<PE-AT>Association Between Periodontitis and Systemic Medications intake:

A Case-control Study

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One-Sentence Summary: Patients with periodontitis exhibited significantly higher medication intake frequency related to cardiovascular disease and diabetes with a potential disease severity-dependent association.

Keyword: *Drug therapy, Periodontitis, Cardiovascular diseases, Diabetes mellitus<PE-FRONTEND>*

ABSTRACT

Background:

To investigate the frequency of systemic drugs taken by elderly patients with or without periodontitis and the possible association between medication consumption and the severity of periodontitis.

Methods:

A total of 1221 patients, including 608 with generalized moderate to severe periodontitis (periodontitis group) and 613 age- and gender-matched individuals with healthy periodontium (healthy group) were selected. Systemic conditions, medications and periodontal status were recorded. Medication intake frequency (%) was compared using unconditional logistic regression.

Results:

The top three most common medications were angiotensin-converting enzyme (ACE) inhibitors (17.9%), antidepressants (17.8%), and lipid-lowering medications (16.5%). Both ACE inhibitors and antidepressants showed statistically higher intake frequency in the

periodontitis group relative to healthy controls (21.5 vs. 14.4%; odds ratio (OR) = 1.64), (21.1 vs. 14.5%, OR=1.57) ($p<0.01$). Additionally, intake of oral hypoglycemic agents, calcium channel blockers, insulin and diuretics were significantly higher in the periodontitis group with OR= 2.49, 2.32, 2.08 and 1.79, respectively ($p<0.05$). Several medications demonstrated a disease severity-dependent association comparing generalized severe periodontitis with moderate periodontitis and healthy group: oral hypoglycemic agents (17.4 vs. 16.8 vs. 8.0%), calcium channel blockers (14.8 vs. 14.4 vs. 8.0%) and anticonvulsants (13.4 vs. 7.7 vs. 6.4%) with OR of 2.43, 1.99, and 2.28 (severe periodontitis vs. healthy group), respectively.

Conclusion:

There was a significantly higher frequency of medication intake related to cardiovascular disease and diabetes in patients with periodontitis. A disease severity-dependence with medication intake frequency was also noted. This study provides indirect evidence for the possible relationship between systemic diseases and periodontitis.

INTRODUCTION

The association between systemic diseases and periodontitis has been widely investigated[1]. In the past 20 years, a diversity of 57 systemic conditions have been hypothesized to be linked with periodontal disease[2]. The evolving knowledge of the role of chronic inflammation in systemic diseases, such as cardiovascular diseases[3], diabetes mellitus (DM)[4], rheumatoid arthritis[5], metabolic syndrome[6], Alzheimer's disease[7], cancer[8, 9], and other inflammatory diseases contributes to the understanding of potential biological pathways linking periodontal disease with systemic inflammation. Constantly , they were described as multifactorial diseases in the presence of multiple comorbidities, and concurrently shared multiple risk factors with periodontal disease[10]. Plausible biologic mechanisms underpinning the link between periodontitis and systemic diseases include metastatic infection, systemic spread of inflammatory mediators, activation of adaptive immunity, and elevated total burden of systemic inflammation[11]. Medication intake frequency may directly reflect systemic disease severity and can indirectly represent the systemic inflammatory burden in chronic inflammatory diseases. However, little is known regarding the systemic medications taken by patients with chronic periodontitis, especially in elderly populations.

Currently, there is limited information regarding the medication profile in patients with periodontitis and whether there is a difference compared with individuals with a healthy periodontal status. Hence, the aim of this study was to investigate the frequency and types of systemic medications taken by elderly patients with or without periodontitis and the possible association between medication intake frequency and the severity of periodontitis.

MATERIALS AND METHODS

Study design

This case-control retrospective study was approved with exemption for informed consent by the Institutional Review Board of the University of Michigan (IRB protocol # HUM00147292) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. Furthermore, all patient data and charts were anonymized since the data were retrieved without any identifiable information. The present age- and gender-matched case-control study was designed to assess whether periodontitis is associated with the intake of systemic drugs. In order to increase the detection power of systemic inflammatory burden, "cases" were selected based on diagnosis with generalized moderate to severe periodontitis on the basis of exhibiting pocket depth ≥5 mm in more than 30% teeth without previous history of periodontal treatment. The randomly selected "controls" represented periodontally healthy individuals with a 1:1 ratio between cases and controls. A power calculation was performed under the expectation of a crude odds ratio of 2 with power of 85%. It was assumed that 5% of controls were exposed to the medication consumption in general with an alpha risk of 5%. The estimated sample size was 1146 (573 matched pairs). The final sample size of 1200 (600 matched pairs) was determined to increase the power of detection.

Patient screening and sample selection

The electronic health records (EHRs) of patients seen in the Graduate Periodontics Clinic, School of Dentistry, University of Michigan between 2012 and February 2018 were screened by electronic search of American Dental Association (ADA) codes in the EHR software[†] to identify the cohort with periodontitis who had received scaling/root planing treatment. Three investigators (ICW, HA, IG) performed screening through periodontal charts at the initial

examination to document the number of remaining teeth, and the number of teeth with pocket depth (PD) ≤ 4 mm, >4 to <7 mm and ≥ 7 mm.

Case Definition of Periodontitis

According to the 2015 Update to the 1999 Classification of Periodontitis[12], generalized moderate periodontitis was defined as more than 30% of remaining teeth with PD ≥ 5 mm and < 7 mm. Severe periodontitis was identified as PD ≥ 7 mm with extent being defined as either localized (involvement of ≤ 30% of remining teeth) or generalized (> 30% of remaining teeth). Only the disease severity more than generalized moderate or severe periodontitis patients at the initial examination were included in the "case" group.

After the characteristics (age/gender) of periodontitis group were established, the control cohort was constructed accordingly by randomly selecting periodontally healthy individuals who had a history of periodontal examination in the EHR system. Periodontal status was confirmed by comprehensive examination of the initial periodontal chart.

Inclusion criteria

1. A minimum age of 40 years old
2. Patients with diagnosis of generalized moderate to severe chronic periodontitis at the baseline examination were included in the "case" group
3. Individuals with healthy periodontal condition to mild periodontitis (PD of all teeth ≤ 4 mm) were included in the "control" group
4. Adequately completed health history questionnaire was available in the EHR
5. At least 20 remaining teeth

Exclusion criteria

1. Patients had periodontal treatment within 1 year of initial examination at the University of Michigan
2. Age < 40 years old

Data Extraction

Data was extracted from the EHRs by three investigators (ICW, HA, IG) including demographic information (age, gender) and self-reported history of systemic diseases including cardiovascular diseases, hypertension, diabetes, other endocrine disorders, metabolic symptoms, rheumatoid disease, allergy, depression, Alzheimer's disease or other psychogenic disorders, cancer, and other systemic conditions. Oral intake of systemic medications taken over more than three months was recorded including types of medication, purpose of intake, and history of use. International nonproprietary names (INN), also known as generic names, were used in the descriptive analysis to allow precise identification and communication. Certain systemic medications including antibiotics, corticosteroids, and non-steroid anti-inflammatory drugs as well as non-oral routes of administration or intake history less than 3 months were excluded from the analysis.

Statistical analysis

Continuous variables were presented with absolute number (n), mean and standard deviation (SD). Two groups were compared using the Wilcoxon signed rank test after a normality test. Medication consumptions were converted in percentages as the intake frequencies (%) among groups and analyzed using unconditional logistic regression. Univariate logistic regression was performed to detect the significant differences of all the possible confounding covariates, including age, gender and number of remaining teeth. Significant covariates were adopted in the multivariable logistic regression model, and categorical covariates with predetermined cut-off points (such as every 10-year increase of

age, and remaining teeth number ≥ 20 or < 20 teeth) were combined to facilitate interpretation. Odds ratio (OR) represents the relative intake frequency in the periodontitis group relative to the control group. OR>1 indicates the intake frequency was higher in the periodontitis group compared to the control group. Stratified analysis according to the disease severity and extent was performed using a chi-square test to evaluate the association between periodontitis severity and medication frequency and number of types. The association between the number of remaining teeth, the amount and the types of systemic medications and the disease severity were analyzed using Pearson chi-square test. P-value < 0.05 was considered as statistically significant. All statistical analysis was performed by using a software package[‡].

RESULTS

The demographics of the study participants were presented in Table 1. The demographic characteristics, including age and gender distribution, were similar between the "case" periodontitis and "control" healthy groups (female 37%/male 63% in both groups; mean age of 61.8 versus 59.8 years (periodontitis versus healthy)).

A total of 33 kinds of medications for treatment of 12 categories of systemic diseases or conditions were documented, including diabetes mellitus, cardiovascular diseases, thyroid disorder, gastrointestinal conditions, respiratory diseases, osteoporosis or bone-related disorder, immune condition, prostate hyperplasia, genitourinary disorder, muscle-skeletal condition, gout and neurologic disorders. The most frequent medication types and prevalence of consumption in both the periodontitis and health groups were shown in Table 2. The three most common medications found in both groups were ACE inhibitors for cardiovascular diseases (17.9%), antidepressants (17.8%) and lipid-lowering medication (16.5%). Both ACE inhibitors and antidepressants showed statistically significantly (P<0.01)

higher intake frequency in the periodontitis group relative to the healthy group (21.5% vs. 14.4%; OR=1.64; 21.1% vs. 14.5%, OR=1.57, respectively). In contrast, the lipid-lowering agents showed less prevalence (26.1% vs 6.7%; OR=0.21) in periodontitis group. The complete information of the frequencies of all systemic medications collected in the current investigation were presented in supplemental Table 1 (see Supplemental Table 1 in online Journal of Periodontology).

Significant difference between periodontitis and healthy groups

In the results of unconditional logistic regression, only 12 kinds of medications showed significant differences between periodontitis and healthy groups. They were presented in Table 3 and illustrated below. Figure 1 demonstrated these 12 drugs in the ranking of intake prevalence among the periodontitis group. Three medications displayed a disease severity-dependent association with the intake frequency, including oral hypoglycemics, calcium channel blockers, and anticonvulsants (Figure 2). Significant results in the subgroup analysis of the generalized severe periodontitis (GSP) group under the multiple logistic regression model were reported in supplemental Table 2 (see Supplemental Table 2 in online Journal of Periodontology).

A statistically significant negative correlation was found between the number of remaining teeth and the severity of periodontal disease ($R= -0.35$, $p< 0.01$). No significant difference between the amount of medication consumption between groups ($p=0.12$) or different disease-severity subgroups was found ($p=0.22$).

Medications for Cardiovascular Diseases

Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors were found to be the most common medication taken in general and specifically within the periodontitis group. The prevalence of ACE inhibitor usage was significantly higher in the periodontitis group (21.5%) compared to the control group (14.4%) (OR= 1.64, p= 0.001). However, after adjusting for age, gender and number of remaining teeth, the positive association didn't reach the threshold of significance with an adjusted OR (aOR)=1.26 (p=0.19).

Calcium channel blockers

Calcium channel blockers were found more commonly in patients with periodontitis (16.8%) than healthy controls (8.0%) with OR= 2.32 (p< 0.001). After adjusting for age, gender and number of remaining teeth, those who consumed calcium channel blockers had higher odds of developing periodontitis (adjusted OR= 2.09, p<0.001). Compared to healthy controls, the frequency of intake was significantly higher in the generalized moderate periodontitis group (14.4%, OR= 1.94, p=0.01) and even higher in GSP group (14.8%, OR= 1.99, p=0.01) with aOR= 2.1 (p=0.03), which implied a severity-dependent association.

Diuretics

Diuretics including thiazide (hydrochlorothiazide, HCTZ) or thiazide-like (chlortalodone) diuretics, loop diuretics (furosemide), and potassium-sparing diuretics (such as spironolactone, triamterene) were recorded in this study. Taken together, the prevalence of diuretic intake in periodontitis group was 15.0%, which was significantly higher than the healthy group (9.0%) with OR= 1.79 (p=0.001). Higher intake frequency of diuretics was significantly associated with periodontitis, independent of age, gender and the remaining

number of teeth (adjusted OR= 1.6, p=0.02). The difference between the GSP and control groups reached borderline significance (p=0.07) with an OR of 1.66.

Anti-coagulants

Two categories including anti-coagulants (heparin, warfarin, rivaroxaban, apixaban and dabigatran) and antiplatelet drugs (aspirin, clopidogrel, ticagrelor) were documented in the current investigation. It was found that healthy individuals took blood-thinners more often than the periodontitis group (21.0% vs. 11.7%, OR= 0.5, p< 0.001). After adjusting for the possible confounders, the adjusted OR was 0.41 (p< 0.001). However, when the prevalence in healthy group was compared to the GSP group (15.4%), it was not significant different (p=0.14).

Blood-lipid lowering medications

Statins (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and fluvastatin), ezetimibe and fibrate were recorded in this category. Significantly lower intake frequency was found in the periodontitis group (6.7%) compared to the healthy group (26.1%) with OR=0.21 (p<0.001). The intake of lipid-lowering medications was associated with an 87% reduction in the odds of periodontitis (adjusted OR= 0.13, p< 0.001) after adjusting for age, gender, and the number of remaining teeth. This significant difference remained when comparing the GSP group (9.4%) with the healthy group (OR=0.29, p<0.001).

Alpha2-agonists

The consumption of alpha2-agonists had a higher prevalence in the periodontitis group (1.48%) compared to the control group (0.33%) with OR=4.59 (p=0.03). After adjusting for age, gender and number of remaining teeth, the difference didn't reach significance

(adjusted OR=3.38, p=0.14). Similarly, the difference between the GSP group (0.67%) and control was insignificant (p=0.48).

Medications for Neurologic Disorders

Antidepressants

Antidepressant consumption was reported by 21.1% of the periodontitis group, and it was associated with a 57% increase of odds compared to the healthy group (14.5%, p= 0.003). After adjusting for age, gender, and number of remaining teeth, the adjusted OR was 1.48 (p=0.03). Those who consumed antidepressants demonstrated higher odds of generalized moderate periodontitis (26.0%, OR= 2.1, p< 0.001). Although the frequency of intake was 18.8% in the GSP group, there was a non-significant difference compared to the control group (OR=1.36, p= 0.21).

Anticonvulsant

It was shown that patients in the periodontitis group had a higher chance of taking anticonvulsants (9.5%) compared to the healthy group (6.4%) with a crude odds ratio 1.55 (p=0.04). After the adjustment of age, gender and number of remaining teeth, the adjusted odds ratio was statistically insignificant (aOR=1.6, p=0.12). Nevertheless, a severity-dependent association was observed (7.7% in GMP group; 13.4% in GSP group) with OR=2.28, p< 0.01 (aOR=2.02, p=0.03) for generalized severe periodontitis.

Antipsychotic Drugs

Antipsychotic drugs interestingly demonstrated a higher prevalence in the periodontitis group (4.4%) with 2 times the odds compared to the healthy control (2.1%) (p=0.03). Independently

of age, gender and number of remaining teeth, the adjusted odds ratio was higher as 2.42 (p=0.02). The frequency of intake was higher in the generalized moderate periodontitis group (8.2%) with 4 times higher odds than the healthy group (p< 0.001). A disease periodontitis severity-dependent association was not observed in the GSP group (OR= 0.63, p=0.75).

Medications for Diabetes Mellitus

Insulin

The intake frequency of insulin was reported as 4.18% of the total population. Patients in the periodontitis group had a higher chance of taking insulin (5.59%) compared to the control group (2.77%, OR=2.08, p=0.02). Insulin intake was significantly associated with periodontitis independently of age, gender and number of remaining teeth (adjusted OR=2.13, p= 0.03). However, insulin intake did not reach significance in a comparison between the generalized severe periodontitis group (GSP) (5.37%) and the control group (OR=1.99, p=0.12).

Oral hypoglycemic agents

The total prevalence of use was 12.9%, and it was significantly higher in the periodontitis group relative to the healthy control group (17.8% vs. 8.0%, OR=2.49, p< 0.001). The percentage of intake was significantly higher in the generalized moderate periodontitis group (16.8%, OR= 2.3, p= 0.001) compared to the control group. Moreover, the prevalence was highest in the GSP group (17.4%) with an OR of 2.43 compared to the control (p= 0.001) (aOR=2.56, p< 0.01), which indicates that frequency of intake of hypoglycemics is directly correlated with increasing periodontitis severity.

Medications for Asthma

Bronchodilators

The prevalence of intake of bronchodilators for treatment of asthma, including albuterol, formoterol, levalbuterol and montelukast, was 2.3% in the periodontitis group compared to 4.6% in the healthy group. A negative association was found (OR= 0.49, p= 0.03). The significance remained in the multivariable logistic regression model (adjusted OR= 0.45, p=0.04). In the GSP group, the frequency of intake was 2.7% with no significant difference compared to the healthy control group (OR= 0.58, p= 0.37).

DISCUSSION

To the best of our knowledge this is the first study to investigate the potential association between systemic medication consumption and periodontal disease severity. The current investigation aimed to evaluate a possible indirect association between systemic diseases and periodontitis based on the axial relationship of medication intake and systemic diseases. Furthermore, stepwise logistic analyses in disease severity were performed to discern the possible severity-dependent association between systemic diseases and the inflammatory burden augmented in severe periodontitis.

The results of the current investigation demonstrated that medications for cardiovascular diseases (including calcium channel blockers and diuretics), diabetes (insulin and hypoglycemics) and antidepressant/antipsychotic drugs were positively associated with periodontitis after adjusting for age, gender, and the number of remaining teeth. On the contrary, anticoagulants, lipid-lowering medication, and bronchodilators were negatively associated with periodontitis after adjustment for all the confounding factors. Moreover, oral

hypoglycemics, calcium channel blockers and anticonvulsants demonstrated a severity-dependent relationship, in which the frequency of intake correlated with periodontal disease severity after the adjustment for confounders.

The most common medication unveiling in the current study was ACE inhibitors for the treatment of hypertension and congestive heart failure by reducing the activity of the renin-angiotensin-aldosterone system. ACE inhibitors are often the first drug of choice for hypertension, particularly when diabetes is present as a comorbidity. Oxidative stress and endothelial dysfunction have been hypothesized to be involved in the pathogenesis of hypertension[13], which share the common risk factors in chronic inflammation localized in periodontal tissues[14]. Although a number of cross-sectional studies[15-17] documented an association between hypertension and periodontitis, in the present study, no significant association was found between ACE inhibitor consumption and periodontitis after adjusting for confounding factors. This result may be explained by the multiple pharmacological effects of ACE inhibitors throughout the broad spectrum of cardiovascular diseases and that ACE inhibitors are often used in combination with other antihypertensive drugs, especially thiazide diuretics[18].

Calcium channel blockers (CCB) are used in the management of cardiovascular conditions, including angina pectoris, cardiomyopathy, cardiac arrhythmias and hypertension. It has been reported that CCB administration, especially nifedipine, diltiazem and verapamil was associated with gingival overgrowth, and rarely, amlodipine and felodipine, as well[19]. Amlodipine was the most common (75%) CCB found in the present study, which is often the primary choice in the elderly population. Since this study only recorded pocket depth without the measure of clinical attachment loss, the significant association cannot be ruled out from the influence of gingival enlargement. However, a significant disease severity-dependent relationship was found under the common side-effect of gingival hyperplasia, which may

underline the substantial association between periodontitis severity and atherosclerotic cardiovascular disease.

Diuretics were associated with periodontitis with an adjusted odds ratio of 1.6. Almost three-fourth of diuretics in the present study were thiazide-like diuretics (THZs). A recent meta-analysis demonstrated that no class of medication was significantly better than THZs as a first-line antihypertensive therapy[18]. The potential impact of diuretics on the periodontium might be explained by reduced salivary flow and composition[20], contributing towards the development of periodontal disease. In a cross-sectional study among older adults, severe periodontitis was linked to high blood pressure with an OR of 2.93. In addition, the association was stronger when restricted to those with hypertension or taking anti-hypertensive medications (OR= 4.2)[21].

Insulin and oral hypoglycemics were reported with significantly higher prevalence in the periodontitis group after adjustment. More importantly, the prevalence of oral hypoglycemics correlated directly with increasing severity of periodontitis. Epidemiologic evidence demonstrated an increase in extent and severity of periodontitis in diabetic adults[22], and susceptibility to periodontitis was increased by nearly 3-fold in individuals with diabetes[23]. DM was recognized as a risk factor affecting the rate of periodontitis progression in longitudinal studies[24]. Furthermore, DM was identified as a modifiable contributor to systemic inflammatory burden[25]. Hence, metabolic control of diabetes was incorporated by the 2017 World Workshop as a grade modifier to estimate the risk of future disease progression[26].

Depression is the most common psychiatric diagnosis amongst the elderly[27]. Epidemiologic studies provide substantial evidence that chronic stress and depression are associated with increased morbidity and negative outcomes for many chronic diseases, including: cardiovascular diseases[28], diabetes[29] and periodontitis[30]. Chronic stress and depression may result in dysregulation of the immune system and behavioral changes (smoking, alcohol consumption, and neglect of care) which can influence susceptibility to pathogenic infection

and periodontal breakdown[31]. The 17.8% of those taking antidepressants in our study population was in-line with a large epidemiologic study conducted in 2013 that found 16.7 % of US adults reported filling ≥ 1 prescription for psychiatric drugs[32]. Consumption of antidepressants in the present study was positively associated with periodontitis after adjustment (OR= 1.48, p=0.03), which might be related to drug-induced xerostomia, as well as a potential bidirectional relationship between depression and periodontitis. A plausible mechanism for this relationship could involve dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and behavioural changes[33]. It was noteworthy that half of the antidepressants reported in our study were selective serotonin reuptake inhibitor (SSRIs), which has gained more recognition recently as decreasing proinflammatory cytokine levels in chronic inflammatory diseases[34, 35]. However, evidence for a potential benefit as host-modulating effect on periodontal disease in humans remains weak[36].

Risperidone was the most common antipsychotic drug found in the current investigation (37.5%), which is an atypical antipsychotic used to treat schizophrenia, bipolar disorder, and autistic irritability. It was followed by clozapine (10%), which was mainly used for those unresponsive to other antipsychotics in treating schizophrenia[37]. A number of studies pointed out a higher prevalence and severity of periodontal disease among patients with schizophrenia or other psychiatric disorders[38-40] and this may be related to poor oral hygeine and smoking[41]. In addition, the majority of antipsychotic medications, such as risperidone, quetiapine and olanzapine induce xerostomia which can aggravate the onset of periodontitis[42].

A few observational studies linked epilepsy to the likelihood of periodontitis and tooth loss[43]; moreover, the frequency of refractory seizures was significantly associated with periodontitis severity and poor oral hygeine[44]. Gabapentin (Neurontin) accounted for almost half of the reported anticonvulsants (44.3%) in the current study, followed by valproic acid (8.2%) and diazepam (6.2%). One study showed twice the likelihood of having severe periodontitis due

to drug-related xerostomia after exposure to anticonvulsants due to altered wound healing and inability for proper dental care[45]. It has been widely documented that anticonvulsants can cause gingival hyperplasia[46, 19]; yet, the prevalence is significantly reduced for the new generation of anticonvulsants such as gabapentin[47].

Interestingly, the results demonstrated an inverse relationship between periodontitis and lipid-lowering medications, anticoagulants and bronchodilators after adjustment for confounders. Exposure to lipid-lowering agents was associated with 80% reduced odds of having severe periodontitis. Statins are used to decrease lipid levels by inhibiting hydroxymethylglutaryl-coenzyme-A reductase. Atorvastatin (Lipitor) was most commonly prescribed (54%), followed by simvastatin (28%) in the current study. The anti-inflammatory pleiotropic effect of statins includes positive modulation of the inflammatory cascade and anabolic effects on bone formation[48], which were shown to potentially decrease periodontal tissue breakdown after topical application[49]. Our results were in concordance with previous clinical observations[50].

Aspirin is the most frequently used anticoagulant in our study and exhibited a 50% higher likelihood of consumption in the healthy group. Low-dose aspirin acting as an anti-inflammatory agent has been hypothesized to have potential host-modulating effects for periodontitis management. However, the evidence remains inconclusive[51, 52]. Bronchodilators were previously reported to have an inverse association with periodontitis[53]. A recent study revealed an odds ratio of asthma for participant with severe periodontitis was 0.44, and the evidence was even stronger when using asthma medication as the outcome[54]. These results were consistent with our observation that individuals taking bronchodilators had less chance of having moderate to severe periodontitis. Mixed results with no or positive association were reported[55], which warrant further research to assess the relationship between oral microbes, periodontitis and asthma.

The first limitation of the current retrospective study was that common confounding factors such as smoking and alcohol consumption were not included due to the incomplete data available in the EHR system. Secondly, pocket depth was chosen in the current study as the disease determinant which might not completely reflect the true disease severity. Finally, drug-drug interactions, which can produce additive, synergistic, or antagonistic pharmacological responses and alteration of host defense mechanisms was not included in the current analysis. The target population of the present study was an elderly group (mean age of 60.8 years) with generalized moderate to severe periodontal disease. Multiple factors, such as dry mouth, poor oral hygiene, inadequate access to dental care and decreased motor function may contribute to periodontal disease pathogenesis in this population. Given the wide range of the treatment regimens and the presence of multiple comorbidities, this study yielded an indirect implication for the association between periodontitis and multiple systemic diseases, and provides clinically relevant information relating to the management of periodontitis patients.

CONCLUSION

Overall, there was a significantly higher frequency of medication intake related to cardiovascular disease and diabetes in patients with periodontitis. A disease severity-dependent relationship with medication consumption was found. This study provides indirect evidence for the possible relationship between systemic diseases and periodontitis.

Footnotes

[†] AXium, Henry Schein Inc., Melville, NY, USA

[‡] IBM SPSS Statistics for Mac, version 25.0, Armonk, NY, IBM Corp

AUTHOR CONTRIBUTIONS

I.C.W contributed to study design, data collection, draft of manuscript; H.A. and I.G contributed to the data collection. C.W.W contributed to study conception and critical review of manuscript; H.L.W contributed to the critical review of manuscript.

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Tables and Figures:

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Figure 1. The ranking of medications with significant odds ratio between periodontitis and healthy groups

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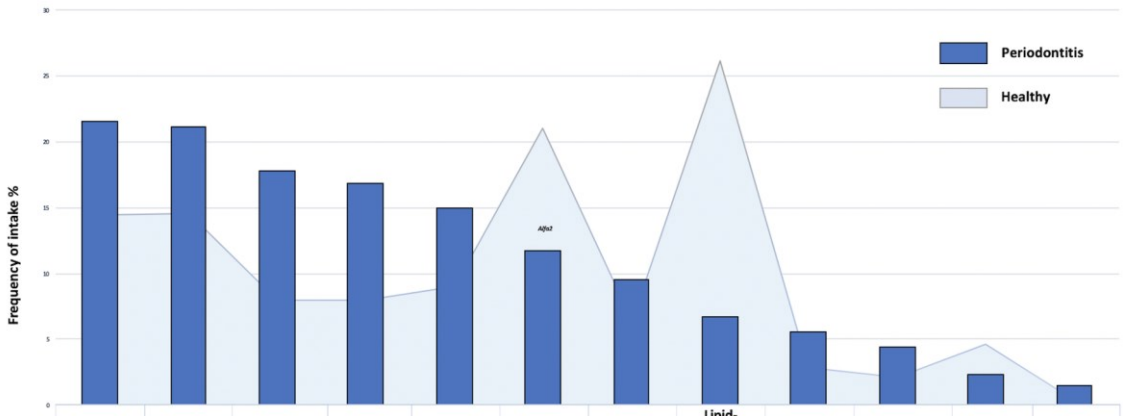

	ACE Inhibitors	Anti-depressants	Oral Hypoglycemics	Ca Channel Blockers	Diuretics	Anti-coagulants	Anti-convulsants	Lipid-lowering Medications	Insulin	Antipsychotic drugs	Broncho-dilators	Alpha 2 agonists
Healthy	14.4	14.5	8.0	8.0	9.0	21.0	6.4	26.1	2.8	2.1	4.6	0.3
Periodontitis	21.5	21.1	17.8	16.8	15.0	11.7	9.5	6.7	5.6	4.4	2.3	1.5
Odds ratio	1.6	1.6	2.5	2.3	1.8	0.5	1.6	0.2	2.1	2.2	0.5	4.6

Figure 2. Medication intake frequency and disease severity relationship

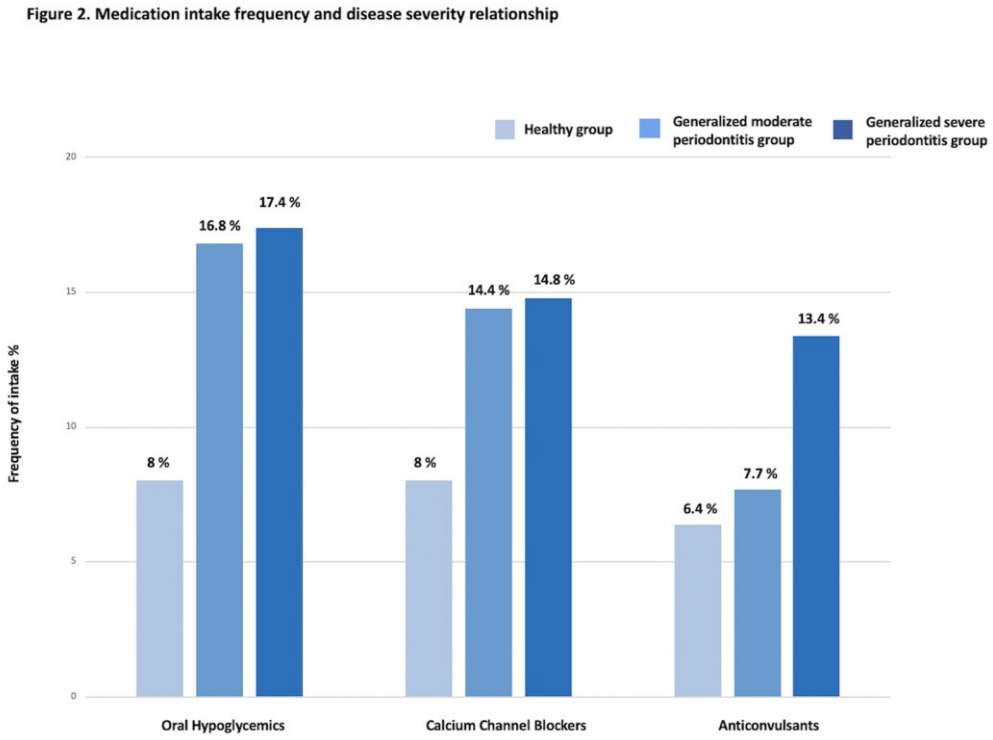

Table 1. Demographics of the study populations

		Subject numbers		Gender (F/M)		Age (range)		Remaining teeth (range)	
Periodontitis	**GMP** *	608	208	225/383 (37%/63%)	85/123	61.8 ± 9.8 (40-90)	61.2 ± 9.5	22.7 ± 5.2 (6-32)	21.9 ± 5.5
	GSP †		149		39/110		61.1 ± 9.8		22.2 ± 5.4
Healthy		613		226/387 (37%/63%)		59.8 ± 13.5 (40-95)		26.6 ± 2.7 (19-32)	
Total		1221		451/770 (37%/63%)		60.8 ± 11.8 (40-95)		24.7 ± 4.5 (6-32)	

Age and remaining teeth was presented with mean ± standard deviation (range)

* GMP represents "Generalized moderate periodontitis", † GSP represents "Generalized severe periodontitis"

Table 2. The most common medications and their consumption profile in each group

Medication	Overall	Healthy Group	Periodontitis Group	Crude Odds Ratio	p-value
ACE Inhibitors	17.9%	14.4%	21.5%	1.64	**0.001**
Antidepressants	17.8%	14.5%	21.1%	1.57	**0.003**
Lipid-lowering Medications	16.5%	26.1%	6.7%	0.21	**<0.001**
Anti-coagulants	16.4%	21.0%	11.7%	0.50	**<0.001**
Beta-Blockers	14.7%	14.7%	14.8%	1.01	0.95
Antacid Medications	14.3%	14.0%	14.5%	1.04	0.87
Oral Hypoglycemics	12.9%	8.0%	17.8%	2.49	**<0.001**
Calcium Channel Blockers	12.4%	8.0%	16.8%	2.32	**<0.001**
Diuretics	12.0%	9.0%	15.0%	1.79	**0.001**
Anticonvulsants	7.9%	6.4%	9.5%	1.55	**0.04**

p-value in bold indicates the significance ($p < 0.05$)

Table 3. The adjusted odds ratio for the effects of medications between "periodontitis" case and "healthy" control groups

	Case		Control		Univariate logistic regression		Multivariable logistic regression			
	n = 608	%	n = 613	%	crude odds ratio (95% CI)	p-value	adjusted odds ratio* (95% CI)	p-value	adjusted odds ratio† (95% CI)	p-value
Insulin										
Yes	34	5.6%	17	2.8%	2.08 (1.15, 3.76)	**0.02**	2.13 (1.1, 4.16)	**0.03**	1.96 (1.02, 3.75)	**0.04**
No	574	94.4%	596	97.2%	1.00		1.00		1.00	
Oral Hypoglycemics										
Yes	108	17.8%	49	8.0%	2.49 (1.74, 3.56)	**<0.001**	2.26 (1.52, 3.35)	**<0.001**	2.21 (1.49, 3.28)	**<0.001**
No	500	82.2%	564	92.0%	1.00		1.00		1.00	
ACE										

Inhibitors										
Yes	131	21.5%	88	14.4%	1.64 (1.22, 2.21)	**0.001**	1.26 (0.89, 1.77)	0.19	1.29 (0.92, 1.82)	0.14
No	477	78.5%	525	85.6%	1.00		1.00		1.00	
Calcium Channel Blockers										
Yes	102	16.8%	49	8.0%	2.32 (1.62, 3.33)	**<0.001**	2.09 (1.40, 3.11)	**<0.001**	2.21 (1.48, 3.29)	**<0.001**
No	596	98.0%	564	92.0%	1.00		1.00		1.00	
Diuretics										
Yes	91	15.0%	55	9.0%	1.79 (1.25, 2.55)	**0.001**	1.60 (1.07, 2.39)	**0.002**	1.57. (1.05, 2.34)	**0.03**
No	517	85.0%	558	91.0%	1.00		1.00		1.00	
Anti-coagulants										
Yes	7	11.	12	21.	0.5 (0.36,	**<0.**	0.41 (0.28,	**<0.**	0.35 (0.24,	**<0.**

	1	7%	9	0%	0.68)	**001**	0.59)	**001**	0.51)	**001**
No	537	88.3%	484	79.0%	1.00		1.00		1.00	
Lipid-lowering Medications										
Yes	41	6.7%	160	26.1%	0.21 (0.14, 0.3)	**<0.001**	0.13 (0.09, 0.2)	**<0.001**	0.13 (0.08, 0.2)	**<0.001**
No	567	93.3%	453	73.9%	1.00		1.00		1.00	
Alpha2 Agonists										
Yes	9	1.5%	2	0.3%	4.59 (0.99, 21.33)	**0.03**	3.38 (0.68, 16.7)	0.14	3.74 (0.77, 18.26)	0.1
No	599	98.5%	612	99.8%	1.00		1.00		1.00	
Broncho dilators										
Yes	14	2.3%	28	4.6%	0.49 (0.26, 0.95)	**0.03**	0.45 (0.21, 0.98)	**0.04**	0.38 (0.18, 0.82)	**0.01**
No	59	97.7	58	95.4	1.00		1.00		1.00	

	4	%	5	%						
Anti-depressants										
Yes	128	21.1%	89	14.5%	1.57 (1.17, 2.11)	**0.003**	1.48 (1.05, 2.08)	**0.03**	1.49 (1.07, 2.07)	**0.02**
No	480	78.9%	524	85.5%	1.00		1.00		1.00	
Antipsychotic Drugs										
Yes	27	4.4%	13	2.1%	2.15 (1.1, 4.2)	**0.03**	2.42 (1.13, 5.21)	**0.02**	2.15 (1.02, 4.54)	**0.04**
No	581	95.6%	600	97.9%	1.00		1.00		1.00	
Anticonvulsants										
Yes	58	9.5%	39	6.4%	1.55 (1.02, 2.37)	**0.04**	1.6 (0.9, 2.35)	0.12	1.39 (0.87, 2.22)	0.17
No	550	90.5%	574	93.6%	1.00		1.00		1.00	

P-value in bold indicates the statistically significant difference as $p < 0.05$

[*] Adjusted for age stratified by every 10-year strata (reference category 40-49 y), gender (reference female), and remianing teeth number stratified by two groups (< 20, ≥ 20 teeth)

[†] Adjusted for age, gender (reference female), and remaining teeth number