INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

PERIODONTAL INFLAMED SURFACE AREA, DIABETES MELLITUS AND BLOOD PRESSURE: ANALYSES FROM TWO REPRESENTATIVE CROSS-SECTIONAL STUDIES

Trabalho submetido por
Francisco Xavier Gomes Tormenta
para a obtenção do grau de Mestre em Medicina Dentária

outubro de 2022

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Abstract

Aim: To deploy secondary analyses using the Study of Periodontal Health in Almada-Seixal (SOPHIAS) datasets to explore whether periodontitis, diabetes mellitus and hypertension present association results in a representative sample.

Material & Methods: It was not possible to use the data from the National Health and Nutrition Examination Survey as initially purposed. The SOPHIAS had a target population of subjects over 18 years of age (adults and elderly), living in the municipalities of Almada and Seixal, in Portugal (Botelho, Machado et al., 2019). For the purpose of this study, the following inclusion criteria were defined: participants with 18 years old or older, undergone periodontal examination and measurement of blood pressure. Regarding diabetes the SOPHIAS gathered information through self-reported diabetes. Data was analysed by means of descriptive and inferential methodologies, using IBM SPSS Statistics v.25 software.

Results: Patients with hypertension and diabetes mellitus (DM) had a mean periodontal inflamed surface area (PISA) of 1118.3 (±2723.0) mm^2; patients with hypertension and no DM had a mean PISA of 826.2 (±1758.0) mm^2; patients with no hypertension and DM had a mean PISA of 1318.6 (±2099.0) mm^2; and patients without hypertension or DM had a mean PISA of 867.2(±1627.0) mm^2. However, none of the values were statistically significant. According to the generalized linear adjusted models on the association of PISA with DM, hypertension, blood pressure readings, age, body mass index (BMI), education, and smoking status, DM, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were associated to higher PISA, while age links to lower levels. The results of the association between smoking status, education, and BMI were not statistically significant.

Conclusion: Diabetes mellitus and high blood pressure were associated to periodontitis and higher periodontal inflamed surface area. Age was a significant variable in these associations.

Keywords: Periodontal Disease; Periodontitis; Diabetes; Blood Pressure

Resumo

Objetivos: Realizar uma análise secundária usando o conjunto de dados do Study of Periodontal Health in Almada-Seixal (SOPHIAS) para explorar se a periodontite, diabetes mellitus e hipertensão apresentam resultados de associação em uma amostra representativa.

Materiais e Métodos: Não foi possível usar os dados do National Health and Nutrition Examination Survey como proposto inicialmente. O SOPHIAS teve como população-alvo sujeitos maiores de 18 anos (adultos e idosos), residentes nos concelhos de Almada e Seixal, em Portugal (Botelho, Machado et al., 2019). Para fins deste estudo, foram definidos os seguintes critérios de inclusão: participantes com idade igual ou superior a 18 anos, realização de exame periodontal e aferição da pressão arterial. Em relação à diabetes o SOPHIAS recolheu informações através do autorrelato de diabetes. Os dados foram analisados por meio de metodologias descritivas e inferenciais, utilizando o software IBM SPSS Statistics v.25.

Resultados: Pacientes com hipertensão e diabetes mellitus (DM) apresentaram uma média de área de superfície periodontal inflamada (PISA) de 1118,3 (±2723,0) mm^2; pacientes com hipertensão e sem DM apresentaram um PISA médio de 826,2 (±1758,0) mm^2; pacientes sem hipertensão e DM apresentaram um PISA médio de 1.318,6 (±2.099,0) mm^2; e pacientes sem hipertensão ou DM apresentaram um PISA médio de 867,2(±1627,0) mm^2. No entanto, nenhum dos valores foi estatisticamente significativo. De acordo com os modelos lineares generalizados ajustados sobre a associação do PISA com a DM, hipertensão, leituras de pressão arterial, idade, índice de massa corporal (BMI), nível de escolaridade, e tabagismo, a DM, pressão arterial sistólica (SBP) e pressão arterial diastólica (DBP) foram associadas a um PISA mais elevado, enquanto a idade foi associada com níveis mais baixos. Os resultados da associação entre tabagismo, nível de escolaridade e IMC não foram estatisticamente significativos.

Conclusão: Diabetes mellitus e hipertensão arterial foram associados à periodontite e a maior área de superfície inflamada periodontal. A idade foi uma variável significativa nessas associações.

Palavras-chave: Doença Periodontal; Periodontite; Diabetes; Pressão Arterial

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List of Abbreviations

AAP – America Academy of Periodontology

AGE – Advanced Glycation End Products

BMI – Body Mass Index

BoP – Bleeding on Probing

CAL – Clinical Attachment Level

CRP – C-Reactive Protein

DBP – Diastolic Blood Pressure

DM – Diabetes Mellitus

EFP – European Federation of Periodontology

HbA1C – Glycated Haemoglobin

IL-6 – Interleukin 6

IL1-β – Interleukin 1-β

PI – Plaque Index

PISA – Periodontal Inflamed Surface Area

PPD – Probing Pocket Depth

RANKL/OPG - Receptor Activator of NF-jB Ligand/Osteoprotegerin

SBP – Systolic Blood Pressure

SD – Standard Deviation

SOPHIAS – Study of Periodontal Health in Alamada-Seixal

TNF-α – Tumour Necrosis Factor α

I. INTRODUCTION

1. PERIODONTITIS

Periodontal diseases comprehend gingivitis and periodontitis. Gingivitis is a reversible inflammatory illness, whereas periodontitis is characterized by irreversible alveolar bone loss (Preshaw et al., 2012; Kinane et al., 2017).

The aetiology of periodontal diseases is dental plaque, and often if gingivitis is left untreated progresses to periodontitis. Both the periodontal ligaments and the alveolar bone are impacted, resulting in pathological periodontal pockets, which are the predominant clinical signs of the disease (Kinane et al., 2017; Liccardo et al., 2019).

Periodontitis is a highly prevalent disease, with severe periodontitis affecting 10-15% of individuals and moderate periodontitis impacting 40-60% of adults (Preshaw et al., 2012; Kassebaum et al., 2014; Tonetti et al., 2017). In 2018, periodontitis led to an estimated loss of $154.06 billion in the United States of America and €158.64 billion in Europe. (Botelho et al., 2022).

The Study of Periodontal Health in Almada-Seixal (SOPHIAS) found that 59.9% of people in the Southern Lisbon Metropolitan Area had some form of periodontitis (Botelho, Machado et al., 2019).

Periodontitis ultimate consequences are tooth loss, increased morbidity, lowers quality of life, and decreased work productivity (Machado, Aguilera et al., 2020). Furthermore, systemic health has been increasingly linked to periodontitis, with diabetes mellitus (DM) and cardiovascular diseases being factors to consider (Hajishengallis & Chavakis, 2021).

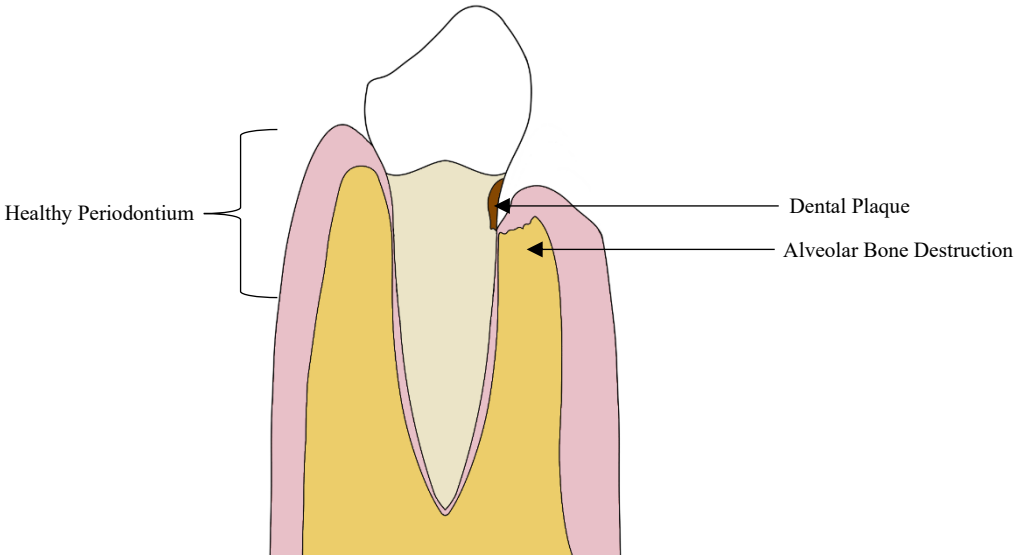

Figure 1 | Schematic representation of periodontitis. The left side of the figure depicts a periodontal health scenario, whereas the right side depicts a situation of periodontitis. Original image.

1.1. Pathophysiology

Periodontal disease requires the presence of a subgingival bacterial biofilm (Liébana & Castillo, 1994; Meyle & Chapple, 2015). To date, over 500 species of bacteria have been found in human subgingival plaque (Curtis et al., 2020; Abusleme et al., 2021).

The composition of the subgingival bacterial community varies depending on whether the periodontium is healthy, with gingivitis, or affected by periodontitis (Curtis et al., 2020; Abusleme et al., 2021). The disease arises when a symbiotic microbial population (mostly of facultative anaerobic genera) transitions to a dysbiotic microbial ecosystem (primarily of anaerobic genera) (Hajishengallis, 2015).

Furthermore, the inflammatory immunological response of the host, has an essential role in the development of periodontal disease (Hajishengallis, 2015; Meyle & Chapple, 2015).

If the oral biofilm is not disrupted on a regular basis, it begins to favor bacterial species such as *fusobacterium nucleatum*, which can evoke a more intense immune response, promoting gingival inflammation and nutrient availability, promoting the growth of *porphyromonas gingivalis* (Meyle & Chapple, 2015). This can result in an overactive immune response in vulnerable patients, resulting in the production of excess cytokines, oxidative stress, and matrix metalloproteinases, culminating in collateral periodontal tissue damage (Meyle & Chapple, 2015).

The binding of glucose, advanced glycation end products (AGE), and oxidized low-density lipoproteins to their corresponding receptors on the neutrophil surface enhances tissue responses to inflammatory stimuli in diabetes, resulting in accelerated tissue damage and attachment loss (Meyle & Chapple, 2015; Sonnenschein & Meyle, 2015).

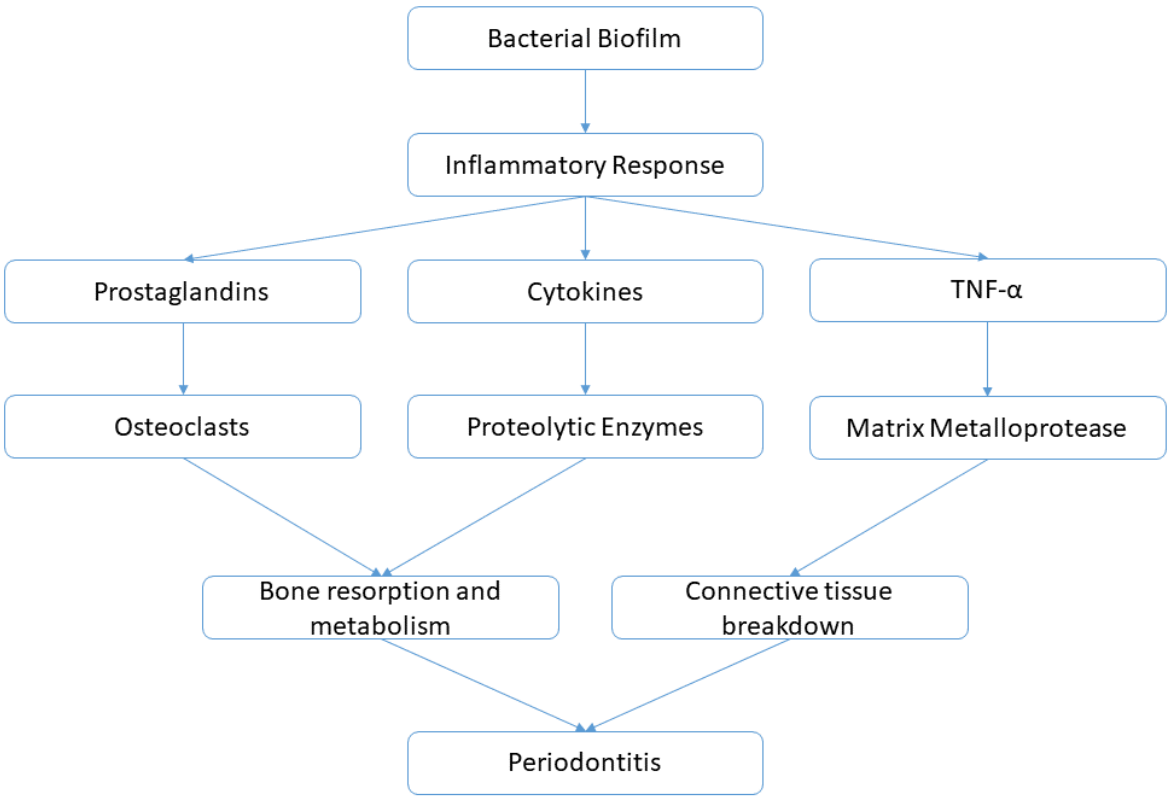

Figure 2 | Pathogenesis of Periodontitis. Adapted from Yadav et al., 2015.

1.2. Classification

The American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) recommended a new classification of periodontal diseases in 2018. This new classification involves categorizing periodontal diseases using a multidimensional staging and grading system (Tonetti et al., 2018).

In terms of staging (Table 1), it seeks to classify the severity and extent of periodontitis based on an individual's currently detectable extent of damaged periodontium. Furthermore, staging also tries to analyze the complexity of disease management. Periodontitis stage is divided into two dimensions: severity and complexity. Ideally, the severity is determined by the clinical attachment level (CAL) of an individual's most affected tooth. Radiographic bone loss should be utilized instead of CAL if CAL is not available. It is possible that tooth loss caused by periodontitis may change the stage. The

presence of features such as vertical deformities, furcation involvement, tooth hypermobility, drifting and/or flaring of teeth, tooth loss, ridge deficiency, and loss of masticatory function increases the complexity and may shift stage to a higher level (Tonetti et al., 2018).

In respect to grading (Table 2), the goal is to assess the rate of periodontitis progression and its responsiveness to treatment, as well as the impact of periodontitis on systemic disorders and vice versa, allowing for co-therapy with medical colleagues. Grading is based on direct or indirect evidence of periodontitis progression. The first uses longitudinal data, such as older radiographs, to measure bone loss over the last 5 years, whereas the second is based on the ratio of current bone loss to the individual's age. Additionally, risk factors such as smoking, and diabetes can influence grade (Tonetti et al., 2018).

Moreover, three types of periodontitis have been identified in terms of pathophysiology: necrotizing periodontitis, which is characterized by pain, ulceration of gingival margin and/or fibrin deposits at sites with decapitated gingival papillae and, occasionally, exposure of the alveolar bone; periodontitis as a direct manifestation of systemic diseases; and periodontitis (Tonetti et al., 2018).

Table 1 | Periodontitis Staging. Adapted from Tonetti et al., 2018.

Periodontitis stage		**Stage I**	**Stage II**	**Stage III**	**Stage IV**
Severity	**Interdental CAL**	1 to 2 mm	3 to 4 mm	≥5mm	≥5mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤4 teeth	Tooth loss due to periodontitis of ≥5 teeth

Complexity	**Local**	Maximum probing depth ≤4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to stage II complexity: Probing depth ≥6 mm Vertical bone loss ≥3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree ≥2) Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth
Extent and distribution	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern				

Table 2 | Periodontitis Grading. HbA1c: Glycated hemoglobin. Adapted from Tonetti et al., 2018.

Periodontitis Grade			**Grade A**	**Grade B**	**Grade C**
Primary criteria	**Direct evidence of progression**	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years

Primary criteria (continuation)	**Indirect evidence of progression**	% Bone loss/age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease
Grade modifiers	**Risk Factors**	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic	HbA1c <7.0% in diabetic patients	HbA1c ≥7.0% in diabetic patients

1.3. Innovative Clinical Periodontal Measures

Periodontitis is classified according to the CAL. The degree of attachment loss is indicated by the sum of gingival recession and probing pocket depth (PPD) (Park et al., 2017; Leira et al., 2018). One shortcoming of this classification is that it is based on linear measurements and may not quantify the quantity of inflamed periodontal tissue that is at the root of any potential relationship between periodontitis and other diseases (Leira et al., 2018).

As a result, a new categorization, the periodontal inflamed surface area (PISA), was developed in 2008. PISA is a periodontal health index that measures the surface area of bleeding pocket epithelium in square millimetres (mm2) and is calculated using clinical periodontal health parameters such as bleeding on probing (BoP), a sign of active inflammation, combined with either PPD or CAL and gingival recession (Nesse et al., 2008; Leira et al., 2018; Nomura et al., 2021). The bleeding surface area is significant

because it has a high infiltration of inflammatory cells, which may contribute to a systemic inflammatory response (Nesse et al., 2008).

PISA has an advantage over traditional periodontal indices in that it represents periodontal condition as a continuous variable, preventing information loss during statistical analysis (Park et al., 2017). Furthermore, rather than reporting periodontal conditions as discrete data that can be difficult to integrate for statistical analysis, PISA incorporates them into a value (Park et al., 2017).

1.4. Risk Factors

Although periodontitis being a disorder where the accumulation of dental plaque is the primary etiological factor, several other factors can influence its pathogenesis (Albandar, 2002; Van Dyke & Sheilesh, 2005; Genco & Borgnakke, 2013; Wellapuli & Ekanayake, 2017; Machado et al., 2018).

The risk factors for periodontitis are divided into modifiable and non-modifiable. The first are frequently behavioural or environmental, while the second are intrinsic to the individual (Van Dyke & Sheilesh, 2005).

Examples of common modifiable risk factors for periodontitis are smoking, poorly controlled diabetes, obesity, osteoporosis, low dietary calcium and vitamin D, and stress. Eliminating or controlling these risk factors will have a positive impact on periodontal health, and therefore should be implemented as part of periodontal treatment (Genco & Borgnakke, 2013).

Non-modifiable risk factors such as being male, genetic factors, other systemic disorders, and age, although not possible to eliminate, are important in identifying risk individuals (Van Dyke & Sheilesh, 2005; Genco & Borgnakke, 2013; Wellapuli & Ekanayake, 2017).

2. DIABETES MELLITUS

Diabetes mellitus (DM) is a metabolic condition that causes persistent hyperglycaemia due to abnormalities in insulin secretion, action, or both (American Diabetes Association, 2013; Kerner & Brückel, 2014; Preshaw & Bisset, 2019).

Its global incidence is increasing due to an aging population, socioeconomic development, urbanization, highly processed meals, and decreased physical exercise (Glovaci et al., 2019). Diabetes affected around 422 million persons globally in 2014. (Kanter & Bornfeldt, 2016). This figure is expected to climb to 642 million by 2040. (Zheng et al., 2018). Type 2 DM accounts for more than 90% of all DM diagnoses and was responsible for around 5 million fatalities in 2015. (Zheng et al., 2018). Additionally, it is anticipated that diabetes and its consequences will have a global economic effect of more than $2.1 trillion by 2030. (Bommer et al., 2018).

2.1. Pathophysiology of DM

As stated above, the main clinical characteristic of DM is hyperglycaemia caused by deficiencies in insulin secretion and/or action. Although many pathways may be related to this increase in blood glucose levels, the great majority of cases are classified as type 1 diabetes or type 2 diabetes (Skyler, 2004).

Type 1 diabetes has a strong genetic component and is most commonly caused by an auto-immune related loss of pancreatic islet β-cells mass and/or function which will result in insufficient insulin production (Skyler, 2004; Skyler et al., 2017).

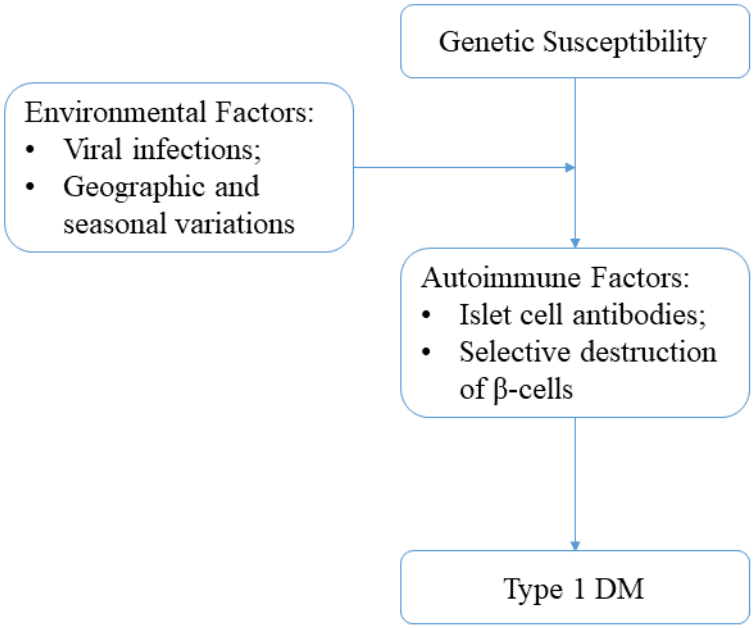

Figure 3 | Pathogenesis of type 1 diabetes mellitus. Adapted from Parveen et al., 2017.

Type 2 diabetes, on the other hand, is usually caused by insulin resistance together with a deficient compensatory insulin secretion response by the pancreatic islet β-cells (Skyler, 2004). While insulin resistance originates with fat deposition in the liver and muscle, the deficiency in insulin secretion is the result of fat deposition in the pancreas in conjunction with the stress caused by hyperglycaemia which will lead to reduced β-cell function and potentially β-cells apoptosis (Skyler et al., 2017).

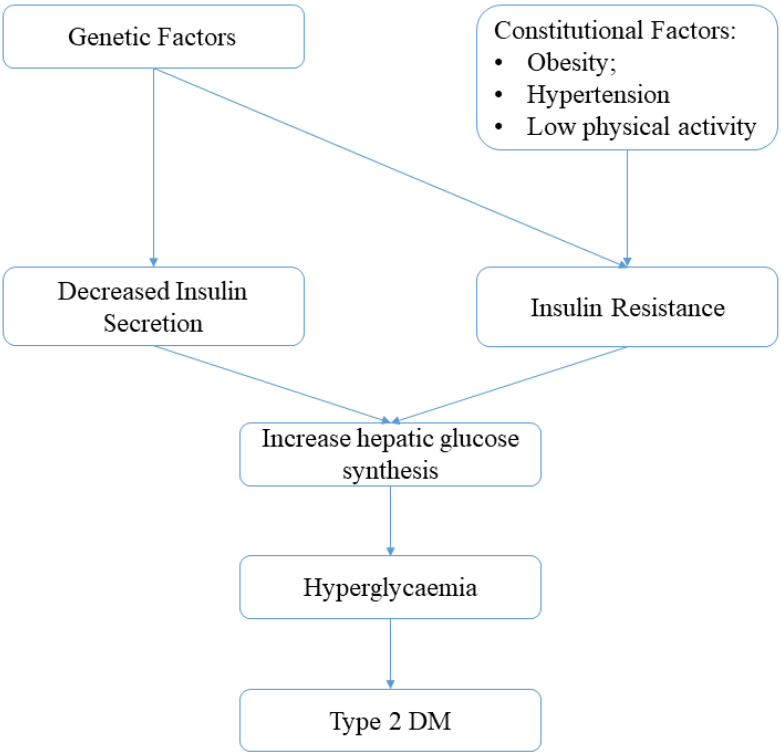

Figure 4 | Pathogenesis of type 2 diabetes mellitus. Adapted from Parveen et al., 2017.

Furthermore, the inflammatory burden of an individual has been associated with the development and progression of both type 1 and type 2 diabetes (King, 2008). Long term type 1 diabetes has been associated with an increase in levels of C-reactive protein (CRP) and interleukin 1- β (IL1- β) (King, 2008).

Additionally, increases in CRP and interleukin-6 (IL-6) have been associated with higher risk of developing type 2 diabetes (King, 2008). Moreover, tumour necrosis factor α (TNF- α) and other cytokines were associated with increased insulin resistance (Shoelson, 2006).

2.2. DM and Periodontitis

DM is intimately linked to periodontitis because the two chronic diseases have a bidirectional interaction and, therefore, influence the course and outcome of each other (Sanz et al., 2018; Preshaw & Bisset, 2019; Anil et al., 2021). On the one hand, poor glycaemic management is linked to worse periodontal state (Sanz et al., 2018), with diabetic patients having a 2-3 times greater chance of being diagnosed with periodontitis (Preshaw & Bisset, 2019).

This has been attributed to increased deposition of AGE in periodontal tissues, which will affect collagen stability, vascular integrity, and cell functions, as well as stimulate the release of proinflammatory cytokines such as IL1- β, TNF- α, IL-6, and shifts in the receptor activator of NF-jB ligand/Osteoprotegerin (RANKL/OPG) ratio. This will result in greater periodontal destruction (Polak & Shapira, 2018; Anil et al., 2021).

Poor periodontal health, on the other hand, is associated with dysglycaemia and increased insulin resistance in people with DM. This may be explained by the inflammatory burden of periodontitis (for example, proinflammatory cytokines entering circulation) interfering with glycaemic homeostasis and insulin resistance (Sanz et al., 2018; Preshaw & Bisset, 2019; Anil et al., 2021).

Furthermore, periodontitis might raise the risk of DM complications such retinopathy, nephropathy, neuropathic foot ulceration, cardiovascular diseases, and even death (Sanz et al., 2018).

As a result, some guidelines were developed, including: patients with diabetes should be informed that they are at a greater risk for gingivitis and periodontitis, and that if they have periodontitis, their glycaemic control may be more difficult to attain (Sanz et al., 2018); patients with diabetes should bring a copy of their most recent glycated haemoglobin (HbA1C) result to their dental appointment (Sanz et al., 2018); patients with diabetes should receive a full periodontal evaluation (Sanz et al., 2018); non-surgical periodontal therapy is suggested regardless of diabetes control level, since it may help to improve glycaemic control (Sanz et al., 2018) (interventional data suggests that periodontal therapy can help reduce glycated haemoglobin levels by an average of 0.40% (Preshaw & Bisset, 2019)); patients with poor diabetes control should not undergo surgical periodontal therapy and, in patients medicated with insulin or sulfonylureas, the patient's physician should be consulted about the timing of the procedure and a possible

change in dosage of therapy to reduce the risk of intraoperative hypoglycaemia (Sanz et al., 2018).

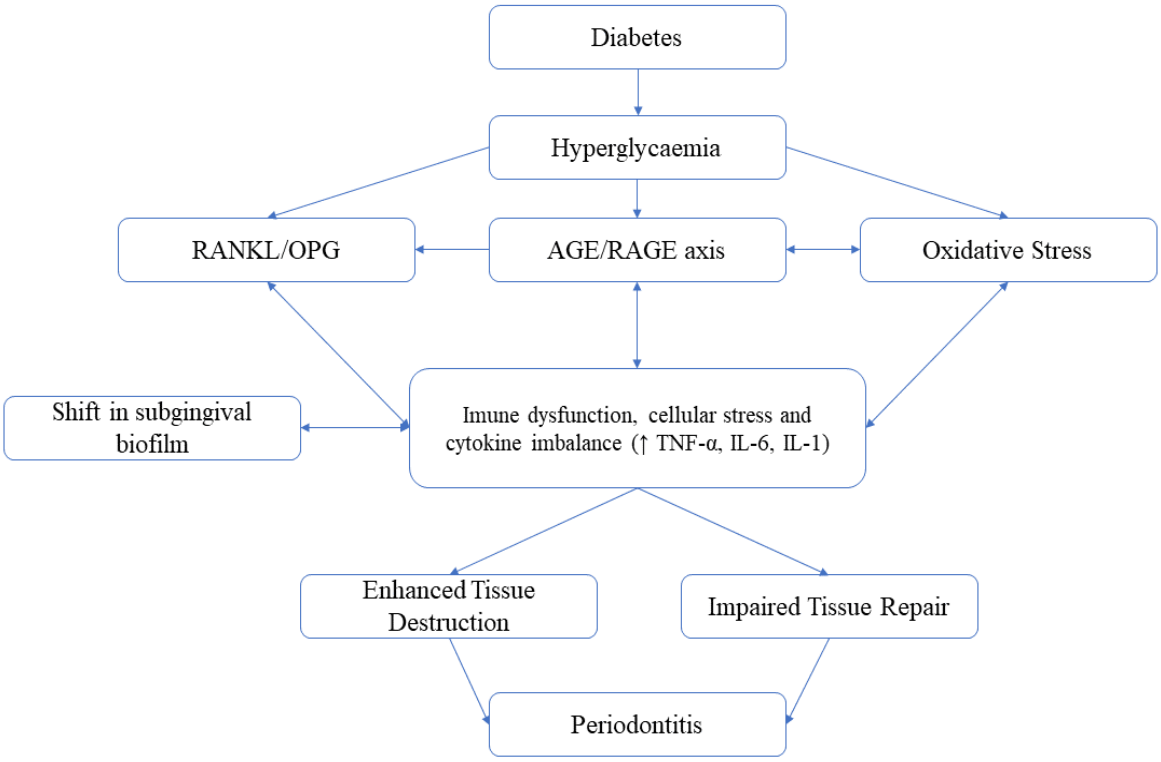

Figure 5 | Possible mechanisms linking diabetes and periodontitis. RAGE: Advanced Glycation End product receptor. Adapted from Taylor et al., 2013.

3. BLOOD PRESSURE

Hypertension, defined as an increase in systolic blood pressure (≥140 mmHg) and/or diastolic blood pressure (≥90 mmHg), is the main cause of cardiovascular disease and global mortality, accounting for approximately 9.4 million deaths each year (Poulter et al., 2015; Mills et al., 2020). Hypertension affected around 1.39 billion individuals in 2010. It is anticipated that global prevalence will rise by 10% between 2000 and 2025, resulting in an additional 560 million individuals suffering with hypertension (Poulter et al., 2015). This increase in prevalence, just like in diabetes, can be ascribed to an increase in sedentary lifestyle and unhealthy diet (Mills et al., 2020). Additionally, this disease has societal costs (Machado, Aguilera et al., 2020), which were around $370 billion in 2001, accounting for 10% of global healthcare expenditures (Gaziano et al., 2009).

3.1. Pathophysiology of Hypertension

Hypertension is classified in primary hypertension or secondary hypertension (Beevers, 2001). Primary hypertension is the most prevalent type, representing 95% of all hypertension cases, and is defined by increased blood pressure where the precise cause cannot be identified (Hall et al., 2012). Secondary hypertension however may be the result of some form of renal or adrenal disease (Beevers, 2001).

Blood pressure regulation is dependent on the coordinated actions of many cardiovascular, renal, neurological, endocrine, and local tissue regulatory systems (Hall et al., 2012).

Genetics, sympathetic nervous system overactivity, increased salt consumption, endothelial cell dysfunction, nitric oxide pathway, renin-angiotensin-aldosterone system, obesity, and insulin resistance are all linked to primary hypertension (Saxena et al., 2018).

Furthermore, hypertension has been associated with inflammation (Dinh et al., 2014; Guzik & Touyz, 2017; Xiao & Harrison, 2020). Higher plasma levels of CRP, IL-6, IL1-β and TNF-α have been found in patients with hypertension in comparison with normotensive patients (Dinh et al., 2014). Additionally, higher baseline levels of CRP have been linked to a greater risk of developing hypertension (Dinh et al., 2014).

Moreover, CRP and TNF-α may cause endothelial dysfunction by reducing nitric oxide production wish in turn leads to reduced endothelial-dependent vasodilation (Dinh et al., 2014).

3.2. Hypertension and Periodontitis

Periodontitis and hypertension are associated due to their common demographics and risk factors such as older age, male gender, non-Caucasian race, smoking, being overweight, diabetes, having a low socioeconomic status, and having a poor education (Del Pinto et al., 2020).

In Portugal, undiagnosed hypertension has been associated to severe periodontal states (Machado, Aguilera et al., 2020). Furthermore, moderate to severe periodontitis cases are more prone to have hypertension, with the more severe the periodontitis, the higher the odds of having hypertension, indicating a positive linear connection between these two disorders (Muñoz Aguilera et al., 2020). Moreover, hypertension patients have a higher prevalence of periodontitis (Muñoz Aguilera et al., 2020).

Periodontitis, on the one hand, can raise the risk of hypertension due to a rise in CRP, which has been found to predict the development of hypertension (Tsioufis et al., 2011). Other systemic inflammatory mediators, such as IL-6 and TNF-α, that are increased in periodontitis, can also impair endothelial function (Muñoz Aguilera et al., 2020).

Furthermore, both PISA and periodontal epithelium surface area have been demonstrated to strongly affect the relationship between homocysteine (an amino acid linked to elevated blood pressure) and systolic and diastolic blood pressure (Botelho et al., 2021).

Moreover, periodontal bacteria such as *porphyromonas gingivalis* can reach the bloodstream and colonize atherosclerotic plates (Tsioufis et al., 2011). Additionally, immunological response to *porphyromonas gingivalis* has been demonstrated to produce blood pressure increase, vascular inflammation, and endothelial dysfunction (Muñoz Aguilera et al., 2020).

On the other hand, the higher prevalence of periodontitis in hypertensive patients may be explained by microcirculatory alterations in the gingival tissue, which may contribute to ischemia, increased inflammation, and disturbances in the microbial content of the dental plaque (Muñoz Aguilera et al., 2020).

Given the link between these two chronic diseases, several guidelines were developed, including the following: patients with periodontitis and a cardiovascular disease diagnosis should be alerted that they may be at higher risk for cardiovascular problems (Sanz et al., 2020); regardless of their level of cardiovascular illness, these patients should receive non-surgical periodontal treatment, preferably in 30 to 45 minute sessions, to lessen the acute systemic inflammation induced by the treatment (Sanz et al., 2020). However, in the event of surgical intervention in hypertensive patients, it is advisable to assess the blood pressure beforehand, and if the blood pressure is greater than 180/100, the surgery should be delayed (Sanz et al., 2020).

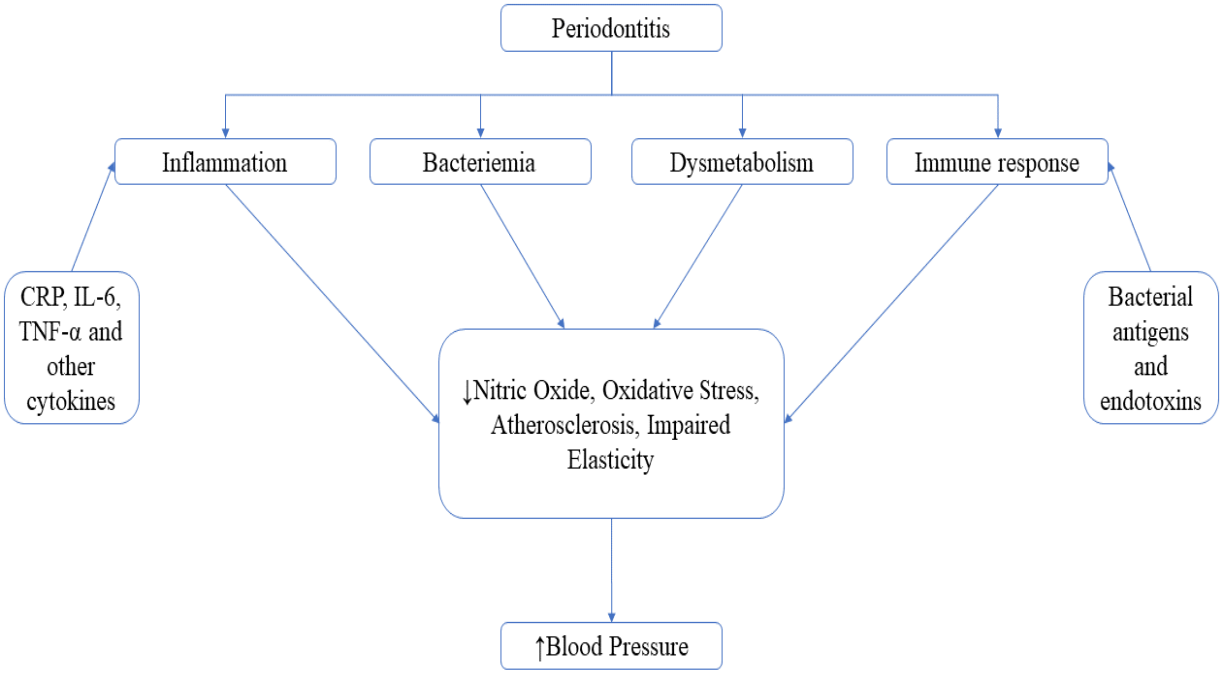

Figure 6 | Possible mechanisms linking periodontitis to increases in blood pressure. Adapted from Tsioufis et al., 2011.

4. AIM

Given the clinical interloping between periodontitis, diabetes, and hypertension, we aim to deploy secondary analyses using the SOPHIAS datasets to explore whether these conditions present association results in a representative adult population. Therefore, the following PICO question was formulated: "Are diabetes mellitus and blood pressure associated with periodontal inflamed surface area?", with the following statements:

- P (Population): Patients aged 18 and above who underwent a periodontal examination and had diabetes mellitus and/or high blood pressure.
- I (Intervention): Periodontal examination and blood pressure testing
- C (Comparison): Patients aged 18 and above who underwent a periodontal examination and did not have diabetes or high blood pressure.
- O (Outcome): Periodontal inflamed surface area.

II. MATERIALS AND METHODS

This study was reported following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline (Cuschieri, 2019).

1. STUDY DESIGN

A secondary analysis was conducted in this study utilizing SOPHIAS records. SOPHIAS dataset was acquired through questionnaires, followed by a periodontal examination (Botelho, Machado et al., 2019). The study was approved by the Research Ethics Committee of the Regional Health Administration of Lisbon and Tagus Valley, IP (Portugal). All participants signed written informed consent forms. It was not possible to use the data from the National Health and Nutrition Examination Survey as initially purposed.

2. SETTINGS AND PARTICIPANTS

The SOPHIAS had a population of individuals over the age of 18 (adults and the elderly) residing in the Portuguese municipalities of Almada and Seixal (Botelho, Machado et al., 2019). The following inclusion criteria were established for the purposes of this study: Participants aged 18 and above who had undergone periodontal examination and blood pressure testing.

3. VARIABLES

In the SOPHIAS, two calibrated investigators used a manual periodontal North Carolina probe to do a full-mouth periodontal exam. Plaque index (PI), gingival recession, PPD, and BoP were also measured at six different locations on each tooth. The clinical attachment loss was calculated as the algebraic sum of each site's gingival recession and PPD values (Botelho, Machado et al., 2019).

To categorize periodontitis, the SOPHIAS resorted to the latest available EFP/AAP consensus for gingivitis and periodontitis cases (Botelho, Machado et al., 2019).

The SOPHIAS obtained diabetes information by self-reported diabetes. In terms of blood pressure, an automated sphygmomanometer equipment (Omron M3 Comfort®) was utilized, and blood pressure measurements were taken as a single measurement. Caffeine,

exercise, and smoking were prohibited for 30 minutes before blood pressure monitoring (Machado, Aguilera et al., 2020).

The SOPHIAS collected sociodemographic information such as age, gender, marital status, employment, degree of education, and monthly family gross income (Botelho, Machado et al., 2019).

4. STATISTICAL METHODS

Data was analysed by means of descriptive and inferential methodologies, using IBM SPSS Statistics v.25 software. The level of statistical significance is set at 5%. Descriptive measures are reported through mean ± standard deviation (SD) for continuous variables and number of cases (n), percentage (%) for categorical variables. We will compare baseline variables between periodontitis and non-periodontitis groups using Chi-square test for categorical variables and Mann–Whitney test for continuous variables. Multivariate analyses (binary logistic and linear regressions) will be used to model the influence of the arterial hypertension and diabetes on periodontal status. Odds ratio (OR) and 95% confidence intervals (95% CI) will be calculated within the logistic regression analyses, for different adjustment levels.

III. RESULTS

It was not possible to use the data from the National Health and Nutrition Examination Survey as initially purposed.

1. SOCIODEMOGRAPHIC VARIABLES

Table 3 shows the characteristics of the 1057 study participants based on the presence or absence of periodontitis. Individuals with periodontitis had a mean age of 65.2 (±13.5) years, while those without periodontitis had a mean age of 54.8 (±17.8) years. In terms of gender, 43.3% were men, with 68.7% suffering from periodontitis. In contrast, only 53.7% of women had periodontitis. In terms of race, 86.7% of those who took part were Caucasian, 12.3% were Black, and 1% were Asian. Regarding education, only 3.9% of the individuals had no education, 38.8% had basic education, 46.4% had medium education, and 10.9% had higher education. Relative to the smoking habits 59% of the individuals refer never smoking, 27.3% were former smokers, and 13.7% were active smokers. Additionally, the participants with periodontitis had a lower mean income when compared to the participants with a healthy periodontium.

Table 3 | Characteristics of the participants included in the SOPHIAS study.

	No Periodontitis (*n* = 423)	**Periodontitis (*n* = 634)**	***p*-Value [#]**
Age, mean (SD)	54.8 (17.8)	65.2 (13.5)	<0.001
Gender, *n* (%)			
Female (*n* = 610)	283 (46.4)	327 (53.6)	<0.001
Male (*n* = 447)	140 (31.3)	307 (68.7)	
Race, *n* (%)			
Caucasian (*n* = 916)	359 (39.2)	557 (60.8)	0.164
Black (*n* = 130)	57 (43.8)	73 (56.2)	
Asian (*n* = 11)	7 (63.6)	4 (36.4)	

Education Level, *n* (%)			
No education (*n* = 42)	11 (26.2)	31 (73.8)	<0.001
Basic (*n* = 410)	134 (32.7)	276 (67.3)	
Medium (*n* = 490)	205 (41.8)	285 (58.2)	
Higher (*n* = 115)	73 (63.5)	42 (36.5)	
Smoking Habits, *n* (%)			
Never (*n* = 624)	294 (47.1)	330 (52.9)	<0.001
Former (*n* = 288)	83 (28.8)	205 (71.2)	
Current (*n* = 145)	46 (31.7)	99 (68.3)	
Income, mean (SD) (€)	1097.0 (767.3)	981.5 (667.9)	0.023
Clinical Variables			
Hypertension, *n* (%)			
No (*n* = 357)	188 (52.7)	169 (47.3)	<0.001
Yes (*n* = 700)	235 (33.6)	465 (66.4)	
SBP, mean (SD)	129.5 (20.1)	136.5 (20.4)	<0.001
DBP, mean (SD)	77.9 (13.2)	79.6 (13.6)	0.082
Diabetes Mellitus, *n* (%)			
Yes (*n* = 204)	53 (26.0)	151 (74.0)	<0.001
No (*n* = 853)	370 (43.4)	483 (56.6)	
BMI, mean (SD)	27.1 (4.9)	27.5 (4.7)	0.051
Periodontal Clinical Parameters, Mean (SD)			
Missing Teeth (*n*)	6.6 (6.1)	10.8 (7.1)	<0.001
Mean PPD (mm)	1.51 (0.30)	2.22 (0.83)	<0.001
Mean CAL (mm)	1.72 (0.35)	3.39 (1.52)	<0.001
Mean Rec (mm)	0.22 (0.27)	1.18 (1.15)	<0.001

BoP (%)	5.6 (9.3)	20.9 (23.6)	<0.001

2. CLINICAL VARIABLES

In what blood pressure regards, 66.2% of the individual suffered from hypertension, from which 66.4% had periodontitis. In comparison, only 47.3% of those without hypertension had a diagnosis of periodontitis.

Furthermore, the mean systolic blood pressure (SBP) in patients without periodontitis was 129.5 (±20.1) mmHg, while being 136.5 (±20.4) mmHg in people with periodontitis. Additionally, individuals without periodontitis had a mean diastolic blood pressure (DBP) of 77.9 (±13.2) mmHg, while patients with periodontitis had a DBP of 79.6 (±13.6) mmHg.

In terms of diabetes mellitus, only 19.3% of the 1057 patients had diabetes, with 74% having periodontitis. In contrast, only 56.6% of individuals without diabetes were diagnosed with some kind of periodontitis.

In terms of periodontal clinical characteristics, the average number of missing teeth was 6.6 (±6.1) in adults without periodontitis and 10.8 (±7.1) in people with periodontitis. Furthermore, in patients without periodontitis, the mean PPD was 1.51 (±0.30) mm, whereas in patients with periodontitis, it was 2.22 (±0.83) mm.

Moreover, the mean CAL in patients without periodontitis was 1.72 (±0.35) mm and 3.39 (±1.52) mm in patients with periodontitis. Additionally, the mean recession in participants without periodontitis was 0.22 (±0.27) mm, but it was 1.18 (±1.15) mm in participants with diagnosed periodontitis. Finally, the mean BoP was 5.6 (±9.3) % in patients with healthy periodontium and 20.9 (±23.6) % in patients with diseased periodontium.

When the mean PISA values of diabetes and non-diabetic patients are compared (Table 4), the following findings are obtained: Patients with hypertension and DM had a mean PISA of 1118.3 (±2723.0) mm^2; patients with hypertension and no DM had a mean PISA of 826.2 (±1758.0) mm^2; patients with no hypertension and with DM had a mean PISA of 1318.6 (±2099.0) mm^2; and patients without hypertension or DM had a mean PISA of 867.2(±1627.0) mm^2. However, none of the values were statistically significant.

Table 4 | Comparison of PISA values according to the blood pressure category, comparing diabetic and non-diabetic patients.

	Hypertension		p-value	No Hypertension		p-value
Mean (SD)	DM	Non-DM		DM	Non-DM	
PISA (mm^2)	1118.3 (2723.0)	826.2 (1758.0)	0.391	1318.6 (2099.0)	867.2 (1627.0)	0.244

According to the generalized linear adjusted models on the association of PISA with DM, hypertension, blood pressure readings, age, body mass index, education, and smoking status, shown in table 5, we can see that in model 1 only two variables had a statistically significant impact on the PISA those being DM (β: 398.3(±156.1); p-value: 0.011) and age (β: -16.1(±4.7); p-value: <0.001).

In model 2, where the value of systolic blood pressure was used, instead of the categorical variable "hypertension", we can see that in addition to DM (β: 409.5(±155.0); p-value: 0.008) and age (β: -18.6(±4.6); p-value: <0.001), the SBP (β: 9.8(±3.2); p-value: 0.002) also had a statistically significant impact on the PISA.

In model 3, the value of diastolic blood pressure was used instead of the value of the systolic blood pressure, and we also have three statistically significant variables, those being, DM (β: 414.9(±153.8); p-value: 0.007), DBP (β: 22.0(±4.4); p-value: <0.001), and age (β: -16.3(±4.3); p-value: <0.001).

In model 4, where both SBP and DBP values were used, we maintained three statistically significant values, which were the same as in model 3, DM (β: 414.3(±153.9); p-value: 0.007), DBP (β: 20.7(±5.2); p-value: <0.001), and age (β: -17.0(±4.6); p-value: <0.001).

Table 5 | Generalized linear adjusted models on the association of PISA with diabetes for hypertension, blood pressure readings (systolic and diastolic), age, BMI, education, and smoking status.

	Model 1		Model 2		Model 3		Model 4	
Variable	ß (SE)	p-value	ß (SE)	p-value	ß (SE)	p-value	ß (SE)	p-value
Intercept	**2034.8 (463.8)**	**<0.001**	**1078.6 (542.0)**	**0.047**	604.2 (530.3)	0.255	529.7 (555.7)	0.341
DM	**398.3 (156.1)**	**0.011**	**409.5 (155.0)**	**0.008**	**414.9 (153.8)**	**0.007**	**414.3 (153.9)**	**0.007**
Hypertension	158.6 (145.9)	0.277	-	-	-	-	-	-
SBP	-	-	**9.8 (3.2)**	**0.002**	-	-	1.7 (3.7)	0.653
DBP	-	-	-	-	**22.0 (4.4)**	**<0.001**	**20.7 (5.2)**	**<0.001**

Age	**-16.1 (4.7)**	**<0.001**	**-18.7 (4.6)**	**<0.001**	**-16.3 (4.3)**	**<0.001**	**-17.0 (4.6)**	**<0.001**
BMI	-7.8 (12.7)	0.539	-11.2 (12.6)	0.376	-13.9 (12.5)	0.266	-14.4 (12.6)	0.254
Education	-240.8 (138.6)	0.083	-223.9 (138.1)	0.105	-265.2 (137.0)	0.053	-260.1 (137.5)	0.059
Smoking status	91.5 (179.0)	0.610	65.5 (178.0)	0.713	61.1 (176.7)	0.730	59.7 (176.8)	0.736

ß – ß Coefficient
Bold face – significant values.

IV. DISCUSSION

The current investigation sought to explore the association of two systemic conditions of increasing prevalence – DM and hypertension – with PISA. In addition to the primary purpose of SOPHIAS, the collected data was secondarily used to explore for connections between PISA and periodontitis risk factors such as smoking, advanced age, high BMI, and poor education.

According to the findings of this study, periodontitis affects around 60% of the population. This value, however, may be exaggerated due to the study's population's advanced mean age. Table 3 shows that various sociodemographic characteristics were associated with a higher prevalence of periodontitis.

In terms of gender, males have a higher prevalence of periodontitis (68.7%) than females (53.6%). These findings support prior data that gender influences the risk of developing periodontal disease (Zhang et al., 2014; Eke et al., 2015; Wellapuli & Ekanayake, 2017). We can discover similar results when comparing studies from different countries. A study conducted in the United States discovered a periodontitis prevalence of approximately 54.9 (±1.6) % in males and 37.4 (±1.8) % in females (Eke et al., 2015). Another study, this time in China, discovered that males were around 3.5 times more likely than females to suffer from periodontitis (Zhang et al., 2014). This relationship between gender and periodontitis may be explained by lifestyle differences between males and females (Genco & Borgnakke, 2013). Furthermore, sex-specific genetic architecture and the circulating amounts of sex-steroid hormones may influence the immunological response, making males more susceptible to periodontitis (Shiau et al., 2014).

Previous research indicates that race is a risk indicator for periodontitis (Eke et al., 2015). However, there were no statistically significant differences in prevalence by race in the current investigation. This finding may be explained by the low proportion of non-Caucasian people relative to Caucasians.

In this survey, the majority of participants had a medium or lower level of education, with only 10.9% having a higher degree of education. Having said that, it was found that when education level fell, the prevalence of periodontitis increased. This can be explained by the fact that low education is connected with low socioeconomic status, and low socioeconomic status is related with poor oral health literacy (Batista et al., 2018).

Moreover, patients with lower socioeconomic level might be unable to afford the costs of dental treatments.

Smoking is one of the leading risk factors for developing periodontitis (Leite et al., 2018). In the present study, the majority of study participants (59%) never smoked, and only 145 (13.7%) were active smokers. However, as expected, we detected an increase in periodontitis prevalence among both active and past smokers.

In terms of blood pressure, the study found a high prevalence of hypertension (66.2%). This result is almost double the national prevalence of hypertension of 36% (Rodrigues et al., 2017). This discrepancy may be explained by the advanced mean age of the study's participants. Furthermore, those with hypertension had a higher prevalence of periodontitis (66.4%) compared to those with normal blood pressure (47.3%). Nonetheless, people with periodontitis had higher mean SBP and DBP. This could point to a bidirectional link between periodontitis and high blood pressure.

In terms of DM, the present study found a prevalence of 19.3%, which, once again, is higher than the national prevalence of diabetes of 13.6% (Raposo, 2020). This result, just like the high prevalence of hypertension, may be explained by the advanced mean age of the study's population. We found that diabetic participants had a higher prevalence of periodontitis (74%) than non-diabetic participants (56.6%).

The results shown in table 4 were unexpected as we can see that there is no statistically significant difference between the PISA scores between participants who had had both DM and hypertension and those who did not have either. It can even be observed that the participants who had hypertension and no DM had a lower PISA than those with neither of these systemic diseases, which, while not statistically significant, contradicts earlier findings that hypertension affects periodontal health (Muñoz Aguilera et al., 2020). Nevertheless, we can see that in both patients with and without hypertension, the ones who suffered from DM had a higher mean PISA reinforcing past findings that DM is closely related to periodontal health (Chávarry et al., 2009; Wellapuli & Ekanayake, 2017)

Table 5 shows that some variables have a greater impact on the value of PISA than others. DM was the variable with the greatest detrimental impact on PISA in all four models. This result once again corroborates previous findings that DM is an important risk factor for periodontitis (Chávarry et al., 2009; Wellapuli & Ekanayake, 2017).

Furthermore, in table 5, we can see a possible reason why the results of table 4 were not statistically significant, which is due to the variable "hypertension" being a categorical variable, and as we can see in table 5, this variable did not have a statistically significant impact on PISA. However, when the values of SBP and DBP, which are quantitative variables, are employed, it can be seen that both of those values have a detrimental effect on the PISA score. Moreover, the DBP had a greater influence on the PISA value than the SBP. This result is consistent with previous evidence that hypertension is associated with periodontitis (Vidal et al., 2011; Wellapuli & Ekanayake, 2017)

Although the variables mentioned above can increase the value of PISA, the variable "age" had the opposite impact, where a rise in age leads to a drop in the PISA value, which contradicts earlier findings that age is a predisposing factor for periodontitis (Eke et al., 2015). Maybe this can be explained by the increase of edentulism with age (Eke et al., 2016).

Body mass index (BMI) and education had no statistically significant influence on PISA.

Furthermore, smoking status effect on PISA value was not statistically significant, contradicting earlier evidence that smoking is one of the leading risk factors for periodontitis (Leite et al., 2018). This inconsistency may be due to the low prevalence of active smokers in the study's sample. Another reason may be that, just like what happened with hypertension, the categorical variable “smoking status” was used instead of a quantitative variable like the number of cigarettes smoked per day.

Because of the greater inflammatory burden present in the periodontium of people with these systemic conditions, the findings of this study suggest that controlling and preventing periodontal disease in those with DM and hypertension should be a task not only for oral health professionals, but also for general medicine doctors.

4.1. Strengths and Limitations

This study has several strengths, including its representativeness and global geographic coverage based on the family health units where the data from the SOPHIAS was gathered and the use of the AAP/EFP case definition, which allows for future comparability across studies (Botelho et al., 2019). However, there are some limitations to note. The majority

of the individuals were 61 years old or older, which may have exaggerated the prevalence of periodontitis, hypertension, and diabetes mellitus. Furthermore, the majority of the population had medium or low education which might have had an impact on the oral health literacy and as a consequence on the prevalence of periodontitis. Additionally, we failed to find a statistically significant impact of smoking on the PISA which may be due to not using a quantitative variable like “number of cigarettes smoked per day”.

V. CONCLUSION

Diabetes mellitus and high blood pressure were associated to periodontitis and higher periodontal inflamed surface area. Age was a significant variable in these associations.

5.1. Future Perspectives

This study provides more evidence that systemic health may be closely related to periodontal health. Having said that, is increasingly important to incorporate oral health in the national health system so that the access to oral health treatment becomes more affordable.

The present investigation failed to find a link between smoking and an increase in PISA so its important to explore in depth whether or not these two variables are connected in a future study.

Furthermore, the present study had a population where that majority had 61 or more years of age which may have had an effect on the finding that an increase in age leads to a reduction on the PISA value which contradicts previous evidence that age increases the susceptibility for periodontitis (Eke et al., 2015). Therefore, a future investigation with a population of more diverse age groups is needed to confirm this result.

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