents in systemic circulation have been hypothesized to reach the brain, causing the activation of primed microglial cells (major innate immune-system cells in the CNS), which can initiate the neurodegenerative cascade found in neurodegenerative diseases such as PD, ultimately leading to the necrosis of dopaminergic neurons (Hashioka et al., 2019; Kaur et al., 2016). For instance,

microbial agents from the nasal cavity and the gastrointestinal tract (and their low-grade inflammatory states) are thought to instigate α-synuclein pathology both in the olfatary bulb and intestines, ultimately reaching the CNS and triggering neurodegeneration in PD (Heintz-Buschart et al., 2018; Nair et al., 2018). Enteric α-synuclein pathology usually causes the gastrointestinal dysfunctions that are typicall prodromal signs of PD (Nair et al., 2018). Therefore, the likelihood of PD development is presumably increased in scenarios where neuroinflammation or neurodegeneration are present, namely secondary inflammatory responses of chronic and infectious conditions (Chen et al., 2017; Hashioka et al., 2019).

Remarkably, higher urate levels, the consumption of tobacco (nicotine), coffee (caffeine), tea, beer, unsaturated fatty acids (arachidonic acid, omega 3 and α −linolenic acid) and non-steroidal anti-inflammatory drugs may reduce the risk of developing PD due to their neuroprotective effects (Figure 2) (Asanuma et al., 2001; Boulos et al., 2019; Hernán et al., 2002; Noyce et al., 2016; Obeso et al., 2010; Quik, 2004; Youdim et al., 2000). Also, research has shown that not only estrogens, but also the intake of vitamin E, both associate with a lower risk of developing PD, since both show antioxidant properties that inhibit the pathogenic mechanism of oxidative stress in PD (de Rijk, 1997; Saunders-Pullman, 2003). Additionally, physically active individuals seem to present a lower chance of developing PD, since physical exercise is thought to be neuroprotective (Chen et al., 2005).

Ultimately, further studies evolving these risk factors will probably lead to more understanding on PD etiology (Obeso et al., 2010).

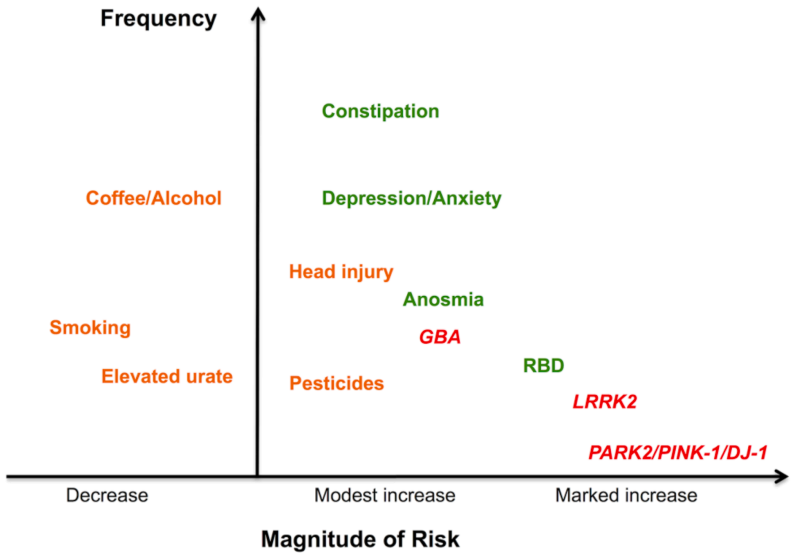

Figure 2 | Association between PD risk factors and pre-motor/prodromal signs with the decreased/increased risk of disease development and diagnosis.
PD presents several idiopathic, environmental (orange) and genetic (red) risk factors, all of which synergically interact amongst each other, either to potentiate or diminish the risk of PD development. Specific PD pre-motor/prodromal signs (green) also mark higher/lesser risk of PD establishment. GBA - Glucocerebrosidase gene; LRRK2 - Leucine-Rich Repeat Kinase gene; PARK2 - Parkin 2 gene; PINK-1 - PTEN-induced kinase 1 gene; DJ-1 - Deglycase 1 gene (Adapted from Noyce et al. (2016), by permission of corresponding author).

1.5. Etiopathogenic Mechanisms

Neurodegeneration in PD is characterized by two major hallmarks: 1) the death of dopaminergic neurons in the SNc (Figure 4) and other brain sights; and 2) also the presence of Lewy bodies (abnormal ubiquinated protein deposits in the cytoplasm) and Lewy neurites (thread-like ubiquinated protein inclusions within the axonal processes) in the remaining neurons, in which α-synuclein is the main proteic component (Eriksen et al., 2003; Lebouvier et al., 2010; Nussbaum & Ellis, 2003). α-synuclein is a short presynaptic protein of unidentified function, tangled in the molecular cascade of events that culminate in some neurodegenerative disorders, including PD (Nussbaum & Ellis, 2003).

The main established etiopathogenic mechanism of PD is the selective neurodegeneration of the nigrostriatal pathway, which is a bilateral dopamine pathway (originating in the SNc and emerging in the dorsal striatum), composed by dopaminergic neurons (Figure 3) (Obeso et al., 2010). The latter secrete dopamine and synapse with GABAergic medium

spiny projection neurons, involved in the production of movement (Figure 3) (Poewe et al., 2017). Being a neurotransmitter, dopamine functions through a signalling transmission system between neurons in the CNS (Iversen & Iversen, 2007).

Therefore, the death of these dopaminergic nigrostriatal neurons in the SNc results in the marked decrease of striatal dopamine concentration, inhibiting GABAergic projections, causing the depletion of voluntary movements and ultimately being the key to motor manifestations in PD (Barone, 2010; Obeso et al., 2010; Tysnes & Storstein, 2017).

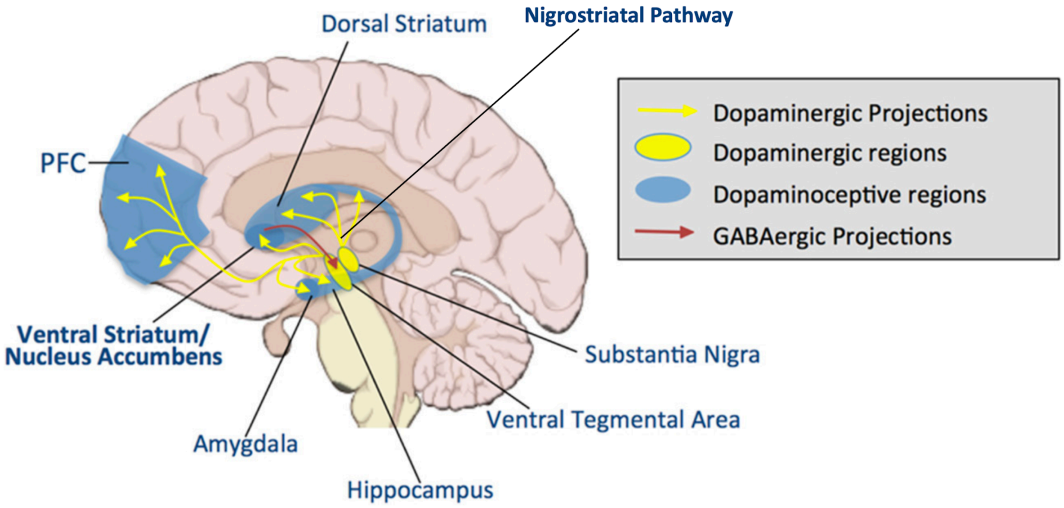

Figure 3 | Representation of the nigrostriatal pathway and other dopaminergic pathways (yellow) in the brain.
The nigrostriatal pathway originates in the substantia nigra pars compacta (SNc) and emerges into the dorsal striatum (composed of caudate nucleus and putamen) of the midbrain. The dopaminergic neurons of this pathway secrete dopamine and synapse with GABAergic medium spiny projection neurons, involved in the production of movement. PFC - Prefrontal cortex (Adapted from Telzer (2016) ©, used under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/), modified from original).

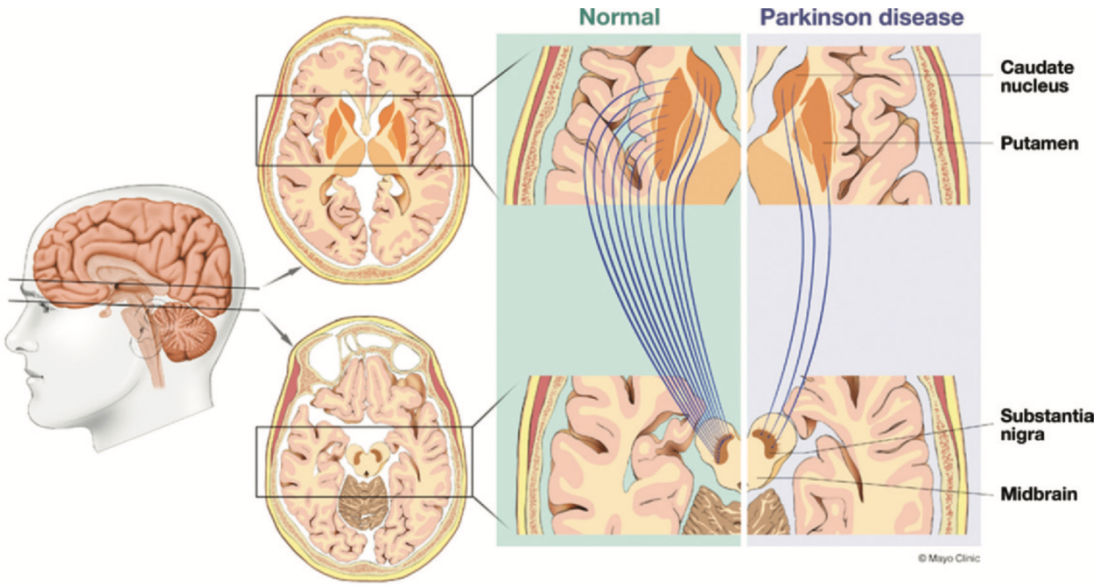

Figure 4 | Loss of dopaminergic neurons in PD.
This image schematically shows the neurodegeneration's effects on the neural projections from the substantia nigra pars compacta (SNc) to the dorsal striatum (composed of caudate nucleus and putamen) upon PD installation (Adapted from Broski et al. (2014), by permission of Mayo Foundation for Medical Education and Research).

As aforementioned, the homeostatic balance in the SNc is susceptible to the influence of genetic, cellular and environmental factors. Although not yet fully understood, these factors (isolated or associated) may overtime trigger the intracellular mechanisms that ultimately result in neuronal death, which are as follows (Figure 5) (de Lau & Breteler, 2006; Nussbaum & Ellis, 2003; Obeso et al., 2010):

- Mitochondrial dysfunction, consequent oxidative stress and intracellular toxicity;
- Abnormal protein degradation through proteosomal and lysosomal dysfunction and the compromised ubiquitination process (ubiquitin-mediated metabolism);
- Abnormal aggregation of α-synuclein, which forms lewy bodies and lewy neurites and ultimately causes intracellular toxicity (most common).

Gene mutations also play a role in PD pathogenesis, although the means by which they cause SNc cell death and Lewy body aggregations remains unknown. Some of the mutated loci result in inherited autosomal dominant PD (with only one mutant allele) and others in autosomal recessive PD (if both alleles of the mutated gene are altered) (Nussbaum & Ellis, 2003).

For instance, gene mutations in SNCA (α-synuclein encoding gene), LRRK2 (Leucine rich repeat kinase 2 gene) and eIF4G1 genes are responsible for about 2-3% of the late-onset, autossomal dominant forms of PD. Likewise, mutations in GBA, PRKN, PINK-1 and DJ-1 genes associate with 50% of the early-onset, autossomal recessive forms (Figure 2) (Obeso et al., 2010). Actually, the LRRK2-G2019S mutation is thought to be the most frequent PD causal factor, both in familial and sporadic forms of PD (Ferreira et al., 2017).

Besides gene mutations, excitotoxicity (neural receptors overactivations by excitatory neurotransmitters) and inflammation may also be involved in this progressive neural degeneration (Obeso et al., 2010).

Additionally, with PD progression, α-synuclein aggregation into lewy bodies becomes more widespread, extending to other brain sites (Tysnes & Storstein, 2017). Also, other affected neurotransmission systems (involving glutamate, acetylcholine and γ-aminobutyric acid (GABA)) ultimately translate into PD clinical manifestations (Barone, 2010).

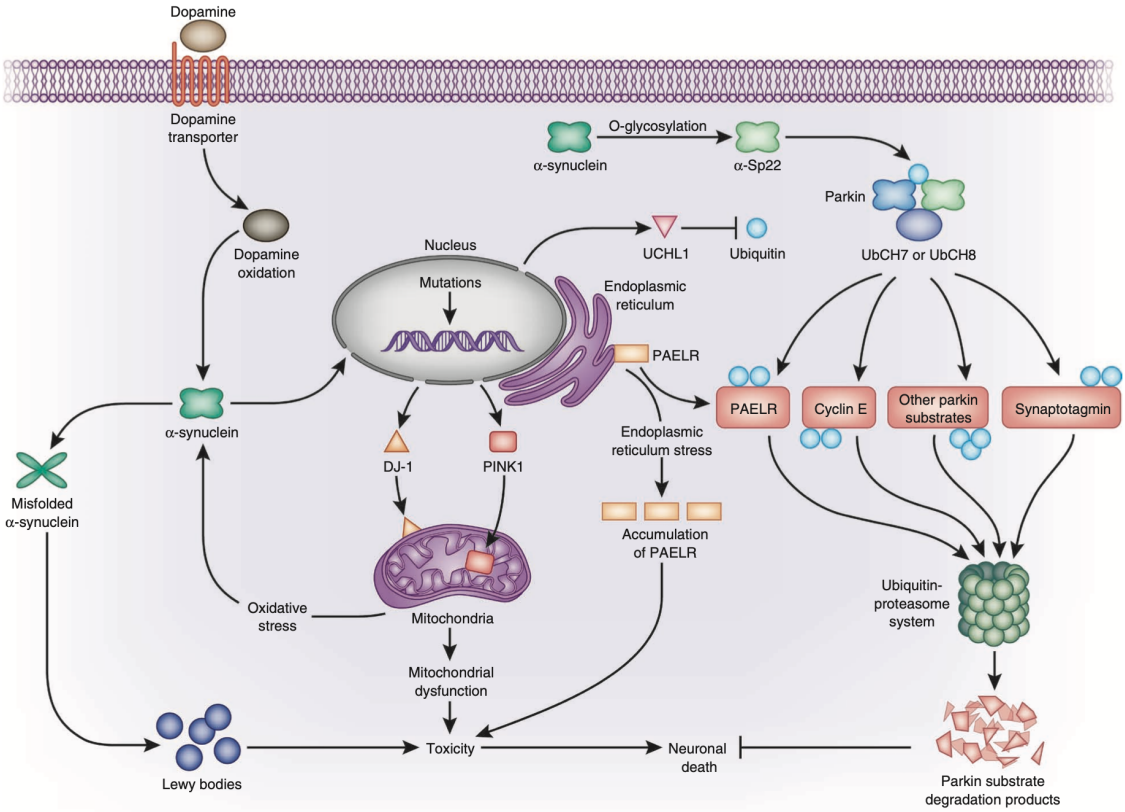

Figure 5 | Etiopathogenic intracellular mechanisms responsible for dopaminergic neuronal death in PD.
Mitochondrial dysfunction (causing oxidative stress and intracellular toxicity), lysosomal (not represented) and proteosomal dysfunction (affecting the ubiquitin-mediated metabolism and originating abnormal protein degradation), abnormal $\boldsymbol{\alpha}$-synuclein aggregation (forming lewy bodies which cause intracellular toxicity) and further intertwined gene mutations are here schematically represented, as they are supposed etiopathogenic intracellular mechanisms responsible for neuronal death in PD (Adapted by permission from Springer Nature Customer Service Centre GmbH: Nature Springer, Nature Medicine, Missing pieces in the Parkinson's disease puzzle, Obeso et al., © (2010)).

The degeneration of nondopaminergic transmitter systems is now known to partially cause the nonmotor features in PD, and it may present similar cellular mechanisms in its origin: it not only relates with the α-synuclein gene copy number, but also with gene and protein overexpression, though the latter seem to be especially toxic to dopaminergic neurons (Obeso et al., 2010).

1.6. Therapeutic Approaches

There are pharmacological and non-pharmacological treatments for PD (Lang & Lozano, 1998).

Levodopa has been the primary pharmacological treatment, while other dopaminergic drugs like dopamine agonists and atypical neuroleptics (antipsychotics) have been later introduced in treatment plans (Obeso et al., 2010).

Although useful in stabilizing the progression of motor symptoms, the chronic use of dopaminergic drugs like levodopa has the tendency to become less efficient overtime, as well as to increase disability and lead up to complications such as motor and non-motor fluctuations, dyskinesias and behavioral changes (Kalia & Lang, 2015). Hence, levodopa treatment may ultimately be responsible for shifting motor to nonmotor dysfunction in PD (Obeso et al., 2010).

Also, deep brain stimulation (DBS) is therapeutically used when patients present unmanageable levodopa related motor complications, and functional neurosurgery is an option in severe disabling PD cases (Poewe et al., 2017).

The focus of these standard treatments is in attenuating symptoms to hopefully improve PD patients quality of life and longevity, although tending to be a universal solution to a non-uniform disease (Johnson et al., 2019; Kalia & Lang, 2015; Schapira, 2009). Lately, ongoing research has been directed in the development of individualized disease-modifying therapies that target the etiopathogenic mechanisms responsible for the core neurodegenerative process, and aim to prevent or slow down PD installation and progression, as well as the consequent non-motor complications (Kalia & Lang, 2015; Schapira, 2009). For instance, whilst its causes and consequences are not fully comprehended, the aggregation of α-synuclein and its increased neuronal levels seem to be a primary factor to PD. Therefore, a potential therapeutic approach may involve the depletion of α-synuclein expression (Obeso et al., 2010).

Other non-pharmacological rehabilitation therapies such as physiotherapy, occupational therapy, psychological support, cognitive rehabilitation and speech therapy, are also essential parts in PD treatment plans and can be engaged either as monotherapy, or as part of a team approach (interdisciplinary or multidisciplinary rehabilitation) (H. Chen et al., 2005; Lang & Lozano, 1998).

2. PERIODONTITIS

Periodontitis is a chronic, infectious and inflammatory disease of the periodontium, where a dysbiotic microflora triggers an immune response in the supporting structures of the teeth (Hajishengallis, 2015). Clinically, periodontitis is characterized by chronically inflamed gingivae and alveolar bone destruction (Darveau, 2010).

Periodontitis is part of the periodontal disease family, alongside other conditions, such as gingivitis, necrotising periodontal disorders, periodontal manifestations of systemic conditions, periodontal abscesses and endo-perio lesions (Armitage, 1999; Caton et al., 2018).

From an epidemiologic standpoint, periodontitis is one of the most prevalent inflammatory diseases in the adult population (with its severe form ranked as the 6th most prevalent disease worldwide in 2010), affecting up to 50% of the world's population alongside other periodontal diseases (Kassebaum et al., 2014; Nazir, 2017; Tonetti et al., 2017).

Moreover, periodontitis slightly affects more men than women, with both its prevalence and severity being age-related (Ebersole et al., 2016; Eke et al., 2016).

2.1. Clinical Manifestations

In a healthy periodontium, the oral epithelium connects itself to tooth surfaces through a specialized junctional epithelium (Figure 6) (Nibali, 2018). The slight space resulting from such union forms the gingival sulcus, which is normally populated with a polymicrobial niche and filled by gingival crevicular fluid (a serous exudate containing pro-inflammatory cytokines, enzymes leukocytes, oral bacteria, etc.) (Donos, 2018; Nibali, 2018). Underneath, the alveolar bone and surrounding connective tissue completely brace tooth roots (Figure 6) (Darveau, 2010).

The daily accumulation of dental plaque in the oral cavity is inevitable, in which aggregates of diverse microbial species from the saliva or jugal mucosa attach onto coronal and radicular tooth surfaces, and ultimately participate in the homeostatic battle held with the host's immune system (Marsh, 2006; Socransky et al., 1977). The dental

plaque is an organized biofilm that mimics tissues, not only through its systematized architecture, but also through its codependent and metabolically integrated polymicrobial community function (Marsh, 2004; Marsh, 2006). It lodges a characteristic channel system and a quorum sensing mechanism: a signalling system between species that allows a rapid density-dependent and gene regulated adaptation of the biofilm when exposed to environmental stress (Marsh, 2004).

Whereas upon periodontal disease installation, some bacterial species in the subgingival dental plaque manage to invade the ulcerated epithelium, to breakdown the periodontal ligament fibers and to destroy the underlying connective tissue, creating the so-called periodontal pocket – a crevice of destruction (Figure 6) (Donos, 2018; Nibali, 2018).

A typical sign of periodontitis is bleeding on probing (BOP), which is currently accepted as a proxy of tissue inflammation and consistent with bad oral hygiene habits (Tonetti et al., 2018).

Eventually, periodontitis exacerbation might progress into permanent alveolar bone loss (which stands as the major disease hallmark), causing consequent gum recession, root furcation involvement, tooth mobility or, eventually, tooth loss (Figure 6) (Darveau, 2010; Haffajee & Socransky, 1986; Newman et al., 2018).

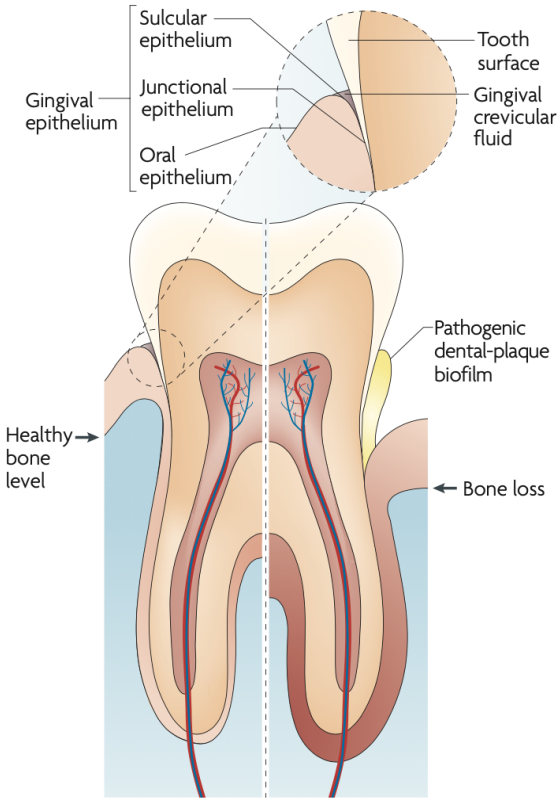

Figure 6 | Local effects of periodontitis.
On the left side a healthy periodontal insertion is schematized, where a specialized junctional epithelium properly connects the gingival sulcus epithelium to tooth surfaces and the alveolar bone is fully supporting tooth roots. Whereas, on the right side, the local effects of periodontitis are shown. Microbial species in the subgingival dental plaque destructively detach intact sulcus epithelium, breakdown the periodontal ligament fibers and destroy the underlying connective tissue and alveolar bone (Adapted by permission from Springer Nature Customer Service Centre GmbH: Nature Springer, Nature Reviews Microbiology, Periodontitis: a polymicrobial disruption of host homeostasis, Darveau, R. P., © (2010)).

The involvement of the hole dentition rarely occurs in periodontitis, since periodontal damage is usually site-specific and therefore constricted to certain teeth or tooth sites in the oral cavity (Haffajee & Socransky, 1986; Slots, 2017).

The burden of periodontitis may result in severe consequences to the patients, such as masticatory dysfunction and impaired patient's oral health-related quality of life (OHRQoL) (Buset et al., 2016), which can be restored after successful periodontal treatment (Botelho et al., 2020) However, self-perception of periodontitis is often misunderstood by patients (Machado et al., 2019) and has repercussions in the prediction of periodontal therapy adherence (Machado et al., 2020), hence the education of patients towards periodontal health is key to obtaining good clinical control of this disease.

Apart from its local effects as a peripheral inflammatory process of the oral cavity, periodontitis can also instigate slight systemic inflammation, which end up setting off or aggravating other chronic systemic inflammatory diseases, for instance cardiovascular diseases such as atherosclerosis and infective endocarditis (Muñoz-Aguilera et al., 2020; Sanz et al., 2020), *diabetes mellitus* and obesity (Preshaw et al., 2012; Winning & Linden, 2017), renal diseases, adverse pregnancy outcomes and ultimately cancer (Hajishengallis, 2015; Michaud et al., 2017). Additionally, periodontitis has been consistently associated with solid organ transplants and stress (Botelho et al., 2020; Machado et al., 2020), and very recently with polycystic ovary syndrome (Machado et al., 2020).

Recent evidence raised the possibility of periodontitis inducing neuroinflammation through the activation of microglia (CNS immune cells) (Hashioka et al., 2019). Hence, activated microglia in the brain are thought to be a common feature in the neuropsychiatric pathologies spectrum, which include both psychiatric disorders, such as Schizophrenia and Major Depression, and neurodegenerative disorders, such as Alzheimer's Disease (Dominy et al., 2019), Multiple Sclerosis, Amyotrophic Lateral Sclerosis and PD (Hashioka et al., 2019).

2.2. Onset and Progression

While presenting a high prevalence within all age groups, the risk of developing periodontitis exponentially increases with age (Flemmig, 1999). Apart from the immunological impairments associated with aging, the higher risk of periodontitis in the elderly has also strongly to do with long-term exposure to certain environmental risk factors (Borrell & Papapanou, 2005; Ebersole et al., 2016; Neely et al., 2001). Nonetheless, the onset of periodontitis most often occurs in early adulticy (with the peak of active disease being estimated at 38 years) (Slots, 2017).

Periodontitis initial breakdown can be quite pronounced and widespread, and long term be followed by disease-stable periods of inactivity or spontaneous remission, or acute outbursts in disease exacerbation periods (Goodson et al., 1982; Socransky et al., 1984). Therefore, disease progression is not slow or continuous, nor the periodontal attachment loss is linear throughout the periodontium: periodontitis is a dynamic site-specific condition with occasional active burts (Haffajee & Socransky, 1986).

The microbiology, immunology and clinical features of each compromised periodontal site in this transient condition is dependent on individual factors (Kamma et al., 2001). Notwithstanding, a persistent and unresolved status of periodontitis endures a persistent subgingival infection and associated inflammation, which can be clinically compatible with gingivitis (Slots, 2017).

2.3. Causal and Risk Factors

Periodontitis onset and progression are thought to be triggered by inadequate oral hygiene behaviors or motor hygiene impairments, which inevitably become more prevalent with age (Ebersole et al., 2016; Eke et al., 2016). Nevertheless, although being necessary factors, bad hygiene habits and pathogenic biofilm build-up seem insufficient to solely instigate periodontitis (Hajishengallis, 2015; Kornman, 2008; Meyle & Chapple, 2015; Newman et al., 2018).

Accordingly, a multitude of etiological factors and risk factors (modifiable or non-modifiable) make periodontitis a complex condition (Stabholz et al., 2010).

The association of dental plaque build-up, specific destructive dysbiosis and the host's immune response may collectively be considered periodontitis' etiological factors (Slots, 2017). That is to say, neither microbial dysbiosis or biofilm formation in the oral cavity will solely cause periodontitis in prone hosts (Hajishengallis, 2015).

Some examples of patient-specific risk factors, which play a role in the asseberbation of the host's immune response, are as follow (Borrell & Papapanou, 2005; Hajishengallis, 2015; Laine et al., 2012; Meyle & Chapple, 2015; Slots, 2010; Stabholz et al., 2010):

- Genetic predisposition (main responsible for the host's susceptibility);
- Age and gender;
- and Environmental factors, such as:
    - Systemic health status (uncontrolled diabetes mellitus, obesity or immunosuppression followed by an herpesvirus outbreak or HIV infection);

- Medication;
- Stress;
- Diet;
- Nocive behaviours (smoking, drinking alcohol and bad hygiene habits);
- and Socioeconomic status and educational levels.

Additionally, retentive local anatomy and restorative treatments with overflowing margins exemplify site-specific risk factors (Meyle & Chapple, 2015).

Regarding the genetic influence in periodontal diseases, periodontitis majorly stands as a polygenic condition, meaning that multiple genes determine individual risk of disease settlement (for example, IL1B, IL6, TNF, CD14, FCGR2A and WNT5A153 genes) (Laine et al., 2012). On the other hand, there are also reports of a monogenetic form of periodontitis, usually associated with young aggressive cases (Hajishengallis, 2015).

2.4. Etiopathogenic Mechanisms

The periodontium is closely related to a polymicrobial community present in the oral cavity, which exceed 800 different bacterial species (Nazir, 2017).

Knowing that junctional epithelial cells are merely attached through some desmosomes and gap junctions, forming a rather porous barrier with major intercellular spaces, periodontium defense machinery mostly relies on well organized immune defence mediators to fight the perpetual stimuli produced by microorganisms of the dental plaque (Darveau, 2010).

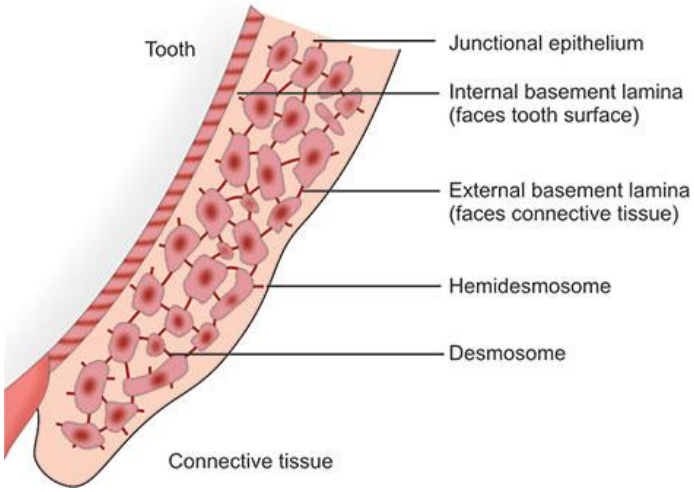

Figure 7 | Junctional epithelium permeability.
Junctional epithelial cells are connected through a few scattered desmosomes, forming large intercellular spaces between them (Adapted from Bathla, 2011, by permission of the publisher).

The permeable junctional epithelium allows for the constant flow of non-resident polymorphonuclear neutrophils (PMNs) and other immune cells (summoned by previously secreted proinflammatory mediators), which end up forming a barrier between the periodontium and the dental plaque biofilm (Darveau, 2010). Consequently, subgingival bacteria in healthy periodontal tissues trigger a chronic low-grade controlled defense response from the host's innate immune system, preventing further pathogenic colonization and disease installation (Newman et al., 2018).

On other hand, periodontitis oftentimes is the development of an established reversible gingivitis condition, through dysbiotic mechanisms (Hajishengallis, 2014). Hence, the consistent accumulation of non-disrupted supragingival dental plaque begins to favor commensal quorum-sensing bacteria (like *Fusobacterium nucleatum*) (Meyle & Chapple, 2015). The latter release chemical signalling and ultimately develop an inflammatory process, while also altering available nutrients (like heme) (Meyle & Chapple, 2015). Such process overtime potentiates a switch in the normal oral microflora, lessening commensal bacteria and/or asseberbating periodontopathic bacterial colonization that reaches subgingival tissues, or even through diminishing the host's defensive mechanisms (Hajishengallis, 2015; Newman et al., 2018).

Therefore, upon installation of a pathologic state, a transition from a previous majority of gram-positive bacteria to gram-negative bacteria occurs, who stand as major periodontopathic agents (Darveau, 2010).

Traditionally, red-complex bacteria (*Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia)* were thought to specifically be key pieces to periodontal pathogenesis, negatively modulating the host's innate immune response (Hajishengallis, 2015). However a change in paradigm now helds polymicrobial synergy and dysbiosis accountable for the debilitation of the host's innate immune response, the consequent imbalance of destructive proinflammatory cytokines exaggeratedly allocated to the region and the consequent irreversible destruction of periodontal soft and mineralized tissues, which end up being a paradoxical side effect to the defense response itself (Darveau, 2010; Hajishengallis, 2014; Newman et al., 2018).

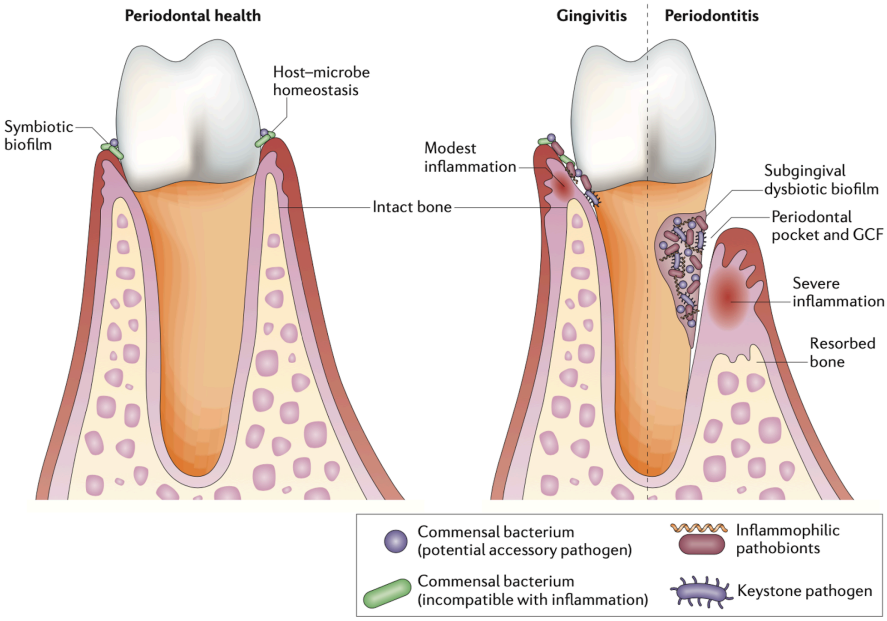

Figure 8 | Etiopathogenesis of periodontitis.
In healthy periodontal tissues (left), microbiota in the subgingival biofilm triggers a chronic low-grade proportionate defense response from the host's innate immune system, establishing host-microbe balanced homeostasis. However, upon consistent accumulation of supragingival dental plaque, a modest gingival inflammation usually settles - gingivitis (middle). In prone hosts, and if dental plaque build-up is non-disrupted, some commensal bacteria (potential accessory pathogens) might initiate a more severe inflammatory process, which overtime might lead to a microbial shift. This dysbiotic mechanism might lessen commensal bacteria and/or assebartate periodontopathic bacteria (keystone pathogens) in subgingival tissues, while also diminishing the host's defensive response - periodontitis (right). Periodontitis clinical repercussions involves periodontal attachment loss, which include soft and mineralized tissues (periodontal pockets and bone reabsorption) (Adapted by permission from Springer Nature Customer Service Centre GmbH: Nature Springer, Nature Reviews Immunology, Periodontitis: from microbial immune subversion to systemic inflammation, Hajishengallis, G., © (2015)).

2.5. Periodontitis in the Portuguese Context

The oral health status of the adult Portuguese population has been reportedly weak, regardless of the existing regional and socioeconomic discrepancies, and especially when compared to other European counterparts (Marques et al., 2000; Melo et al., 2017).

Recent data showed that the estimated prevalence of periodontitis in the adult Portuguese population of the South Lisbon Metropolitan Area stands at 59.9%, although known risk factors such as age, socioeconomic status, educational levels, smoking habits and systemic health issues like Diabetes Mellitus seemed to be heavily present in the evaluated sample (Botelho & Machado et al., 2019). The majority of the confirmed periodontitis cases presented moderate to severe disease forms (Botelho & Machado et al., 2019) With that reported, the authors find that an updated and thorough investigation at a national level is necessary, following strict full-mouth periodontal examination protocols and the new American Association of Periodontology (AAP)/European Federation of Periodontology (EFP) case definition of periodontal diseases, to find the real prevalence of periodontitis in Portugal (Botelho & Machado et al., 2019).

In addition, Machado et al. (2018) reported that severe cases of generalized periodontitis seem to be more prevalent in the male gender. Also, approximately 68% of adults in Portugal show some level of tooth loss and 6% are fully edentulous, both of which are directly associated with deficient oral hygiene habits (OMD, 2017).

Recognizing the need for treatment and seeking professional help, as well as maintaining good oral hygiene habits, are aspects still far from meeting clinician's expectations in the Portuguese scenario (with greater prevalence in men, lower income individuals and in the elderly) (Melo et al., 2017; Santos et al., 2019).

Therefore, a widespread promotion of oral educational programs, as well as the need for a universal dental health care accessibility, stand as a major current priority (Santos et al., 2019).

2.6. Periodontitis in the United States of America Context

According to the National Health and Nutrition Examination Survey (NHANES, 2009-2012), the burden of periodontitis in the adult United States (US) population stands at about 46%, with the predominance of non-severe forms of periodontitis (Eke et al., 2015).

There is reason to believe, both due to the aging of the population and to the chronicity of periodontitis, that the tendency moving forward is that of increasing numbers in periodontitis cases (Eke et al., 2020).

Expectably, poorer oral health status in US citizens also follows socioeconomic disparities, such as ethnicity (higher periodontitis prevalence among Mexican Americans), low income and low educational levels (Dye et al., 2012; Eke et al., 2012). Furthermore, periodontitis increased with age, and affected both more men and active smokers (Eke et al., 2012).

Also, nationwide geographic distribution affects the total prevalence of periodontitis (and in severe cases as well), with the southeastern and southwestern states being heavily affected by this disease, as is Hawaii and secluded regions in western Alaska (Eke et al., 2020).

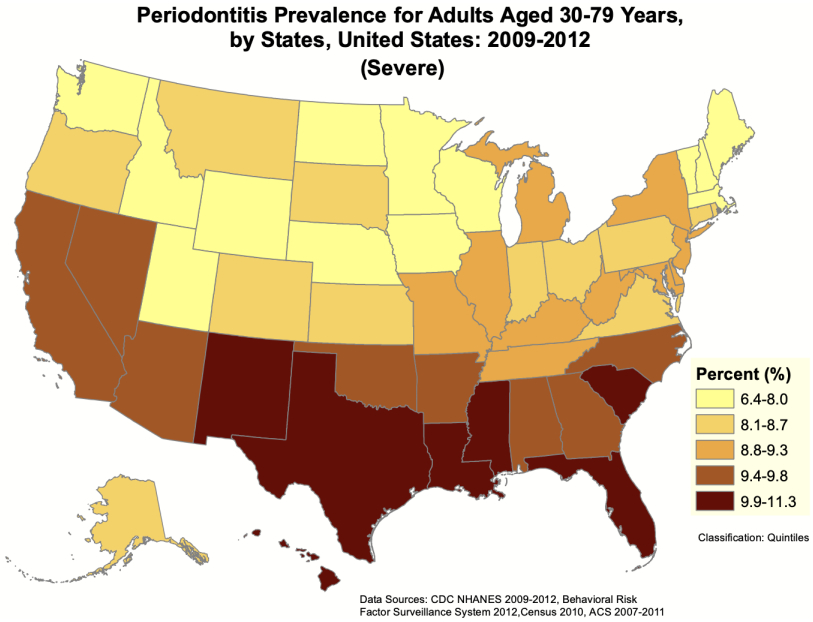

Figure 9 | Geographic distribution of the estimated prevalence of severe periodontitis in US adults. The southeastern and southwestern states are heavily affected by periodontitis, as is Hawaii (Adapted from Eke et al. (2020) ©, used under the CC-BY license (https://creativecommons.org/licenses/by/3.0/)).

Overall, periodontitis is considered a relevant public health issue in the US, and the active decrease of periodontitis cases is a present-day top priority (Healthy People 2020).

3. PERIODONTITIS AND PARKINSON'S DISEASE INTERPLAY

The motor degeneration PD patients face tends to affect their ability to perform everyday life activities, such as swallowing and the performance of their oral hygiene habits (Hashioka et al., 2019; Kalia & Lang, 2015; Poewe et al., 2017). Also, the frequency of oral hygiene care may be compromised due to the cognitive impairment PD patients might experience (Hashioka et al., 2019).

Furthermore, although PD is normally associated with sialorrhea, the daily intake of numerous medications (mostly of PD) may diminish the salivary flow rate and the quality of the secreted saliva, possibly contributing to an impaired oral condition (Kaur et al., 2016).

Therefore, it has been speculated that PD clinical signs and symptoms have a negative effect in the periodontium, which causes the deterioration of patient's oral status and can ultimately lead to the development and progression of periodontal disease (Kaur et al., 2016).

Although PD individuals are supposably at high risk of developing periodontitis, the oral status in people with PD remains poorly studied, even with a number of observational studies reporting weakened oral health status and reduced oral hygiene care in PD patients (Einarsdóttir et al., 2009; Hanaoka & Kashihara, 2009; Nakayama et al., 2004; Schwarz et al., 2006; van Stiphout et al., 2018). The periodontal assessment performed in these studies was inadequate because partial mouth strategies were employed that increases the risk of reporting bias (Botelho et al., 2019; Machado et al., 2018).

Accordingly, assessing the periodontal status in PD patients with a consistent periodontal examination method is of the utmost importance, as well as the impact of self-perceived oral-health related quality of life (OHRQoL) and xerostomia in the quality of life of PD individuals.

4. AIMS

With all being said, the aim of the present study is twofold:

- To investigate the association of periodontitis and PD, along with self-reported quality of life and xerostomia (Section II);
- To investigate whether periodontitis might cause systemic changes in PD patients via blood and biochemical levels (Section III).

4.1. Parkinson's Disease, Periodontitis and Patient-Related Outcomes: A Cross-Sectional Study

Firslty, to address the primary aim of the study, we proposed the PECO question: "What is the prevalence of periodontitis in PD patients?" (A), in order to evaluate the periodontal status of people with PD through the following statements:

- P (Population): PD patients;
- E (Exposure): Periodontitis;
- C (Control): PD patients without periodontitis;
- O (Outcome): Prevalence of periodontitis.

Additionally, to assess the relationship between periodontal clinical measures and clinical characteristics of PD, we proposed another PECO question: "In PD patients is periodontitis associated with worse levels of PD clinical characteristics?" (B), with the following statements:

- P (Population): PD patients;
- E (Exposure): Periodontitis;
- C (Control): No periodontitis;
- O (Outcome): PD clinical characteristics levels.

Lastly, we proposed the PECO question: "In PD patients how does the quality of life in PD correlate with self-perceived levels of OHRQoL and self-perceived levels of xerostomia?" (C), serving the primary aim of the study with the following statements:

- P (Population): PD patients;
- E (Exposure): Quality of life in PD;
- C (Control): Not applicable;
- O (Outcome): Self-perceived levels of OHRQoL and self-perceived levels of xerostomia.

4.2. Relationship between Blood and Standard Biochemistry Levels with Periodontitis in Parkinson's Disease Patients: Data from the NHANES 2011–2012

To assess the presence of altered biomarkers in PD individuals with periodontitis, we advanced the secondary aim of the study with the PECO question: "Are there altered blood and standard biochemical surrogates in PD patients diagnosed with periodontitis and PD patients without periodontitis?" (D), with the statements:

- P (Population): PD patients;
- E (Exposure): Periodontitis;
- C (Control): PD patients without periodontitis;
- O (Outcome): Altered blood and standard biochemical surrogates.

II. PARKINSON'S DISEASE, PERIODONTITIS AND PATIENT-RELATED OUTCOMES: A CROSS-SECTIONAL STUDY

Adapted from:

Lyra, P.; Machado, V.; Proença, L.; Domingos, J.; Godinho, C.; Mendes, J.J.; Botelho, J. Parkinson's Disease, Periodontitis and Patient-Related Outcomes: A Cross-Sectional Study. *Medicina* **2020**, *56*, 383.

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Parkinson's Disease, Periodontitis and Patient-Related Outcomes: A Cross-Sectional Study

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Abstract: *Background and objectives:* People with Parkinson's disease (PD) may be at risk of having bad periodontal status. A consistent periodontal examination is critical to investigate how it impacts on PD quality of life. We aimed to assess the periodontal status of people with PD, and its association with quality of life and self-perceived xerostomia. *Materials and Methods:* To this end, from February to March 2020, we consecutively enrolled 28 PD individuals, and motor and non-motor symptoms of PD were assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). We performed full-mouth periodontal examination and gathered information on self-perceived quality of life in PD, oral health impact profile (OHIP-14) and xerostomia. *Results:* The prevalence of periodontitis was 75.0% and most cases were identified as severe (46.4%). Upper extremity rigidity, hand posture and kinetic tremors were significantly correlated with worse periodontal status. PDQ-8 showed to be correlated with self-perceived oral health-related quality of life and xerostomia levels. *Conclusions:* This group of people with PD had a high prevalence of periodontitis. Deteriorated levels of the upper extremities in advanced stages of PD were associated with worse periodontal status and hygiene habits. Quality of life in PD appears to be associated with self-perceived OHRQoL and xerostomia.

Keywords: Parkinson's disease; movement disorders; Parkinsonian disorders; oral health; periodontitis; periodontal diseases; quality of life

1. Introduction

Parkinson's disease (PD) is one of the most frequent, disabling and progressive neurodegenerative conditions [1–3]. It is a growing condition, especially in a globally aged population [4]. PD prevalence increases with age, affecting 1% of individuals over 60 and up to 4% in higher age groups [3]. PD is clinically characterized by a multitude of motor and nonmotor features, heavily affecting patient's quality of life [5]. PD motor symptoms such as resting tremor, rigidity and bradykinesia are all commonly targeted by the standard available therapies, which include dopaminergic drugs and functional neurosurgery [1,5]. Other symptoms may include loss of balance, gait dysfunction, swallowing and

speech impairment, autonomic disturbances and cognitive impairments [5]. PD progression may interfere with daily activities, among them oral hygiene habits, increasing the risk for oral diseases.

Periodontitis is a chronic, polymicrobial and inflammatory disease of the oral cavity, which is characterized by chronic inflamed gums and bone destruction surrounding the teeth due to a dysbiotic microflora [6,7]. Periodontitis is one of the most prevalent diseases, being its severe form the 6th most prevalent condition worldwide [8,9]. The onset and progression are triggered by inadequate oral hygiene behaviours and motor hygiene impairments, becoming more prevalent with age [10,11]. Periodontitis is associated with masticatory dysfunction and impacts negatively on the patient's oral health-related quality of life (OHRQoL) [12], which can be restored after successful periodontal treatment [13].

Periodontitis has been consistently associated with a number of chronic diseases, such as diabetes mellitus [14], cardiovascular diseases [15,16], neurological diseases such as Alzheimer's [17], rheumatoid arthritis [18], solid organ transplants [13] and stress [19]. Nevertheless, the oral status in people with PD is poorly studied. A number of observational studies reported weakened oral health status and reduced oral hygiene care in PD patients [20–23], although the periodontal assessment performed in these studies was inadequate because partial mouth strategies were employed that increases reporting bias risk [13,24]. Furthermore, data from Taiwan's National Health Insurance Research Database revealed that periodontal inflammatory disease may increase the risk of developing PD [25], though clinical definitions followed the ninth revision of the International Classification of Diseases (ICD-9-CM) and lack scientific robustness. Therefore, assessing the periodontal status in PD patients with a consistent periodontal examination method is of the utmost importance. As well, the impact of self-perceived oral-health related quality of life (OHRQoL) and xerostomia in the quality of life of PD individuals have never been investigated within this purpose.

Our primary aim was to investigate the periodontal status of people with PD. Secondly, we assess the relationship between periodontal clinical measures and clinical characteristics of PD and how quality of life in PD correlates with self-perceived levels of OHRQoL and xerostomia.

2. Experimental Section

2.1. Study Design

We recruited individuals from the Portuguese Parkinson's Disease Patient Association (Lisbon branch), between February and March 2020. Inclusion criteria were as follows: people with PD and other parkinsonisms. Exclusion criteria included: unwilling to participate; edentulous; cerebrovascular disease; periodontal treatment during the past six months; and treatment with immunosuppressive chemotherapy. All participants were taking dopaminergic medications, and L-DOPA equivalent doses were calculated for each patient [26].

The study was approved on February 2020 by the Egas Moniz Ethics Committee (Institutional Review Board, protocol 824), and all participants gave informed written consent to the study procedures. We followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (Supplementary Table S1) [27].

2.2. PD Assessment

Motor and non-motor symptoms were assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [28], up to one month prior to the periodontal evaluation. Patient's motor impairment severity was assessed by the Modified Hoehn and Yahr (H and Y) scale [29]. We categorized H and Y stages as mild (1–2.5) and moderate to severe (3.0–5.0). To assess health-related quality of life (HRQoL), we used the Portuguese version of the eight-item PD Questionnaire (PDQ-8) [30,31]. The PDQ-8 is calculated from eight items representing eight different dimensions. All items are scored on a five-point Likert scale ranging from 0 ("never") to 4 ("always"). The summed score is divided by total possible score and given in a percentage score out of 100, and higher scores indicate worse HRQoL.

2.3. Periodontal Examination and Diagnosis

Full-mouth periodontal examination was performed using a manual periodontal North Carolina probe by two trained and calibrated examiners (VM and JB) (Hu-Friedy; Chicago, IL, USA).

The following parameters were circumferentially measured at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual and distolingual) in all teeth (except third molars, implants and retained roots): plaque index (PI) [32], gingival recession (REC), periodontal pocket depth (PPD) and bleeding on probing (BoP). PPD referred to the distance from the free gingival margin to the bottom of the pocket. REC was the distance from the cementoenamel junction (CEJ) to the free gingival margin and this assessment was assigned a negative sign if the gingival margin was located coronally to the CEJ. CAL was the algebraic sum of REC and PD measurements for each site. The measurements were rounded to the lowest whole millimetre (mm). Tooth mobility was further appraised [33].

Intra-class correlation coefficient (ICC) values were 0.98 and 0.99, for CAL and PPD, respectively. The intra-examiner ICC ranged from 0.97 to 0.99, for both PPD and CAL.

Periodontitis cases were defined if: interdental CAL ≥ 2 non-adjacent teeth, or Buccal or Oral CAL ≥ 3 mm with PD > 3mm is detectable at ≥ 2 teeth [34]. Then, periodontitis staging was defined according to the 2018 World Consensus. Staging was defined as:

- CAL at site of greatest loss of 1–2 mm—Stage 1 or mild;
- CAL at site of greatest loss of 3–4 mm—Stage 2 or moderate;
- and, CAL at site of greatest loss of ≥ 5 mm—Stage 3/4 or severe/advanced.

2.4. Sociodemographic and Oral Health Covariates

By means of a structured questionnaire, we collected information regarding: (1) gender, age, marital status, educational level, occupation; (2) smoking habits; (3) oral hygiene-related behaviors (toothbrush type, toothbrushing frequency, and interproximal cleaning); (5) attitudes and awareness towards oral health; and (6) diabetes mellitus (DM).

We categorically registered Education levels according to the 2011 International Standard Classification of Education (ISCED-2011): elementary (ISCED 1–2 levels), middle (ISCED 3–4 levels), higher (ISCED 5–8 levels). Smoking status was defined as non-smoker (category 0), former smoker (category 1); or active smoker (category 2). DM was based on insulin regimen and/or oral hypoglycaemic medications and was confirmed through haemoglobin A1c (HbA1c).

2.5. OHRQoL and Xerostomia Self-Perception Questionnaires

Before the periodontal examination, we used the Portuguese versions of the Oral Health Impact Profile-14 (OHIP-14-PT) [35] and the Summated Xerostomia Inventory (SXI-5) to assess OHRQoL and dry mouth symptoms, respectively.

We measured OHRQoL through the Portuguese version of the Oral Health Impact Profile-14 (OHIP-14-PT) [35], a 14 questions tool with seven domains (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap) of OHRQoL. Each question is scored categorically (0 = never, 1 = hardly ever, 2 = occasionally, 3 = fairly often and 4 = very often) [36]. A higher score indicates poorer OHRQoL.

Dry mouth perception was evaluated through the Portuguese version of the Shortening the Xerostomia Inventory (SXI-5), a five-question tool where each question is scored by 0 = never, 1 = occasionally and 2 = frequently. The scores from the five questions are summed, with the result representing the degree of xerostomia the subject feels [37].

2.6. Statistical Analysis

The total scores of PDQ-8, OHIP-14 and SXI-5 were calculated and their correspondent descriptive measures, mean and standard deviation (SD), were computed. For analysis purposes, these scores were considered as continuous variables. The data analyses were conducted for all participants and

for sample subsets, according to the patient's motor impairment severity, given by the Modified H and Y scale. The Mann–Whitney test was used to compare the periodontal clinical measures between these subgroups. Spearman's rank-order correlation coefficient (rho) was used to analyze the correlation among questionnaires scores (MDS-UPDRS, PDQ-8, OHIP-14 and SXI-5) and between these and the periodontal clinical variables. Data were analysed using IBM SPSS Statistics, v. 25, (Armonk, New York, NY, USA). A level of significance of 5% was considered in all inferential analyses.

3. Results

3.1. Sample Description

From a total of 33 individuals with PD, five participants were excluded because they were edentulous. A final sample of 28 participants were enrolled, with a mean age of 72.3 (±8.1) years, meeting the required inclusion criteria (Table 1). The group was composed mostly by men (82.1%), with idiopathic PD (82.1%) and diagnosed with moderate to severe patient's motor impairment (H and Y) (64.3%). The prevalence of periodontitis was high (75.0%), and the majority were severe cases (stage III) (46.4%). On average, the participants had 12 teeth missing, and one tooth with pathological mobility. The average percentage of plaque and gum inflammation in the whole mouth were 37.0% (±29.4) and 19.3% (±21.1), respectively. The majority of patients report the use of a manual toothbrush (75.0%) and a last dental visit within the last 6 months (64.3%).

Table 1. Participant characteristics.

Variable	Result
Age, mean (SD) (years)	72.3 (± 8.1)
Age Range (min-max) (years)	57–92
Gender, *n* (%)	
Female	5 (17.9)
Male	23 (82.1)
Education, *n* (%)	
Elementary	6 (21.4)
Middle	12 (42.9)
Higher	10 (35.7)
Hoehn & Yahr Scale, *n* (%)	
Mild (1 to 2.5)	10 (35.7)
Moderate to Severe (3 to 5)	18 (64.3)
Parkinson's Disease, *n* (%)	
Idiopathic	23 (82.1)
Atypical	5 (17.9)
Periodontal status, *n* (%)	
Healthy	7 (25.0)
Periodontitis	21 (75.0)
Stage 1—Mild	2 (7.1)
Stage 2—Moderate	6 (21.4)
Stage 3—Severe	13 (46.4)

Table 1. *Cont.*

Variable	Result
Teeth with mobility, mean (SD)	1 (2)
Missing teeth, mean (SD)	12 (7)
Plaque Index, mean (SD) (%)	37.0 (29.4)
BoP, mean (SD) (%)	19.3 (21.1)
Mean PPD, mean (SD) (mm)	2.1 (0.8)
Mean CAL, mean (SD) (mm)	3.2 (1.8)
Mean REC, mean (SD) (mm)	1.2 (1.2)
Toothbrush type, *n* (%)	
Manual Electric	21 (75.0) 7 (25.0)
Last dental visit, *n* (%)	
< 6 months 6–12 months > 12 months	18 (64.3) 4 (14.3) 6 (21.4)
Toothbrushing	
Once a day Twice or more a day	9 (32.1) 19 (67.9)
Interproximal cleaning	
Never No Often/Yes	9 (32.1) 8 (28.6) 11 (39.3)
Smoking habits, *n* (%)	
Never Former smoker Active smoker	16 (57.1) 7 (25.0) 5 (17.9)
Diabetes Mellitus, *n* (%)	**3 (10.7)**

BoP—Bleeding on Probing; CAL—Clinical Attachment Loss; PD—Probing Depth; REC—Recession; SD—Standard Deviation.

3.2. Relationship between PD Staging and Periodontal Status

We found no differences between PD stages (Table 2). Mild PD presented lower prevalence of severe periodontitis than more advanced PD stages (Table 3). An increased number of missing teeth was associated with a worsening of speech and eating tasks (Table 4). Further, worse periodontal measures (PI, BoP and mean PPD) were correlated with deteriorated levels of rigidity and kinetic tremors of the upper extremities (Table 4). Likewise, a more depressive state and hands postural tremors also were correlated with worse levels of BoP.

Table 2. Comparison of age, PDQ-8, OHIP-14, SXI-5 total scores and periodontal clinical measures according to PD progression, based on the Hoehn and Yahr (H and Y) scale.

Variable	PD Progression		*P*-Value [#]
	Mild (*n* = 10)	Moderate to Severe (*n* = 18)	
Variable, mean (SD)	70.4 (5.7)	73.3 (9.1)	0.382
Age (years)	5.9 (3.0)	10.6 (7.2)	0.191
PDQ-8 (total score)	7.1 (7.2)	11.0 (12.6)	0.436
OHIP-14 (total score)	7.8 (1.9)	7.7 (2.2)	0.759
SXI-5 (total score)	9.5 (7.9)	13 (7.1)	0.191
No. of missing teeth	31.6 (23.4)	39.9 (32.6)	0.524
Plaque Index (%)	23.9 (32.4)	16.8 (11.5)	0.796
BoP (%)	2.2 (1.2)	2.0 (0.5)	0.382
Mean PPD (mm)	3.3 (2.3)	3.2 (1.6)	0.356
Mean CAL (mm)	1.1 (1.2)	1.2 (1.2)	0.724
Mean REC (mm)	70.4 (5.7)	73.3 (9.1)	0.382

[#] Mann-Whitney test, $p < 0.05$.

Table 3. Periodontal status according to PD progression.

Periodontal Status, *n* (%)	PD Progression	
	Mild (*n* = 10)	Moderate to Severe (*n* = 18)
Healthy	3 (30.0)	4 (22.2)
Mild Periodontitis	2 (20.0)	0 (0.0)
Moderate Periodontitis	1 (10.0)	5 (27.8)
Severe Periodontitis	4 (40.0)	9 (50.0)

Table 4. Correlation between MDS-UPDRS items and periodontal clinical measures.

MDS-UPDRS	No. of Missing Teeth	Plaque Index (%)	BoP (%)	Mean PPD (mm)	Mean CAL (mm)	Mean REC (mm)
1.1 (Cognitive Impairment)	0.072	−0.152	−0.199	−0.321	−0.117	−0.071
1.3 (Depressed mood)	0.234	0.069	0.394 *	0.132	0.280	0.263
1.5 (Apathy)	0.350	−0.066	−0.040	−0.163	0.098	0.203
2.1 (Speech)	0.419 *	0.005	0.101	−0.098	0.044	−0.001
2.2 (Saliva and drooling)	−0.044	0.060	0.175	−0.037	−0.202	−0.256
2.3 (Chewing and swallowing)	0.319	0.137	0.126	0.023	0.225	0.178
2.4 (Eating tasks)	0.404 *	−0.141	0.019	−0.098	0.076	0.046
2.6 (Hygiene)	−0.003	−0.127	0.002	−0.121	−0.013	−0.096
2.7 (Writing)	0.185	−0.055	−0.014	−0.040	0.062	−0.004
2.10 (Tremor)	0.004	0.220	0.269	0.266	0.544	−0.111
3.3. (Rigidity UE)	0.180	0.387 *	0.382 *	0.452 *	0.230	0.004
3.4 (Finger tapping)	0.252	0.145	0.105	0.146	0.288	0.200
3.5 (Hand movements)	0.059	0.080	0.049	0.136	0.049	−0.083
3.6 (Pronation)	0.127	0.013	−0.127	−0.027	0.062	−0.009
3.15 (Hands postural tremor)	0.102	0.060	0.451 *	0.235	0.212	0.120
3.16 (Hands kinetic tremor)	−0.100	0.559 **	0.541 **	0.431 *	0.213	0.018
3.17 (Rest tremor amplitude UE)	−0.134	0.188	0.057	0.258	0.119	0.061
3.17e (Rest tremor amplitude Lip/jaw)	0.263	0.012	0.143	0.048	0.107	0.131
3.18 (Constancy of rest tremor)	−0208	0.128	0.100	0.208	−0.038	−0.123

Spearman correlation, * $p < 0.05$, ** $p < 0.01$.

3.3. PD Quality Of Life Impact on Ohrqol and Xerostomia Self-Perception

Spearman's rank-order correlation coefficient (rho) was used to assess the correlation between total and each domain of PDQ-8 and OHIP-14 (Table 5). All significant correlations were positive, that is the worsening of a domain is associated with worse levels in the other domain. Worse social support was correlated with worse overall OHIP-14 (rho = 0.459, $p < 0.05$), psychological discomfort (rho = 0.518, $p < 0.01$) and psychological disability (rho = 0.534, $p < 0.01$). The deterioration of cognition was correlated with worse psychological discomfort (rho = 0.401, $p < 0.05$) and handicap levels (rho = 0.416, $p < 0.05$) in OHIP-14. Likewise, worse levels of mobility and activities of daily living were correlated with worse levels of psychological disability (rho = 0.445, $p < 0.05$) and handicap (rho = 0.431, $p < 0.05$), respectively.

Table 5. Correlation between Parkinson's Disease Questionnaire (PDQ-8) with Oral Health Impact Profile (OHIP-14) and Summated Xerostomia Inventory-5 (SXI-5) scores, total and per domain.

Variable	PDQ−8 Total	Mobility	ADLs	Emotional Well-Being	Stigma	Cognition	Communication	Bodily Discomfort
OHIP−14 Total	0.278	0.192	0.179	0.000	−0.004	0.459*	0.342	0.116
Functional Limitation	0.243	0.171	0.301	−0.064	−0.035	0.208	0.361	0.148
Psychological Pain	0.096	0.196	−0.035	−0.064	−0.062	0.120	0.183	0.210
Psychological Discomfort	0.283	0.205	0.123	0.275	0.265	0.518 **	0.401 *	−0.022
Physical Disability	0.260	0.197	0.350	0.196	0.111	0.271	0.307	−0.060
Psychological Disability	0.322	0.445 *	0.119	0.004	0.034	0.534 **	0.194	0.154
Social Disability	0.291	0.231	0.291	−0.024	0.023	0.320	0.254	0.272
Handicap	0.317	0.222	0.431*	0.223	0.223	0.007	0.416 *	0.152
SXI−5 Total	0.291	0.183	−0.037	0.068	0.257	0.197	0.318	0.076
Dry mouth	0.121	0.180	−0.031	0.055	0.163	0.127	0.206	−0.034
Difficulty eating dry foods	0.426 *	0.328	0.004	0.069	0.255	0.224	0.270	0.220
Dry mouth when eating meal	−0.093	−0.056	0.025	−0.042	−0.101	0.159	0.109	−0.067
Difficulties swallowing certain foods	0.208	0.087	0.087	0.344	0.149	0.060	0.460 *	−0.039
Dry lips	0.209	0.150	−0.030	−0.201	0.229	0.186	0.152	0.062

ADLs—Activities of Daily Living. Spearman correlation, * $p < 0.05$, ** $p < 0.01$.

The correlation between PDQ-8 and SXI-5 scores, considering total and respective domains/items, was also investigated (Table 5). Higher difficulties in eating dry foods were significantly correlated with worse overall quality of life (rho = 0.426, $p < 0.05$) and bodily discomfort (rho = 0.450, $p < 0.05$). Additionally, self-perceived deteriorated cognition was related to difficulties swallowing certain foods (rho = 0.460, $p < 0.05$).

4. Discussion

To the best of our knowledge, this study is the first to consistently appraise the periodontal status and clinical measures of interest in a group of PD individuals. Our results show that periodontitis and gum inflammation were highly prevalent in this group of people with PD, and about a third of the population had moderate and severe forms of periodontitis.

This prevalence might be explained by the age, the number of males and the smoking habits in the included sample, recognized risk factors for periodontitis based on a recent representative study in this region [19]. In other words, because it is a very aged sample the existence of gum disease may be more increased. Likewise, men have more prevalence of periodontitis than women, and active and former smokers have much more risk to its development (OR = 3.76) [19]. This prevalence is

in line with previous studies, though they have used unsuited periodontal clinical methods [20–23]. Additionally, the prevalence of periodontitis in this age-group is in agreement with previous studies developed in this region, where these age groups have high levels of periodontal disease [19,38,39].

Nevertheless, there are a number of other important characteristics that may elucidate the increased gum inflammation observed, which stands out the hygiene habits. This particular population has good toothbrushing frequency (with a regimen of twice or more per day) and regular dental visits, however the majority does not perform interdental hygiene, and this fact increases the likelihood of gum inflammation [40]. Importantly, we anticipate that interdental cleaning is a major challenge for PD individuals due to the characteristics of the disease itself (fine motor issues, cognitions deficits), thus home interdental cleaning (such as oral irrigation) and electric toothbrushes should be recommended to bypass common fine motor difficulties [41].

Interestingly, the comparison of PD staging through the modified H and Y scale did not find any marked difference between the groups, but the sample was limited and may represent a restrictive characteristic. Using the MDS-UPDRS, deteriorated levels of kinetics tremor, postural tremor and rigidity of the upper extremities were associated with increased plaque accumulation, gum bleeding and, as consequence, deepest periodontal pockets. Comprehensively, the progression of PD may ultimately result in impaired oral hygiene habits, and this is the first study to prove the likelihood of this association. Additionally, severe stages of PD had more teeth missing, and our data confirmed that the more teeth lost the worse perception of speech and eating functions in PD. The number of missing teeth was a relevant measure in this analysis, since severe stages of PD had less teeth presence, though this difference was not significant. Our data show that the more teeth lost, the worse the speech and eating ability in PD.

Our findings also corroborate the premise that perceived quality of life in PD might be interconnected with OHRQoL and xerostomia. On the one hand, psychological domains (psychological discomfort and disability) of OHIP-14 and social support from PDQ-8 had the strongest relation, and further investigations should better explore this interaction. Regarding self-perceived dry mouth, more difficulties eating dry foods influenced PD quality of life and caused more bodily discomfort, while worse cognition levels were associated with difficulties swallowing certain foods. The presence of swallowing impairment in PD individuals is not new and has been previously reported [20]. Others, PD patients have sialorrhea as a characteristic symptom, although dry mouth in this type of older population is frequent due to polymedication [19]. Additionally, xerostomia is poorly rated on the MDS-UPDRS scale and, therefore, the SXI may be a complement in PD clinical follow-up. All in all, the self-reported instruments used are valid for future studies involving PD and oral health.

The interplay between periodontitis and systemic inflammation is well documented [42,43]. A recent systematic review confirmed that periodontal bacterial load and gum inflammatory burden can intensify the neuroinflammation in the central nervous system in Alzheimer's disease (AD), favoring the onset and progression of this neurodegenerative condition [44]. Accumulating evidence has shed light on how neuroinflammation can play a key role on the PD pathogenesis and neurodegeneration [45,46]. As a potential contributor to neuroinflammation, periodontitis can cause a subclinical inflamed state in PD patients and may negatively alter the neuronal environment as in AD as previously proposed [25,47,48], however, this is merely speculative at this stage and shall be investigated in the future.

The present study had some limitations. The small size of the group is the main shortcoming, and for that reason the results should be interpreted with caution, as this limits the validity of these results and warrants future confirmation with prospective studies, since there are inherent biases in cross-sectional studies, such as selection bias. However, these studies comprise two months of inclusion and follows the rigorous STROBE guideline. This study did not ascertain the technique and the brushing efficiency of the participants along with the motor assessment in PD, a factor that should be considered in future studies. Second, we did not consider the patient's dominant arm during tooth brushing, which led us to count the measures of the upper limbs as the average. In the future, studies

shall consider the influence of PD progression on the dominant arm of the patient's adaptive behaviour, for example changing arms during oral hygiene.

This is the first study to use appropriate periodontal assessment methods. The measures of interest were assessed by trained and calibrated examiners and the most up-to-date definitions of PD and periodontitis were used [47], making these results current and of high scientific interest. As an observational study, this investigation is unable to estimate a causality between PD and gum disease as well the impact of particular clinical features of PD on the progression of periodontitis and vice versa.

5. Conclusions

Periodontitis was highly prevalent in this group of people with PD. Deteriorated levels of the upper extremities in advanced stages of PD influence the periodontal status and hygiene habits. Quality of life in PD appears to be associated with self-perceived OHRQoL and xerostomia. Future studies should consider the impact of periodontitis on the quality of life of PD and the potential inflammatory burden of periodontitis.

Supplementary Materials: The following are available online at http://www.mdpi.com/1010-660X/56/8/383/s1, **Table S1**. STROBE Statement—Checklist.

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III. RELATIONSHIP BETWEEN BLOOD AND STANDARD BIOCHEMISTRY LEVELS WITH PERIODONTITIS IN PARKINSON'S DISEASE PATIENTS: DATA FROM THE NHANES 2011–2012

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Relationship between Blood and Standard Biochemistry Levels with Periodontitis in Parkinson's Disease Patients: Data from the NHANES 2011–2012

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Abstract: People with Parkinson's Disease (PD) are associated with the presence of periodontitis. We aimed to compare blood and standard biochemical surrogates of PD patients diagnosed with periodontitis with PD individuals without periodontitis. This retrospective cohort study used a sample from the National Health and Nutrition Examination Survey (NHANES) 2011–2012 that underwent periodontal diagnosis (n = 3669). PD participants were identified through specific PD reported medications. Periodontitis was defined according to the 2012 case definition, using periodontal examination data provided. Then, we compared blood levels and standard chemical laboratory profiles of PD patients according to the presence of periodontitis. Multivariable regression was used to explore this dataset and identify relevant variables towards the presence of periodontitis. According to the medication report, 37 participants were eligible, 29 were secure and 8 were unsecure PD medications regimens. Overall, PD cases with periodontitis presented increased levels of White Blood Cells (WBC) (p = 0.002), Basophils (p = 0.045) and Segmented neutrophils (p = 0.009), and also, lower levels of Total Bilirubin (p = 0.018). In the PD secure medication group, a significant difference was found for WBC (p = 0.002) and Segmented neutrophils (p = 0.002) for the periodontitis group. Further, WBC might be a discriminating factor towards periodontitis in the global sample. In the secure PD medication, we found gender, segmented neutrophils and Vitamin D2 to be potential discriminative variables towards periodontitis. Thus, periodontitis showed association with leukocyte levels alterations in PD patients, and therefore with potential systemic changes and predictive value. Furthermore, Vitamin D2 and gender showed to be associated with periodontitis in with secure medication for PD. Future studies should assess in more detail the potential systemic repercussion of the presence of periodontitis in PD patients.

Keywords: Parkinson's disease; movement disorders; periodontitis; periodontal disease; hematologic tests; Vitamin D; oral health

1. Introduction

Periodontitis is a chronic inflammatory condition that targets the supporting structures of the teeth [1]. Dental plaque build-up, periodontopathic microbial specificity and the host immune response

can collectively be considered as periodontitis etiology factors [2]. The presence of periodontal pockets, inflamed gingiva and alveolar bone loss in certain teeth or tooth sites clinically characterizes periodontitis, which can ultimately result in tooth loss [3]. Apart from its effects in the oral cavity, periodontitis repercussions also instigate slight systemic inflammation, which end up setting off or aggravating known chronic inflammatory diseases, such as cardiovascular diseases including high blood pressure [4], diabetes mellitus [5], rheumatoid arthritis [6] Furthermore and Alzheimer's Disease [7–9]. Being one of the most prevalent conditions of the adult population worldwide, periodontitis frequency seems to be higher in the male gender while also increasing with age [10].

Parkinson's disease (PD) is the second most frequent slowly progressive neurodegenerative condition that mostly affects the central nervous system [11]. Still with elusive causal factors to date, sporadic PD appears to be the conjugation of both genetic and environmental risk factors [12,13]. Being a heterogeneous disorder, PD clinical phenotype is characterized by a broad range of motor and non-motor symptoms, differing in onset age (which is most common at 65–70 years of age) and disease progression rates (faster in late-onset forms) [11,14]. PD classical motor features include resting tremor, muscular rigidity and bradykinesia, while a wide number of other motor and non-motor features contribute to PD disability and the deterioration of PD patients' overall quality of life [15]. Dopaminergic drugs like levodopa and functional neurosurgery are still standard treatments, although tending to be a universal solution to a non-uniform disease [16,17]. PD increases with age and tends to affect more men than women [18–20]. In an overall aging population, PD cases are expected to duplicate in the next couple decades [17,21].

To date, the relationship between PD and periodontitis stands with PD associated motor impairments and cognitive decline that compromises oral hygiene habits and causes the deterioration of patient's oral status [22]. Consequently, PD individuals seem to be at high risk of developing periodontitis [23–27]. Furthermore, it has been proposed that chronic neuroinflammation secondary to periodontitis systemic outcomes may lead to PD pathogenesis, initiation and progression [8,22,28]. However, to the best of our knowledge, the systemic repercussion of the presence of periodontitis on blood and biochemical surrogates on PD has never been investigated. Our hypothesis is that, as an infection, periodontitis in PD subjects might result in an increase of the leukocyte levels, though for the remaining levels this is still undetermined.

Therefore, our primary aim was to compare blood and standard biochemical levels between periodontitis and non-periodontitis cases among Parkinson's disease patients. Additionally, we aimed to evaluate if such changed biomarkers might contribute to predict the presence of periodontitis in PD patients.

2. Material and Methods

2.1. Population

The National Health and Nutrition Examination Survey (NHANES) 2011–2012 data is a representative multistage probability sample of non-institutionalized U.S. civilians survey to assess the health status through the Centers for Disease Control and Prevention (CDC) and Prevention National Center for Health Statistics (NCHS) website at https://www.cdc.gov/nchs/nhanes/index.htm. In this retrospective cohort study, periodontal examination data from the NHANES 2011–2012 was extracted. Our analysis deemed the following exclusion criteria: younger than 18 years of age; participants with medical exclusion from periodontal exam; non-complete periodontal status and edentulous patients.

Oral health data collection protocols were approved by the CDC, NCHS Research Ethics Review Board, Atlanta (USA), and all participants gave written informed consent. All the examinations were conducted in a mobile examination center (see in detail in [29]).

2.2. PD Definition

PD cases were confirmed through specific PD reported medications according to the NHANES database. In this way, patients reporting the use of Benztropine, Carbidopa, Levodopa, Ropinirole, Methyldopa, Entacapone, Cabergoline, Orphenadrine and Pramipexole were categorized as PD cases [30,31]. Then, we divided participants as PD cases according to secure PD medication (Benztropine, Carbidopa, Levodopa, Ropinirole, Methyldopa and Entacapone) [30,31] and unsecure PD medication (Cabergoline, Orphenadrine and Pramipexole) [30–34]. The unsecure PD group was defined because Cabergoline is used to treat high levels of prolactin hormone [32], Orphenadrine is used to treat muscle spasms in musculoskeletal conditions [33] and Pramipexole is also used to treat restless legs syndrome (RLS) [34].

2.3. Periodontal Clinical Examination

Periodontitis was defined as a minimum of 2 or more sites with clinical attachment loss (CAL) ≥ 3 mm and a periodontal pocket depth (PPD) ≥ 4 mm or one site with PPD ≥ 5 mm, as described by Eke et al. (2012). Data from the Periodontal Examination of NHANES 11–12 were treated through appropriate algorithms in Microsoft Office (MO) Excel to render the respective periodontal diagnosis. From this, we were able to render the number of missing teeth.

2.4. Demographics Characteristics

The demographic variables included were age, gender, smoking status and number of teeth. From the self-reported questionnaire, we categorized smoking status as current smoker (smoked more than 100 cigarettes and currently smoking), former smoker (smoked more than 100 cigarettes and currently not smoking) and non-smoker (never smoked). Diabetes mellitus was categorized as "yes" or "no" according to the self-reported questionnaire. High blood pressure was categorized according to previous medical confirmation of high blood pressure and if taking prescription for hypertension.

2.5. Blood and Standard Biochemical Profile Levels

Blood levels data included White Blood Cell (WBC) count (10^9/L), percentage of Lymphocyte (%), percentage of Monocyte (%), percentage of Segmented Neutrophils (%), percentage of Eosinophils (%), percentage of Basophils (%), Lymphocyte (10^9/L), Monocyte (10^9/L), Segmented neutrophils (10^9/L), Eosinophils (10^9/L), Basophils (10^9/L), Red Blood Cell (RBC) count (million cells/uL), Hemoglobin (g/dL), Hematocrit (%), Mean Cell Volume (MCV) (fL), Mean Cell Hemoglobin (MCH) (pg), Mean Cell Hemoglobin Concentration (MCHC) (g/dL), Red Cell Distribution (RCD) width (%), Platelet count (10^9/L), Mean Platelet Volume (MPV) (fL).

For the Standard Biochemical Profile levels we included Albumin (g/dL), Alanine aminotransferase (ALT) (U/L), Aspartate aminotransferase (AST) (U/L), Alkaline phosphatase (AP) (U/L), Blood Urea Nitrogen (mg/dL), Total Calcium (mg/dL), Creatine Phosphokinase (CPK) (IU/L), Cholesterol (mg/dL), Bicarbonate (mmol/L), Creatinine (mg/dL), Gamma Glutamyl Transferase (GGT) (U/L), Glucose, Serum (mg/dL), Iron (refrigerated) (ug/dL), Lactate Dehydrogenase (LDH) (U/L), Phosphorus (mg/dL), Total Bilirubin (mg/dL), Total Protein (g/dL), Uric Acid (mg/dL), Sodium (mmol/L), Potassium (mmol/L), Chloride (mmol/L), Osmolality (mmol/Kg), Globulin (g/dL), Triglycerides (mg/dL), 25-hydroxyvitamin D2 (25OHD2) (nmol/L), 25-hydroxyvitamin D3 (25OHD3) (nmol/L).

2.6. Data Management and Analysis

Data were uploaded through SAS Universal Viewer for Windows and handled with MS Excel. For each periodontal case definition, specific MS Excel datasets were derived in order to formulate appropriate algorithms to define the periodontal status according to the case definition. Data analysis was performed using IBM SPSS Statistics version 25.0 for Windows (IBM CORP: ARMONK, NY, USA). Descriptive measures are reported through mean ± standard deviation (SD) for continuous variables, and number of cases (n), percentage (%) for categorical variables. The main outcome

variable was the presence of periodontitis (P+ vs. P−). We compared baseline variables between periodontitis and non-periodontitis groups. Explicit comparison of mean values was performed by t-Student test when data assumptions for the application of this test were met (normality and homoscedasticity). Mann–Whitney test was used, as an alternative comparison technique, when those assumptions were not verified. To compare significant variables between the subgroups P(−) and P(+) we graphically computed the tendency of WBC, segmented neutrophils and basophils counts according to age using scatterplots from ggplot2 package for R version 4.0, and tendency was computed and fitted via 'geom_smooth'. Then, we made regression analyses in the overall and only in secure PD cases. Preliminary analyses were performed using univariate models. Next, a multivariable model was constructed for the presence of periodontitis. Only variables showing a significance $p \leq 0.25$ in the univariate model were included in the multivariable stepwise procedure. Predictor variables considered in this procedure were: gender (female as reference), WBC count (10^9/L), Segmented neutrophils (10^9/L) and 25-hydroxyvitamin D2 (25OHD2) (nmol/L). The contribution of each variable to the model was evaluated by Wald statistics. A multivariable stepwise adjusted logistic regression procedure was used to model the influence of the investigated factors towards the presence of periodontitis in PD patients. A significance level of 5% was set in all inferential analyses.

3. Results

3.1. Population

From a total of 9756 participants, 3669 individuals had completed periodontal examination. From these, 37 (32 to 80 years old, 57.6 ± 14.6) participants were identified as taking PD medications, 29 secure (32 to 80 years old, 59.6 ± 14.7) and 8 unsecure PD (36 to 73 years old, 50.5 ± 12.5) medications regimens (Table 1). There were no age differences between PD cases with periodontitis (P+) and without periodontitis (P−). Males comprised 40.5% of the sample. The majority of subjects were non-smokers (55.9%). Diabetes and high blood pressure cases were evenly distributed. The number of missing teeth did not differ between PD cases with periodontitis and without periodontitis.

Table 1. Participants characteristics.

Variable	Global (n = 37)			Secure PD Medication (n = 29)		
	P(−)	P(+)	p-value †	P(−)	P(+)	p-Value †
Age, mean (SD) (years)	53.1 (14.6)	61.6 (13.8)	0.069	55.9 (15.4)	62.6 (13.8)	0.215
Gender, n (%)						
Female	12 (44.4)	10 (27.0)	0.204	10 (34.5)	7 (24.1)	0.071
Male	5 (13.5)	10 (27.0)		3 (10.3)	9 (31.0)	
Smoking habits, n (%)						
Never	11 (29.7)	12 (44.4)		7 (24.1)	9 (31.0)	
Former	5 (13.5)	5 (13.5)	0.668	5 (17.2)	4 (13.8)	0.588
Active	1 (2.7)	3 (8.1)		1 (3.4)	3 (10.3)	
Diabetes Mellitus, n (%)	3 (8.1)	2 (5.4)	0.498	3 (10.3)	2 (6.9)	0.453
High Blood Pressure, mean (SD)	10 (27.0)	10 (27.0)	0.591	9 (31.0)	9 (31.0)	0.474
Missing Teeth, mean (SD)	3.9 (5.8)	4.5 (4.3)	0.302	5.1 (6.2)	4.6 (4.6)	0.362

† Chi-square test for categorical variables and Mann-Whitney test for continuous variables, $p < 0.05$. P(−)—No Periodontitis, P(+)—Periodontitis.

3.2. Blood and Standard Biochemical Levels

Complete blood count with 5-part differential was used to compare blood levels of the periodontitis group defined by NHANES measures with the subset of subjects considered periodontally healthy (Table 2). Overall, periodontitis group presented increased levels of WBC (p = 0.002), Basophils (p = 0.045) and Segmented Neutrophils (p = 0.009), also displayed graphically (Figure 1). In the PD secure medication group, the same difference was found for WBC (p = 0.002) and Segmented Neutrophils (p = 0.002) for the periodontitis group (Figure 1).

Then, we investigated the standard biochemistry profile levels to investigate the systemic status of these participants according to the presence of periodontitis (Table 3). The only meaningful result

was found in the global sample, where the periodontitis group presented lower levels of Total Bilirubin ($p = 0.018$).

Table 2. Hematologic levels of PD patients with periodontitis and without periodontitis.

Variable	Global ($n = 37$)			Secure PD Medication ($n = 29$)		
	P(−)	P(+)	*p*-Value †	P(−)	P(+)	*p*-Value †
WBC count (10^9/L)	5.57 (1.28)	7.28 (2.19)	0.002	5.25 (1.02)	7.26 (2.36)	0.002
Lymphocyte (%)	28.75 (6.19)	26.38 (6.91)	0.284	28.84 (6.47)	25.35 (5.87)	0.144
Monocyte (%)	7.36 (3)	7.01 (2.09)	0.988	7.65 (3.36)	6.89 (2.07)	0.812
Segmented neutrophils (%)	60.25 (7.48)	62.85 (8.34)	0.330	59.37 (7.53)	63.88 (6.82)	0.103
Eosinophils (%)	3.16 (2.2)	3.1 (1.5)	0.752	3.66 (2.27)	3.22 (1.56)	0.682
Basophils (%)	0.51 (0.36)	0.75 (0.95)	0.537	0.52 (0.38)	0.73 (1.05)	0.846
Lymphocyte (10^9/L)	1.59 (0.49)	1.89 (0.66)	0.137	1.52 (0.5)	1.81 (0.63)	0.179
Monocyte (10^9/L)	0.39 (0.17)	0.5 (0.19)	0.104	0.38 (0.19)	0.49 (0.19)	0.121
Segmented neutrophils (10^9/L)	3.38 (0.98)	4.61 (1.66)	0.009	3.12 (0.72)	4.68 (1.73)	0.002
Eosinophils (10^9/L)	0.18 (0.13)	0.23 (0.13)	0.297	0.21 (0.14)	0.23 (0.14)	0.682
Basophils (10^9/L)	0.01 (0.03)	0.06 (0.08)	0.045	0.01 (0.03)	0.06 (0.08)	0.101
RBC count (million cells/uL)	4.37 (0.36)	4.45 (0.4)	0.528	4.28 (0.31)	4.48 (0.44)	0.186
Hemoglobin (g/dL)	13.64 (1.35)	13.92 (1.2)	0.519	13.35 (1.22)	14.02 (1.22)	0.155
Hematocrit (%)	39.85 (3.42)	40.48 (3.98)	0.614	39.13 (3.08)	40.9 (4.15)	0.213
MCV (fL)	91.34 (4.56)	91 (3.18)	0.794	91.48 (5.24)	91.33 (2.91)	0.922
MCH (pg)	31.23 (1.89)	31.29 (1.4)	0.919	31.17 (2.16)	31.32 (1.36)	0.822
MCHC (g/dL)	34.18 (0.84)	34.39 (1.01)	0.516	34.05 (0.89)	34.29 (1.1)	0.532
RCD width (%)	12.94 (1.05)	12.78 (0.69)	0.940	13.02 (1.2)	12.93 (0.5)	0.650
Platelet count (10^9/L)	213.82 (41.73)	243.3 (86.16)	0.598	205.62 (38.2)	246.44 (91.76)	0.329
MPV (fL)	8.21 (1.19)	8.17 (0.8)	0.752	8.14 (1.27)	8.13 (0.79)	0.714

† Mann-Whitney for continuous variables without normal distribution and *t*-test for continuous data with normal distribution, $p < 0.05$. Lymphocytes (%), Segmented neutrophils (%), RBC, Hemoglobin, Hematocrit, MCV and MCH were compared with *t*-test, and remaining with Mann-Whitney test. P(−)—No Periodontitis, P(+)—Periodontitis; WBC—White Blood Cells; RBC—Red Blood Cells; MCV—Mean Cell Volume; MCH—Mean Cell Hemoglobin; MCHC—Mean Cell Hemoglobin Concentration; RCD—Red Cell Distribution; MPV—Mean Platelet Volume.

Table 3. Standard biochemical levels of PD patients with periodontitis and without periodontitis.

Variable	Global ($n = 37$)			Secure PD Medication ($n = 29$)		
	P(−)	P(+)	*p*-Value †	P(−)	P(+)	*p*-Value †
Albumin (g/dL)	4.19 (0.31)	4.02 (0.97)	0.775	4.15 (0.32)	3.99 (1.09)	0.714
ALT (U/L)	21.53 (11.12)	20.6 (15.54)	0.517	21.77 (12.45)	21.25 (17.32)	0.682
AST (U/L)	24.53 (8.22)	22.95 (10.68)	0.821	25.38 (9.26)	23 (11.87)	0.650
AP (U/L)	76.41 (26.04)	75.45 (28.62)	0.916	81.92 (27.02)	75.19 (30.63)	0.540
Blood urea nitrogen (mg/dL)	14.12 (6.71)	14.00 (7.83)	0.916	14.92 (7.39)	14.06 (8.68)	0.812
Total calcium (mg/dL)	9.25 (0.39)	8.94 (2.13)	0.209	9.28 (0.42)	8.81 (2.37)	0.449
CPK (IU/L)	117.71 (69.34)	114.4 (71.15)	0.798	113.92 (67.13)	118.5 (73.93)	0.619
Cholesterol (mg/dL)	179.41 (39)	175.15 (48.95)	0.869	176.08 (42.41)	174.94 (54.9)	0.619
Bicarbonate (mmol/L)	25.06 (2.11)	23.1 (5.96)	0.232	25.38 (2.06)	22.69 (6.55)	0.092
Creatinine (mg/dL)	0.92 (0.29)	0.87 (0.3)	0.869	0.95 (0.31)	0.88 (0.33)	0.880
GGT (U/L)	20.76 (14.06)	26.9 (30.47)	0.684	21.92 (15.47)	29.19 (33.77)	0.812
Glucose, serum (mg/dL)	107.82 (51.97)	91.45 (27.09)	0.892	113.54 (58.4)	93.31 (29.78)	0.914
Iron, refrigerated (ug/dL)	89.12 (30.64)	74.65 (38.59)	0.080	85.15 (31.26)	72.88 (42.46)	0.170
LDH (U/L)	131.06 (24.8)	122.25 (36.4)	0.557	138.85 (21.86)	122.81 (39.98)	0.268
Phosphorus (mg/dL)	3.51 (0.51)	3.59 (0.9)	0.232	3.48 (0.57)	3.52 (0.99)	0.398
Total bilirubin (mg/dL)	0.68 (0.22)	0.5 (0.21)	0.016	0.64 (0.19)	0.51 (0.23)	0.110
Total Protein (g/dL)	6.92 (0.6)	6.63 (1.66)	0.940	6.82 (0.59)	6.61 (1.86)	0.475
Uric acid (mg/dL)	4.81 (1.39)	4.95 (1.65)	0.794	4.73 (1.31)	5.14 (1.74)	0.487
Sodium (mmol/L)	139.06 (1.92)	132.3 (31.19)	0.869	139.15 (1.68)	130.44 (34.83)	0.880
Potassium (mmol/L)	4.01 (0.27)	3.84 (0.98)	0.752	4.04 (0.25)	3.84 (1.1)	1.000
Chloride (mmol/L)	104.76 (2.61)	98.85 (23.45)	0.270	104.31 (2.56)	97.38 (26.16)	0.398
Osmolality (mmol/Kg)	278.65 (5.74)	264.75 (62.47)	0.619	279.38 (5.69)	261.31 (69.84)	0.779
Globulin (g/dL)	2.73 (0.45)	2.62 (0.77)	0.916	2.67 (0.45)	2.61 (0.86)	0.779
Triglycerides (mg/dL)	119.82 (86.92)	161.5 (109.11)	0.149	109.31 (68.72)	178.63 (115.18)	0.068
25OHD2+25OHD3 (nmol/L)	75.56 (21.29)	77.11 (34.24)	0.873	71.14 (18.69)	68.59 (30.07)	0.792
25OHD2 (nmol/L)	4.27 (8.53)	11.12 (33.31)	0.478	4.93 (9.73)	4.52 (12.07)	0.423
25OHD3 (nmol/L)	71.28 (23.24)	65.97 (32.46)	0.578	66.18 (21.07)	64.03 (29.9)	0.829
epi-25OHD3 (nmol/L)	3.47 (2.11)	3.68 (2.19)	0.557†	2.89 (1.28)	3.7 (2.36)	0.351

† Mann–Whitney for continuous variables without normal distribution and *t*-test for continuous data with normal distribution, $p < 0.05$. Uric Acid and epi-25OHD3 were compared with Mann-Whitney test, and the remaining with *t*-test. P(−)—No Periodontitis, P(+)—Periodontitis; ALT—Alanine aminotransferase; AST—Aspartate aminotransferase; AP—Alkaline phosphatase; CPK—Creatine Phosphokinase; GGT—Gamma glutamyl transferase; LDH—Lactate dehydrogenase; 25OHD2—25-hydroxyvitamin D2; 25OHD3— 25-hydroxyvitamin D3.

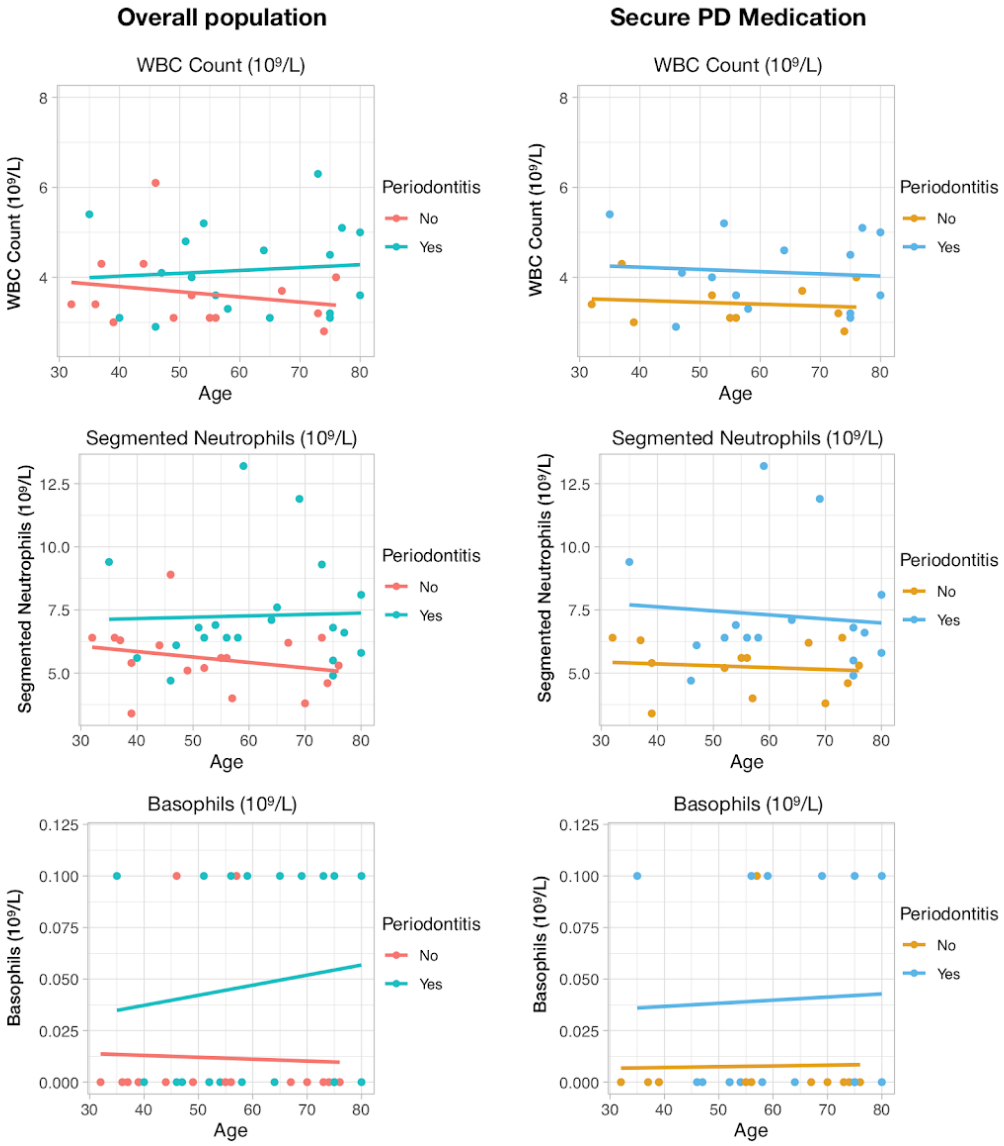

Figure 1. Comparison of WBC Count, Segmented neutrophils and Basophils serum levels between Periodontitis and no Periodontitis PD participants both in the overall sample and Secure PD medications. Lines represent graphically the tendency.

3.3. Predictive Models of Periodontitis on PD Patients

In order to analyze which factors would discriminate the periodontitis presence, we performed multivariable stepwise regression analyses considering each factor. In the overall sample, blood WBC levels were consistently identified as a discriminative factor towards periodontitis (B = 0.773, p =0.025) (Table 4). Among the participants with secure PD medication, we found discriminative factors to be gender (male) (B = 5.126, p = 0.026), Segmented Neutrophils (B = 4.232, p = 0.027) and 25OHD2 (B = −0.127, p = 0.060). The second model evidenced an improved score for correct classification (89.7%).

Table 4. Final reduced logistic regression models for the overall population (n = 37) and patients with secure PD medication (n = 29).

	Crude Model				Adjusted Model			
	B	***p*-Value**	**Exp(B)**	**95% CI for Exp(B)**	**B**	***p*-Value**	**Exp(B)**	**95% CI for Exp(B)**
Model 1—Overall population (n = 37) [1]								
WBC count (10^9/L)	0.773	0.025	2.1	1.1–4.2	0.773	0.025	2.2	1.1–4.3
Model 2—Secure PD medication (n = 29) [2]								
Gender (male)	5.064	0.024	158.3	2.0–12760.6	5.126	0.026	19.2	1.2–297.1
Segmented neutrophils (10^9/L)	3.727	0.090	41.6	0.6–3069.7	4.232	0.027	14.2	1.57–128.8
25OHD2 (nmol/L)	−0.130	0.058	0.9	0.8–1.0	−0.127	0.060	0.9	0.8–1.0

[1] R^2(n) = 0.291, % correct classification = 75.0%. [2] R^2(n) = 0.730, % correct classification = 89.7%. B—unstandardized regression coefficient; WBC—White Blood Cells.

4. Discussion

In the present representative study from the NHANES 2011–2012, periodontitis was associated with increased serum levels in PD patients. Therefore, our hypothesis was confirmed, in which leukocyte levels (WBC count, segmented neutrophils and basophils) and bilirubin were increased in periodontitis cases in this particular population. Furthermore, for the overall population WBC count showed potential predictive value towards periodontitis, while for secure PD medications gender, segmented neutrophils and 25OHD2 were the meaningful elements.

The link between periodontitis and leukocytosis is well documented [35–40]. This result is expected given the infectious nature of periodontitis where bacteria invade the periodontal tissues via the ulcerated epithelium, and leukocytes, in particular neutrophils, are triggered towards the periodontal injury [40–42]. Neutrophils had been associated with periodontitis pathogenesis [40,43,44] and were established as key players involved in many inflammatory chronic and aging-related diseases [44]. Neutrophils represent the vast majority (≥95%) of leukocytes recruited to the periodontal pocket [45]. Despite the homeostasis role of neutrophils in the healthy periodontium [3], they are impaired in periodontitis [1]. The chronic recruitment of excessive neutrophil, and therefore the increase of its serum counts, is learned as a consequence of the persisting microbial dysbiotic challenge [44]. The newness of this study is the likelihood of such parameters presenting predictive value towards periodontitis in PD cases, and future research is warranted to confirm this possibility.

Furthermore, male gender presented a higher risk to have periodontitis, this result being in line with previous reports that show males have a higher prevalence of periodontitis both in representative [10,46,47] and PD populations [23–26]. This result is of particular relevance because, in the same fashion as periodontitis, PD is more prevalent in men [18–20]. Additionally, the prevalence of periodontitis in this age-group is in line with previous studies developed in this region, where this age groups have high levels of periodontal disease [46–48].

Additionally, the presence of 25OHD2 in the predictive models is also in accordance with previous studies, where individuals with periodontitis were associated with lower levels of Vitamin D, compared to non-periodontitis [49–53]. Further, Vitamin D concentrations were associated with higher periodontal destruction, severe periodontitis stages and higher tooth loss [54–58]. Vitamin D also influences the immune response through the regulation of cathelicidin [59]. Interestingly, cathelicidin is an antimicrobial peptide produced by neutrophils and has been shown that dysregulated neutrophils in periodontitis lead to a low secretion of cathelicidin [60], though this should be further investigated. Therefore, Vitamin D levels may be an interesting clinical surrogate to consider in this link of periodontitis with PD, though it demands more studies to allow strong conclusions. However, we should carefully interpret these findings because of the lack of significance according to the periodontal status but its predictive value to infer periodontitis.

The present report has limitations important to mention and discuss. Despite this sample deriving from a large representative U.S. population survey, the final number of included patients was small.

However, this small number can be explained by the fact that PD affects 1% of individuals over 60 [11]. In our study, the overall prevalence of PD patients confirmed by medication represented 0.4% of the entire population and 1.0% of the sample that was examined for periodontitis. Thus, the sample size of this study limits the validity of these results and warrants future confirmation with prospective studies, since there are inherent biases in cross-sectional studies, such as selection bias. Notwithstanding, the identification of PD patients was also a limitation, since was based on the medication consumption present in the NHANES database with inherent selection bias. While for some medications this is somehow secure (Benztropine, Carbidopa, Levodopa, Ropinirole, Methyldopa and Entacapone) for others this is not the case (Cabergoline, Orphenadrine and Pramipexole) [30–34]. Yet, PD clinical diagnosis is even now considered to be speculative, since a definitive diagnosis always implies a post-mortem examination [13,61]. Another shortcoming is the medication itself since this survey was carried out in 2011–2012, and a large variation of medication gained therapeutic relevance in recent years. Furthermore, therapeutic adherence in PD is sub-optimal in a significant proportion of patients with PD [62], and we may have had a sample shortage due to this reason. Further, this approach does not deliver any causality rather an associative conclusion, and future studies should investigate in more depth how PD and periodontitis relate systemically, and if treating periodontitis might alleviate these elevated surrogates. Moreover, white blood cells and neutrophils were used as proxy of systemic inflammation and PISA as proxy to oral inflammation, though more evidence, such as immunohistochemistry staining of the periodontal tissues, indicating the infiltration level of neutrophils, monocytes and related white blood cells are warranted to further confirm our results to expand this matter. Lastly, the number of analyzed markers may be considered excessive, as future studies will narrow analysis to the most relevant measures.

In spite of these limitations, this article has important strengths. Our report is the first to depict the potential effect of the presence of periodontitis on the systemic status of PD. Further, NHANES is prospectively a reliable source of data to determine associations as previously demonstrated [63], and public data bank analysis (such as NHANES) are key towards more comprehensive oral health studies. Furthermore, we were able to produce predictive estimates using serum surrogates, which may be clinically relevant for the multidisciplinary team of PD. These results underline the importance of oral health care and how it can become unbalanced with the progression of this neurodegenerative disease, and the importance of more studies to investigate the systemic influence of periodontitis on PD.

5. Conclusions

Periodontitis was associated with an increase of white blood cells count, segmented neutrophils and basophils in PD patients. Furthermore, white blood cells count, segmented neutrophils, Vitamin D2 and gender showed discriminatory value to predict the existence of periodontitis in PD cases. Future studies should assess in more detail the potential systemic repercussion of the presence of periodontitis in PD patients.

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IV. GENERAL DISCUSSION

First and foremost, the results of the Portuguese sample showed a high prevalence of periodontitis and gingival inflammation (A) in the examined group of PD patients that integrated research article one. In this, about a third of the population was diagnosed as having a moderate to severe form of periodontitis.

Recognized risk factors for periodontitis such as age and the number of males in the included sample might explain the reported high prevalence, according to a recent representative study conducted in this area (Botelho & Machado et al., 2019) That is, the high average age (72.3) and the clear predominance of males (82.2%) might certainly have increased the risk of having periodontitis. Nonetheless, despite lower educational levels and smoking habits are established periodontitis risk factors (Botelho et al., 2019), the majority of cases reported never having smoked (57.1%) and higher educational standards (42.9% middle and 35.7% higher education).

In addition, previous studies reported similar periodontitis prevalence (Einarsdóttir et al., 2009; Hanaoka & Kashihara, 2009; Nakayama et al., 2004; van Stiphout et al., 2018), even having employed unsuitable periodontal clinical protocols. For this reason, to the best of our knowledge, this study seems to be the first to rigorously assess the periodontal status and relevant clinical measures in a group of PD individuals, by trained and calibrated examiners and following the most recent definitions of PD and periodontitis.

Furthermore, the reported increased levels of gingival inflammation might relate to individual oral hygiene habits. Remarkably, this sample of PD patients showed good toothbrushing frequency (following a twice or more brushings per day - 67.9%) and assiduousness towards dental visits (< 6 months - 64.3%). However, interdental hygiene was predominantly neglected (60.7%), which ultimately increases the likelihood of developing gingival inflammation and periodontal disease (Berchier et al., 2008), and might explain once more the high prevalence observed.

To a great extent, interdental cleaning is anticipated as a major challenge for PD patients, due to the disease's physiopathology and clinical manifestations (in particular, fine motor issues and cognitions deficits). Thereafter, oral irrigation devices and the adoption of electric toothbrushes are pertinent recommendations to surpass these common fine motor impairments in PD patients (Worthington et al., 2019).

Interestingly, no significant differences were found between mild and moderate PD to severe stages (via the modified H&Y scale) concerning periodontal clinical measures, age, PDQ-8, OHIP-14 and SXI-5 total scores, besides a higher number of missing teeth in worst PD stages. Also, higher PD stages (moderate to severe) reported higher prevalence of moderate and severe periodontitis. However, the short sample size limits the validity of these results.

Further, upon correlation between MDS-UPDRS and periodontal clinical levels, worst levels of kinetic and postural tremor of the hands and rigidity of the upper extremities were associated with increased dental plaque accumulation, bleeding gums and, consequently, increased periodontal pocket depth (B). Although it seems expected that further PD progression might compromise the patient oral hygiene habits, this is the first study to appraise and confirm such association.

As aforementioned, moderate to severe stages of PD were associated with higher tooth loss. Therefore, our results corroborate our preview of an association between the number of missing teeth and difficulties of speech and eating tasks in PD.

Ultimately, self-perceived quality of life in PD (PDQ-8) seems to be intertwined with OHRQoL (OHIP-14) and self-perceived xerostomia levels (SXI-5) (C). For instance, lack of social support (measured in PDQ-8) revealed strong correlations with worse levels of physiological discomfort and physiological disability from OHIP-14. Furthermore, other PDQ-8 factors, such as lessened mobility and cognition, seem to be related with psychological deficits. Also, cognition impairments and increased challenges in activities of daily living in PDQ-8 seem to aggravate individual handicap levels.

When it comes to self-perceived xerostomia levels, our results show that increased difficulty eating dried foods correlates with added bodily discomfort and worse overall PD quality of life. Additionally, difficulties swallowing certain foods related with worse cognition levels. Previous studies have reported swallowing impairment in PD individuals (Nakayama et al., 2004), and sialorrhea tends to be a common sign in PD patients, even though xerostomia is frequent in the elderly due to polymedication (Botelho et al., 2020). As xerostomia levels are underrated on the MDS-UPDRS scale, the complementary use of the SXI-5 questionnaire is advised in PD clinical follow-ups.

In fact, all self-reported questionnaires applied in this study showed potential validity for future PD-oral health studies.

Besides the limited sample size, not defining the brushing technique and efficiency, while also not considering the patient's dominant arm when performing oral hygiene practices, stand as potential limitations. Thereafter, the average of the upper limbs rates in the MDS-UPDRS scale had to be considered in this study. All in all, a causality between PD and periodontitis cannot be thoroughly appraised in the present observational study, nor can the impact of specific clinical characteristics of PD in periodontitis development and vice-versa.

Research article two encompassed an American sample derived from NHANES 2011–2012. This paper was the first to confirm the hypothesis that periodontitis presented systemic repercussions in PD patients (D). Moreover, certain important biomarkers showed predictive values towards periodontitis, and may have applicability to the clinical practice.

Upon analysis of the completed hematologic profile of PD patients, significantly increased levels of WBC ($p=0.002$), basophils ($p=0.045$) and segmented neutrophils ($p=0.009$) were found in the global periodontitis group of the analysed population. Also, increased levels of WBC ($p=0.002$) and segmented neutrophils ($p=0.002$) paralleled with meaningful statistical significance in the secure PD medication group. Furthermore, when appraising the standard biochemistry levels in PD patients with and without periodontitis, significantly lower Total Bilirubin levels ($p=0.016$) were found in the global periodontitis group.

Due to the infectious nature of periodontitis, the confirmed association with leucocytosis was foreseeable, as it was previously reported (Hirschfeld, 2014; Kumar et al., 2014; Nibali et al., 2019; Papapanagiotou et al., 2009; Temelli et al., 2018; Wang et al., 2015). Upon the persistent invasion of dysbiotic periodontopathic agents through the ulcerated epithelium, leukocytes are chronically summoned to the lesioned site, specially neutrophils (≥95%), witch increase their serum levels, and are knowingly involved in periodontitis etiopathogenetic mechanisms and numerous others inflammatory chronic diseases related with aging (Delima & Van Dyke, 2003; Hajishengallis, 2020; Hirschfeld, 2014; Loesche et al., 1988).

Besides the assessment of systemic repercussions in PD patients, with and without periodontitis, another novelty is the possible predictive value towards periodontitis through altered biomarkers (like leukocytes). Accordingly, WBC count (p=0.025) might contribute in predicting periodontitis, for the examined population (secure and not secure PD). On the other hand, for the secure PD medication group, male gender (p=0.026), segmented neutrophils (p=0.027) and 25OHD2 (p=0.060) showed a potential significant predictive value towards periodontitis.

Men presented higher risk towards periodontitis, which is in line with preceding evidence (Botelho et al., 2019; Machado et al., 2018), specifically in PD populations (Einarsdóttir et al., 2009; Hanaoka & Kashihara, 2009; Nakayama et al., 2004; van Stiphout et al., 2018). In fact, both periodontitis and PD present increased prevalence in the male gender, which supports the scientific relevance of our findings (Alves et al., 2009; Ball et al., 2019; Ferreira et al., 2017; Schrag et al., 2000). Also, the disclosed periodontitis prevalence in this aged population, matches other regional reports of high periodontitis in the elderly (Botelho et al., 2019; Botelho et al., 2020; Machado et al., 2018).

The predictive value of Vitamin D is equally corroborated by literature, since 25OHD2 deficiency has been formerly reported in periodontitis patients (Agrawal et al., 2019; Anbarcioglu et al., 2019; Ebersole et al., 2018; Isola et al., 2020; Ketharanathan et al., 2019), and associated with heightened periodontal destruction, consequent tooth loss and severe forms of the disease (Antonoglou et al., 2015; Botelho et al., 2020; Dietrich et al., 2004; Zhan et al., 2014).

The role of these apparent predictive variables should be carefully evaluated, and future research is needed on the aforementioned biomarkers to strengthen their potential in predicting periodontitis (for instance by increasing the sample size or by refining PD definition criteria).

Finally, research article two presented some limitations worth mentioning. After identifying the group of individuals that underwent periodontal examination from the American NHANES 2011-2012, and subsequently recognizing PD patients through their medication regimen, the resulting sample was small. Limited sample size might undermine the validity of the results, especially since selection bias is inherent in cross-

sectional studies. Nonetheless, the available sample might resign with the fact that PD affects 1% of individuals over 60 (Tysnes & Storstein, 2017). In the present study, PD showed 1.0% prevalence in the sample that underwent periodontal examination, and 0.4% prevalence in the entire American NHANES 2011-2012 population.

Furthermore, the defined criteria for identifying PD patients may have also introduced a limitation, as it was dependent on reported medication regimens in the American NHANES database, which presents inherent selection bias. Reported administration of Benztropine, Carbidopa, Levodopa, Ropinirole, Methyldopa and Entacapone were considered secure PD medications, while Cabergoline (also used to treat high levels of prolactin hormone), Orphenadrine (also used to treat muscle spasms) and Pramipexole (also used to treat restless legs syndrome) intake were considered PD unsecure medications (Abd-Elsalam et al., 2020; de Biase et al., 2019; Fox et al., 2011; Sant' Anna et al., 2020; Seppi et al., 2011). Even though, new pharmacological therapies gained relevance over the past few years, which can be perceived as a shortcoming to this study, the fact that in many PD patients therapeutic compliance is suboptimal might also help explaining the sample shortage (Malek & Grosset, 2014).

Notwithstanding, till this day, PD definitive diagnosis can only be granted upon post-mortem examination, which makes all clinical diagnostic attempts merely speculative (Kalia & Lang, 2015; Litvan et al., 2003).

In this study, systemic inflammation was inferred through WBC and neutrophils count, while periodontal inflamed surface area (PISA) was representative of oral inflammation. Even so, further research involving immunohistochemical staining of periodontal tissues, and leukocyte (neutrophils, monocytes and related WBC) infiltration, is warranted to support present findings.

Ultimately, upcoming research ought to narrow down analysed biomarkers based on statistical relevance, since the present study comprised a vast list of unrelated parameters.

It is also important to mention the strengths of research article two. As aforementioned, this is the first study to portray periodontitis systemic repercussions on PD patients. Moreover, the American NHANES public database has previously been attested as a valid source of discovery for scientific variable associations, specifically in the oral health field, which sustains our findings (Montero et al., 2019). Additionally, these findings might be

of clinical relevance in PD management, especially through oral health care promotion, since oral health can be at risk in this group of people.

V. CONCLUSIONS

All of the initially advanced aims were answered in the present investigation project.

When acknowledging the first question of the primary established aim - "What is the prevalence of periodontitis in PD patients?" (A) - the encountered periodontitis prevalence in the examined group of PD patients was high (75%). Furthermore, the majority of periodontitis cases were severe (stage III).

Secondly, addressing the second question of the primary established aim - "In PD patients, is periodontitis associated with worse levels of PD clinical characteristics?" (B) - deteriorated levels of the upper extremities in advanced stages of PD reportedly influenced the periodontal status and hygiene habits.

Furthermore, quality of life in PD appears to be associated with self-perceived OHRQoL and self-perceived xerostomia levels, which answers the last question of the primary aim, and the last included in research article one - "In PD patients how does the quality of life in PD correlate with self-perceived levels of OHRQoL and self-perceived levels of xerostomia?" (C).

Lastly, regarding the secondary aim of this study, included in the second research article - "Are there altered blood and standard biochemical surrogates in PD patients diagnosed with periodontitis and PD patients without periodontitis?" (D) – evidence showed that PD patients diagnosed with periodontitis presented systemic changes and biomarkers with predictive value to infer periodontitis. Specifically, increased levels of WBC count, segmented neutrophils and basophils were detected, while WBC count, segmented neutrophils, Vitamin D2 and gender showed discriminatory value to predict the existence of periodontitis in PD cases.

VI. FUTURE PERSPECTIVES

In the future, the periodontal status of PD patients should be assessed in a larger population sample in order to validate the present findings. Moreover, it is important to consider the dominant side of PD impairment in upcoming studies, so as to evaluate with precision how it impacts oral hygiene ability in PD patients, and, subsequently, patient's oral status. This will allow the personalization of oral health instructions, which may include changing arms during hygiene tasks or the implementation of specific devices in the routine (irrigation interdental cleaning devices and electric toothbrushes). Additionally, the overall impact of periodontitis on the quality of life of PD patients should continue to be explored, particularly the link between social support and its burden on self-perceived psychological discomfort and disability in PD patients.

The possible predictive value towards periodontitis found in certain parameters (as in specific serum surrogates and gender) should also be further analysed, with a larger sample, refined PD diagnostic criteria and a narrowed list of biomarkers. Also, investigating the hypothesis that "treating periodontitis might ease these elevated blood and biochemistry surrogates" might be of scientific interest.

Nonetheless, and based on the scientific importance of this association, the next step ought to be the search for causality between both conditions, as well as for the impact of PD clinical manifestations in periodontitis development and the overall systemic interaction between these conditions.

In fact, the interaction between periodontitis and systemic inflammation has been previously reported (Loos et al., 2000; Paraskevas et al., 2008), as well as the confirmation that the originated subclinical inflammation process can magnify neuroinflammation in the central nervous system, favouring the onset and progression of the neurodegeneration in Alzheimer's disease (Dioguardi et al., 2020). Furthermore, neuroinflammation secondary to periodontitis, might also be a key element of PD pathogenesis (Chen et al., 2017; Gelders et al., 2018; Hashioka et al., 2019; Kaur et al., 2016; Ransohoff, 2016), although it is still unproven at this point. Therefore, future research in this field will ultimately revolve on the nature of such association, their mechanisms and the potential for treatment in both conditions.

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VIII. APPENDICES

Comissão de Ética EGAS MONIZ

Proc. Interno nº 824

Ex.ma Senhora
Patrícia Soares Lyra

Monte de Caparica, 20 de fevereiro de 2020

Ex.ma Senhora,

Em resposta ao Pedido de Parecer que submeteu à apreciação da Comissão de Ética da Egas Moniz, com o tema denominado **"O estado periodontal em doentes de Parkinson: estudo retrospectivo"**, foi aprovado por unanimidade.

Com os melhores cumprimentos,

A Presidente da Comissão de Ética da Egas Moniz

Profª. Doutora Maria Fernanda de Mesquita

EGAS MONIZ – COOPERATIVA DE ENSINO SUPERIOR, CRL
Campus Universitário – Quinta da Granja – Monte de Caparica
2829-511 Caparica

Lisboa, 11 Novembro 2019

Associação Portuguesa de Doentes de Parkinson

Assunto: Autorização de recolha de dados aos associados da APDPk

Na sequência da solicitação realizada discente Patrícia Soares Lyra aluna nº 111584 do 5º ano do Mestrado Integrado em Medicina Dentária do Instituto Universitário Egas Moniz, declaramos que autorizamos a recolha da informação necessária para a realização do estudo "O estado periodontal em doentes de Parkinson: estudo retrospetivo" sob a orientação do Prof. Doutor Luís Proença e coorientação da Prof. Doutora Catarina Godinho e do Prof. Doutor José João Mendes e ainda com a colaboração da Fisioterapeuta Josefa Domingos.
OS nossos associados que forem convidados a participar de forma voluntária, e assinarem o consentimento informado, poderão participar neste estudo, fornecer as informações necessárias e colaborar com os procedimentos necessários para a realização do mesmo.

Com os melhores cumprimentos,

ASSOCIAÇÃO PORTUGUESA DOENTES DE PARKINSON
Ana Botas

(A Presidente da APDPk, Ana Thelma Botas)

Bairro de Telheiras, 058 Sul
1070-023 LISBOA

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Parkinson's Disease, Periodontitis and Patient-Related Outcomes: A Cross-Sectional Study

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Abstract

Background and objectives: People with Parkinson's disease (PD) may be at risk of having bad periodontal status. A consistent periodontal examination is critical to investigate how it impacts on PD quality of life. We aimed to assess the periodontal status of people with PD, and its association with quality of life and self-perceived xerostomia. *Materials and Methods:* To this end, from February to March 2020, we consecutively enrolled 28 PD individuals, and motor and non-motor symptoms of PD were assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). We performed full-mouth periodontal examination and gathered information on self-perceived quality of life in PD, oral health impact profile (OHIP-14) and xerostomia. *Results:* The prevalence of periodontitis was 75.0% and most cases were identified as severe (46.4%). Upper extremity rigidity, hand posture and kinetic tremors were significantly correlated with worse periodontal status. PDQ-8 showed to be correlated with self-perceived oral health-related quality of life and xerostomia levels. *Conclusions:* This group of people with PD had a high prevalence of periodontitis. Deteriorated levels of the upper extremities in advanced stages of PD were associated with worse periodontal status and hygiene habits. Quality of life in PD appears to be associated with self-perceived OHRQoL and xerostomia. View Full-Text

Keywords: Parkinson's disease; movement disorders; Parkinsonian disorders; oral health; periodontitis; periodontal diseases; quality of life

Open Access Article

Relationship between Blood and Standard Biochemistry Levels with Periodontitis in Parkinson's Disease Patients: Data from the NHANES 2011–2012

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(This article belongs to the Special Issue Personalized Medicine for Parkinson's Disease: New Concepts and Future of Individualized Management)

Abstract

People with Parkinson's Disease (PD) are associated with the presence of periodontitis. We aimed to compare blood and standard biochemical surrogates of PD patients diagnosed with periodontitis with PD individuals without periodontitis. This retrospective cohort study used a sample from the National Health and Nutrition Examination Survey (NHANES) 2011–2012 that underwent periodontal diagnosis (n = 3669). PD participants were identified through specific PD reported medications. Periodontitis was defined according to the 2012 case definition, using periodontal examination data provided. Then, we compared blood levels and standard chemical laboratory profiles of PD patients according to the presence of periodontitis. Multivariable regression was used to explore this dataset and identify relevant variables towards the presence of periodontitis. According to the medication report, 37 participants were eligible, 29 were secure and 8 were unsecure PD medications regimens. Overall, PD cases with periodontitis presented increased levels of White Blood Cells (WBC) (p = 0.002), Basophils (p = 0.045) and Segmented neutrophils (p = 0.009), and also, lower levels of Total Bilirubin (p = 0.018). In the PD secure medication group, a significant difference was found for WBC (p = 0.002) and Segmented neutrophils (p = 0.002) for the periodontitis group. Further, WBC might be a discriminating factor towards periodontitis in the global sample. In the secure PD medication, we found gender, segmented neutrophils and Vitamin D2 to be potential discriminative variables towards periodontitis. Thus, periodontitis showed association with leukocyte levels alterations in PD patients, and therefore with potential systemic changes and predictive value. Furthermore, Vitamin D2 and gender showed to be associated with periodontitis in with secure medication for PD. Future studies should assess in more detail the potential systemic repercussion of the presence of periodontitis in PD patients. View Full-Text

Keywords: Parkinson's disease; movement disorders; periodontitis; periodontal disease; hematologic tests; Vitamin D; oral health

▼ Show Figures

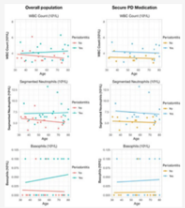


Figure 1

Monte de Caparica, dia de mês de ano

Exmo.(a) Sr.(a),

No âmbito do Mestrado Integrado em Medicina Dentária na Unidade Curricular de Orientação Tutorial de Projeto Final do Instituto Universitário Egas Moniz sob a orientação do Prof. Doutor Luís Proença e assistido pela Prof. Doutora Catarina Godinho e pelo Prof. Doutor José João Mendes, solicita-se autorização para a participação no estudo "O estado periodontal em doentes de Parkinson: estudo retrospetivo" com o objetivo de avaliar o estado periodontal de pacientes com Doença de Parkinson e correlacionar com dados clínicos da Doença de Parkinson.

Ao participar neste estudo **está a dar o seu consentimento** para 1) uma avaliação das suas gengivas e dos seus dentes e 2) uma avaliação dos sinais e sintomas da Doença de Parkinson. Para a avaliação das gengivas e dentes, será aplicado um breve questionário e efetuada uma avaliação clínica da sua boca, medindo o grau de perda de osso ao redor dos dentes e a inflamação das gengivas. Quanto à avaliação dos sinais e sintomas da Doença de Parkinson, a recolha dos dados será realizada com base em questionários de avaliação física já aplicados na Associação Portuguesa de Doentes de Parkinson. **Ao autorizar a sua participação neste estudo irá permitir a recolha e o acesso aos dados constantes no processo clínico da Associação Portuguesa de Doentes de Parkinson**, apenas para efeito desta investigação científica.

A participação neste estudo é voluntária. A sua não participação não lhe trará qualquer prejuízo. Este estudo pode trazer benefícios: 1) ao participar, terá possibilidade de realizar uma triagem, ortopantomografia (radiografia geral da cavidade oral) e destartarização (remoção do tártaro dentário) sem custos; 2) se lhe for diagnosticada doença periodontal terá possibilidade de realizar o tratamento até à primeira consulta após tratamento, sem custos.

A informação recolhida destina-se unicamente a tratamento estatístico e/ou publicação científica, e será tratada pelos orientadores e/ou pelos seus mandatados. A sua recolha é anónima e confidencial, com a atribuição de um código que garantirá a proteção dos seus dados.

Consentimento Informado
Código | IMP:EM.PE.17_02

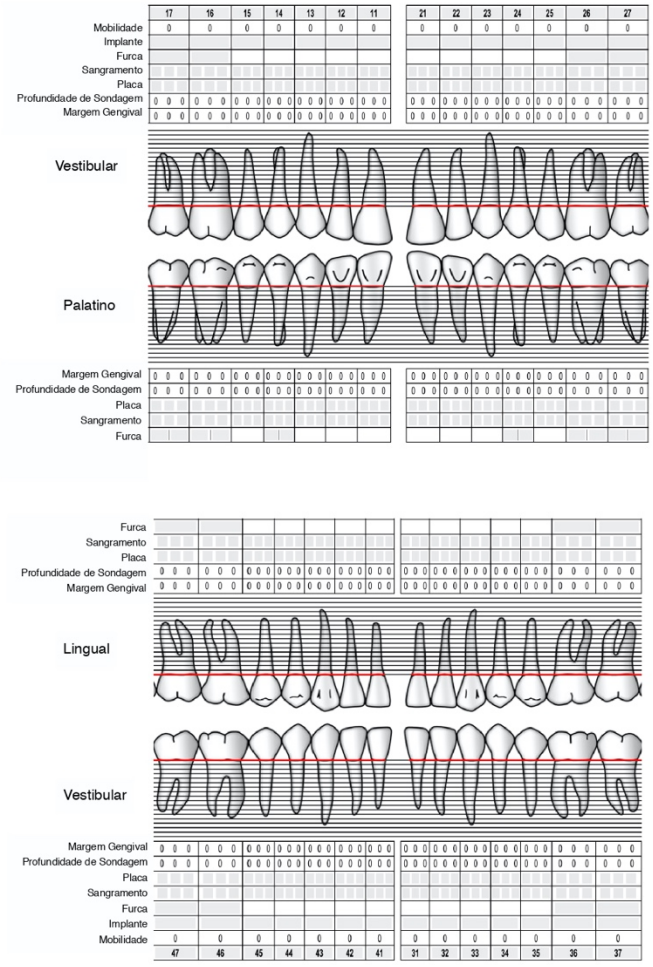
(Riscar o que não interessa)

ACEITO / NÃO ACEITO participar neste estudo, confirmando que fui esclarecido sobre as condições do mesmo e que não tenho dúvidas.

_____

(Assinatura do participante ou, no caso de menores, do pai/mãe ou tutor legal)

Paciente nº:



Perfil de Impacto de Saúde Oral (ORAL HEALTH IMPACT PROFILE - OHIP-14)

Com as perguntas deste questionário pretende-se saber até que ponto as dificuldades com os seus dentes, boca ou prótese dentária causaram problemas na sua vida diária. Agradecíamos que preenchesse o questionário mesmo que tenha uma boa saúde oral. Gostaríamos de saber com que frequência, no último mês, teve cada um dos problemas que a seguir lhe apresentamos. Cada pergunta refere-se a um problema dentário específico. Pense numa pergunta de cada vez e faça uma cruz na opção de resposta que indica com que frequência teve esse problema no **último mês.**

	Quase sempre	Algumas vezes	Poucas vezes	Raramente	Nunca	Não sei	Não se aplica
1. Teve dificuldade em pronunciar alguma palavra por causa de problemas com os seus dentes, boca ou prótese dentária?							
2. Sentiu que o seu paladar piorou por causa de problemas com os seus dentes, boca ou prótese dentária?							
3. Teve dores na sua boca?							
4. Sentiu desconforto a comer algum alimento por causa de problemas com os seus dentes, boca ou prótese dentária?							
5. Tem-se sentido pouco à vontade por causa dos seus dentes, boca ou prótese dentária?							
6. Sentiu-se tenso por causa de problemas com os seus dentes, boca ou prótese dentária?							
7. Já deixou de comer algum alimento por causa de problemas com os seus dentes, boca ou prótese dentária?							
8. Teve de interromper refeições por causa de problemas com os seus dentes, boca ou prótese?							
9. Sentiu dificuldade em relaxar por causa de problemas com os seus dentes, boca ou prótese dentária?							
10. Tem-se sentido um pouco envergonhado por causa de problemas com os seus dentes, boca ou prótese dentária?							
11. Tem sido menos tolerante ou paciente com o(a) seu (sua) companheiro(a) ou família por causa de problemas com os seus dentes, boca ou prótese dentária?							
12. Teve dificuldade em realizar as suas atividades habituais por causa de problemas com os seus dentes, boca ou prótese dentária?							
13. Sentiu-se menos satisfeito com a vida em geral por causa de problemas com os seus dentes, boca ou prótese dentária?							
14. Tem sido totalmente incapaz de funcionar por causa de problemas com os seus dentes, boca ou prótese dentária?							

Continua na página seguinte.

Escala da Percepção de Xerostomia

Nome _____ Data _____

Instrução: Para cada questão indique, com uma cruz (X), a alternativa que melhor se ajusta à sua situação.

	Nunca	**Ocasionalmente**	**Com frequência**
1. Sinto a boca seca durante as refeições:			
2. Sinto a boca seca:			
3. Tenho dificuldade em comer alimentos secos:			
4. Sinto dificuldade em engolir certos alimentos:			
5. Tenho os lábios secos:			

	Nunca	**Ocasionalmente**	**Com frequência**	**Sempre**
6. Com que frequência sente a boca seca?				

Fonte: Cohen, S.; Kamarck, T. & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 24 (December), 385-396. **Tradução, preparação e adaptação da versão portuguesa da PSS de 10 itens:** Trigo, M.; Canudo, N.; Branco, F. & Silva, D. (2010). Estudo das propriedades psicométricas da Perceived Stress Scale (PSS) na população portuguesa, *Revista Psychologica*, 52, 353-378. Email: miguel.trigo70@gmail.com

HEALTH SERVICES RESEARCH UNIT
DEPARTMENT OF PUBLIC HEALTH AND PRIMARY CARE
UNIVERSITY OF OXFORD

Portuguese PDQ-8

Parkinson's Disease Quality of Life Questionnaire

DEVIDO A TER A DOENÇA DE PARKINSON, com que frequência, durante o último mês...

Devido a ter a doença de Parkinson, durante o último mês com que frequência...

Por favor assinale uma caixa para cada questão

		Nunca	Ocasionalmente	Às Vezes	Frequentemente	Sempre *ou não posso de todo fazer*
1.	teve dificuldades em movimentar-se em locais públicos?	☐	☐	☐	☐	☐
2.	teve dificuldades em vestir-se?	☐	☐	☐	☐	☐
3.	se sentiu deprimido?	☐	☐	☐	☐	☐
4.	teve problemas de relacionamento com as pessoas mais chegadas?	☐	☐	☐	☐	☐
5.	teve problemas de concentração, p. ex. ao ler ou ao ver televisão?	☐	☐	☐	☐	☐
6.	se sentiu incapaz de comunicar devidamente com pessoas?	☐	☐	☐	☐	☐
7.	teve cãibras ou espasmos musculares dolorosos?	☐	☐	☐	☐	☐
8.	se sentiu embaraçado em público devido a ter a doença de Parkinson?	☐	☐	☐	☐	☐

Por favor verifique se assinalou uma caixa por cada questão antes de passar à página seguinte.

unesp **Faculdade de Ciências e Tecnologia – Campus de Presidente Prudente**
Centro de Estudos e Atendimento em Fisioterapia e Reabilitação (CEAFIR)

ESCALA DE HOEHN E YAHR MODIFICADA		
NOME:	**Sexo:**	**Prontuário:**
	Idade:	**Data da Lesão:**
Lado Dominante ou parético: (D) (E)		**Data da Avaliação:**
Diagnóstico:		**Avaliador:**

Estágio	Descrição
0	Nenhum sinal da doença
1	Doença unilateral
1,5	Envolvimento unilateral e axial.
2	Doença bilateral sem déficit de equilíbrio (recupera o equilíbrio dando três passos para trás ou menos).
2,5	Doença bilateral leve, com recuperação no "teste do empurrão"(empurra-se bruscamente o paciente para trás a partir dos ombros, o paciente dá mais que três passos, mas recupera o equilíbrio sem ajuda).
3	Doença bilateral leve a moderada; alguma instabilidade postural; capacidade para viver independente.
4	Incapacidade grave, ainda capaz de caminhar ou permanecer de pé sem ajuda.
5	Confinado à cama ou cadeira de rodas a não ser que receba ajuda.

*** Sugere-se iniciar o teste do item 5 para o item 1.**

Classificação
Estágios 1 a 3 = incapacidades leve a moderada
Estágios 4 e 5 = incapacidade grave.

FONTE: SHENKMAN M. L.; CLARK K.; XIE T.; KUCHIBHATLA M.; SHINBERG M.; RAY L.; Spinal movement and performance of standing reach task in participants with and without Parkinson disease. Phys Ther, vol. 81, p. 1400-1411, 2001.

_____	___ ___ ___	__ __ - __ __ - __ __ __ __	___ ___ ___
Nome do paciente ou ID do sujeito	ID do Local	(dd-mm-aaaa) Data da Avaliação	Iniciais do Investigator

Folha de pontuações da MDS UPDRS

1.A	Fonte da informação	□ Paciente □ Cuidador □ Paciente + Cuidador	3.3b	Rigidez – MSD	
			3.3c	Rigidez – MSE	
Parte I			3.3d	Rigidez – MID	
1.1	Disfunção cognitivo		3.3e	Rigidez – MIE	
1.2	Alucinações e psicoses		3.4a	Bater dos dedos das mãos – Mão direita	
1.3	Humor depressivo		3.4b	Bater dos dedos das mãos – Mão esquerda	
1.4	Ansiedade		3.5a	Movimentos das mãos – Mão direita	
1.5	Apatia		3.5b	Movimentos das mãos – Mão esquerda	
1.6	Aspectos da SDD		3.6a	Movimentos de Pronação- supinação – Mão dir.	
1.6a	Quem preenche o questionário	□ Paciente □ Cuidador □ Paciente + Cuidador	3.6b	Movimentos de Pronação- supinação – Mão esq.	
			3.7a	Bater dos dedos dos pés – Pé direito	
1.7	Problemas de sono		3.7b	Bater dos dedos dos pés – Pé esquerdo	
1.8	Sonolência diurna		3.8a	Agilidade das pernas – Perna direita	
1.9	Dor e outras sensações		3.8b	Agilidade das pernas – Perna esquerda	
1.10	Problemas urinários		3.9	Levantar-se da cadeira	
1.11	Problemas de obstipação intestinal		3.10	Marcha	
1.12	Tonturas ao se levantar		3.11	Bloqueio na marcha (Freezing)	
1.13	Fadiga		3.12	Estabilidade postural	
Parte II			3.13	Postura	
2.1	Fala		3.14	Espontaneidade global de movimento	
2.2	Saliva e baba		3.15a	Tremor postural – Mão direita	
2.3	Mastigação e deglutição		3.15b	Tremor postural – Mão esquerda	
2.4	Tarefas para comer		3.16a	Tremor cinético – Mão direita	
2.5	Vestir		3.16b	Tremor cinético – Mão esquerda	
2.6	Higiene		3.17a	Amplitude tremor repouso – MSD	
2.7	Escrita		3.17b	Amplitude tremor repouso – MSE	
2.8	Passatempos e outras actividades		3.17c	Amplitude tremor repouso – MID	
2.9	Virar na cama		3.17d	Amplitude tremor repouso – MIE	
2.10	Tremor		3.17e	Amplitude tremor repouso – Lábio/Mandíbula	
2.11	Sair da cama, carro e cadeira baixa		3.18	Persistência do tremor de repouso	
2.12	Marcha e equilíbrio			Discinesias estiveram presentes?	□ Não □ Sim
2.13	Bloqueios na marcha			Interferiram com as pontuações?	□ Não □ Sim
3a	O paciente toma medicação?	□ Não □ Sim		Estadiamento Hoehn e Yahr	
3b	Estado clínico do paciente	□ Off □ On	**Parte IV**		
3c	O paciente toma Levodopa?	□ Não □ Sim	4.1	Tempo com discinesias	
3.C1	Se sim, minutos desde a última dose:		4.2	Impacto funcional das discinesias	
Parte III			4.3	Tempo em *OFF*	
3.1	Fala		4.4	Impacto funcional das flutuações	
3.2	Expressão facial		4.5	Complexidade das flutuações motoras	
3.3a	Rigidez – Pescoço		4.6	Distonia dolorosa do período *OFF*	