Cognitive impairment related to arterial stiffness in cardiovascular disease patients with severe periodontitis

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ABSTRACT

Severe periodontal disease (SPD) associated with systemic peripheral inflammation, cognitive impairment (CI) and arterial stiffness (AS) has been recognized. The aim of this study was to investigate whether CI and arterial stiffness (AS) occur in cardiovascular disease (CVD) patients with SPD. A cross-sectional case-control study included hospitalized patients with CVD. Demographic characteristics, CVD and atherogenic risk factors were recorded. SPD was diagnosed by clinical and radiographic dental examinations. Dental clinical attachment level (CAL) and CAL % were recorded. A Mini-Mental State Examination test (MMSE) assessed cognition, a MMSE score of < 27 was set as the cut-off point of CI; a score ≥ 27 was considered as no CI. Patients were categorized into: MMSE<27 (cases) and MMSE≥27 (controls). AS was evaluated by pulse wave velocity (PWV). Serum VCAM-1 levels were determined in a random sample. Results: This study comprised 91 patients (cases, n=26; 29.6%; controls, n=65, 71.4%); aged 73±8 vs. 73±7 years, respectively (p=0.73), of whom 53.8% and 36.9% respectively, were women; SPD was found to be a risk factor for CI; the presence of SPD increased the risk for MMSE <27 by an average 5.39 times (model 1). PWV was associated with MMSE < 27 in the three models. The risk of having MMSE < 27 increased an average of 2.404-fold for each 1-unit increase in PWV. SPD and AS had significant and independent associations on the risk for development CI. MMSE negatively correlated with CAL% (r=0.69) and PWV (r=0.70). PWV positively correlated with CAL% (r=0.67). Serum VCAM-1 levels were higher in SPD with lower MMSE scores. In conclusion, SPD increases the risk of development of cognitive decline in CVD patients. PWV was directly associated with the risk of cognitive decline.

These findings denote a significant opportunity to improve periodontal health in order to avert CI in CVD patients.

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Keywords: *arterial stiffness - cognitive impairment - cardiovascular diseases - severe periodontitis - VCAM-1.*

Deterioro cognitivo relacionado a la rigidez arterial en pacientes con enfermedad cardiovascular y periodontitis grave

RESUMEN

La enfermedad periodontal severa (EPS) podría estar asociada a la rigidez arterial (RA) y al deterioro cognitivo (DC). Se realizó un estudio transversal de casos y controles y se investigó la presencia de RA y DC en pacientes con enfermedad cardiovascular (ECV) y EPS. En pacientes hospitalizados con ECV se registraron las características demográficas y factores de riesgo aterogénicos. El DC se diagnosticó a través del Mini-Mental State Examination (MMSE). Punto de corte: MMSE<27 (casos); puntaje ≥27 ausencia de DC (controles). La EPS fue diagnosticada clínica y radiográficamente. Se registraron el nivel inserción clínica (NIC) y NIC %. La RA fue evaluada a través de la velocidad de onda de pulso (VOP). VCAM-1 sérico se determinó en una muestra aleatoria. Se incluyeron 91 pacientes (casos,n=26; 29.6%; controles,n=65, 71.4%); edad promedio: 73±8 vs. 73±7 años, respectivamente (p=0.73); % de mujeres: 53.8 vs. 36.9, respectivamente y EPS (n=54) y ausencia de EP (noEP) en 37. MMSE< 27 en 26 pacientes; 23 de ellos, con EPS. La presencia de EPS aumentó el riesgo de MMSE< 27 en 5.39 veces (modelo 1). La VOP se asoció a MMSE< 27 (Modelo 1, 2 y 3). El riesgo de MMSE< 27 incrementó en promedio en 2.40 veces por cada aumento de unidad de VOP. EPS y RA mostraron asociaciones significativas e independientes sobre el riesgo de DC. MMSE se correlacionó negativamente con NIC % (r=0.69) y POV (r=0.70); y POV, positivamente con NIC % (r=0.67). Los niveles séricos de VCAM-1 fueron más elevados en presencia de EPS y puntajes bajos de MMSE. Puede concluirse que en pacientes con ECV y EPS, el aumento en RA incrementaría el riesgo de DC. Estos hallazgos enfatizan la necesidad de promover y mantener la salud bucal para evitar el DC en pacientes con ECV.

Palabras clave: *rigidez arterial - deterioro cognitivo - enfermedad cardiovascular - Periodontitis severa - VCAM-1.*

INTRODUCTION

The World Health Organization[1] has documented that about 50 million people have dementia worldwide, and epidemiological estimates show an increased incidence of dementia of nearly 10 million new cases every year. Currently, there are no effective approaches to prevent, slow, stop or reverse the dementia process, but there is increasing interest in identifying risk factors for primary prevention or to delay the onset of this disease[2]. Risk reduction of modifiable factors is currently the fundamental strategy to reduce the number of individuals affected by dementia[3].

Periodontal disease (PD) is an infectious chronic inflammatory disease, and one of the most frequent human chronic disorders that may be amendable by oral hygiene. PD is characterized by subgingival infection with chronic inflammatory processes leading to destruction of supportive connective tissues surrounding the roots of teeth[4]. Clinical and experimental studies have demonstrated that chronic peripheral inflammation, as present in PD, could be a key determinant of the pathophysiology of cognitive decline associated with dementia[5]. The odds ratio (OR) for dementia was three times higher in individuals with atherosclerotic CVD than in those without[6].

The low-grade inflammation occurring in PD may be involved in the pathophysiology of atherosclerosis and cardiovascular disease (CVD). PD patients exhibit alterations in arterial wall thickness, arterial wall stiffness[7], arterial distensibility and endothelial function[8]. Arterial stiffness (AS) and vascular endothelial dysfunction may be associated with subclinical cerebrovascular damage, detectable through structural brain alterations and impaired cognition[9]. AS exposes the small brain vessels to highly pulsatile pressure and flow, which may result in cerebral microvascular alterations. Moreover, AS could compromise cerebral perfusion, modifying the blood-brain barrier and causing subcortical brain lesions[10]. The mechanical damage caused by AS may also lead to periventricular white matter lesions, and silent brain infarcts also associated with an increased risk of dementia[11].

The aim of the present study was to assess whether there is a relationship between AS and cognitive impairment (CI) in CVD patients with severe PD (SPD). In this study we demonstrated that the presence AS in CVD patients with SPD was associated with a risk more than five times higher of developing CI.

MATERIALS AND METHODS

Study population

An exploratory cross-sectional, case-control study was conducted in 91 patients with CVD admitted to the Department of Cardiology, Spanish Hospital of Buenos Aires, Argentina, from July-2016 to July-2017. This study population was representative of the older population with CVD at large. The current investigation was conducted in compliance with the STROBE Statement guidelines after securing informed consent from the participants and approved by the Research Ethics Committee of the Hospital.

Inclusion criteria: Patients with CVD, aged more than 60 years, having SPD or No periodontal disease (NoPD) assessed by clinical and radiographic dental examination. The CVD diagnosis included the following conditions: heart failure, ischemic heart disease, heart conduction block, peripheral arteriopathy, surgical myocardial revascularization, percutaneous transluminal coronary angioplasty, and valvular heart disease. Risk factors included: hypertension (blood pressure above 140/90mm/Hg), diabetes, smoking, hypercholesterolemia (>200mg/dl)[12]. Ongoing treatment of chronic CVD and CVD risk factors at the time of the study was recorded. Diabetes was present in 25 of the 91 patients studied.

Exclusion criteria: Patients with l) fewer than 10 teeth (in order to ensure that periodontal diagnosis was representative of the clinical dental status of the patient and to avoid overestimation of diagnosis of periodontal disease), ll) previous stroke, lll) congenital or acquired psychiatric diseases or brain development disorders, lV) chronic inflammatory diseases such as rheumatoid arthritis, v) less than 7 years of elementary education, Vl) kidney dysfunction, VII) prior neoplastic pathology or undergoing chemotherapy or radiation therapy, VIII) patients taking antipsychotic medication and/or anti-inflammatory drugs and IX) mild or moderate PD.

Periodontal examination

The radiographic study included a digital panoramic X-ray using a CS9000-3D extraoral imaging system (Carestream Health, Inc., Rochester, NY, USA) which was digitally analyzed using Kodak Dental Imaging Software, version 6.12.10.0. All permanent

teeth, except for the third molars, were evaluated. Clinical periodontal examination was performed by a single trained operator. Periodontal measurements were performed at six sites per tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual/palatal, mid-lingual/ palatal and disto-lingual/palatal) on all present teeth, using a manual Marquis Type periodontal probe (Hu-Friedy Co., Chicago, IL, USA).

The periodontal parameters measured included probing depth and clinical attachment level (CAL) assessed by a standardized protocol[13]. Average periodontal parameters were calculated by the arithmetic mean of the six determinations performed on each tooth. This method precludes overdiagnosis of periodontal disease, as patients may have high CAL values at one periodontal site and no alterations at other sites, due to trauma or other associated factors i.e. harmful oral habits, tooth brushing, removable prosthesis, among others. CAL was expressed as CAL% which represents the percentage of total number of sites with ≥ 5mm CAL with respect to the total sites examined per participant.

Intra-examiner reproducibility of probing depth and CAL measurements was assessed before the study. The weighted K coefficient was 0.96 for probing depth and 0.91 for clinical attachment level. Alveolar bone loss, determined on the radiographic images, was assessed as an adjuvant parameter to confirm diagnosis of PD, as described below. The diagnosis of SPD was made according to Caton *et al*.[14] jointly by the American Academy of Periodontology and the European Federation of Periodontology. PD was established when: 1. Average CAL values were ≥ 5 mm, 2. Average CAL values < 5 mm, but with values ≥ 5mm at > 30% of studied sites, 3. Horizontal alveolar bone loss > 1/3 of the root length in at least 30% of teeth, as measured on the radiographic images.

Measurement of Arterial Stiffness

AS was evaluated by pulse wave velocity (PWV) using Doppler ultrasound synchronized with carotid-femoral electrocardiogram. Quantification of carotid–femoral PWV was assessed as a measure of AS. Simultaneous electrocardiogram (ECG) and the pulse wave of the carotid, and femoral arteries (Toshiba Nemio) were recorded.

All subjects were studied in the supine position, the carotid artery was located at the suprasternal node supraclavicular in mode B. Doppler flow and ECG were recorded simultaneously (Toshiba Nemio ultrasound). Subsequently, PWV was measured and the data expressed as m/sec. The time delay between the feet of simultaneously recorded pulse waves and the carotid and the femoral artery was measured. The same procedure was carried out with the femoral artery at the level of the inguinal crease. The average of 6 determinations was taken at each site. Mean femoral time was subtracted from the carotid average and divided by 80% of the distance between the two points[15].

However, due to the strong dependence of PWV on age, each value was compared with the reference range obtained by others in a healthy non-hypertensive population who had no CV risk factors, independently of age[16].

Assessment of cognitive impairment

Cognitive functioning was assessed using the Mini-Mental State Examination (MMSE). This test consists of 11 items to assess orientation in time and place, attention, memory, language, and visual construction. The maximum obtainable score of cognitive function was the sum total points of all the items, yielding a single total score ranging from 0 to 35 (35 being the maximum score), with lower scores denoting impaired cognition.

A cut-off point for the MMSE, equal to or above 27 defined normal cognitive function[17]. This cut-off point score was also applied to the 25 patients who had diabetes mellitus, as defined by Yamazaki et al.[18]. Lower scores defined various degrees of mental cognition deficits (26–25, borderline cognitive deficit; 24–21, mild/early impaired cognition; 20–10, moderate impairment; less than 9, severely impaired cognition).

Two certified trained professionals carried out the cognitive evaluation, recording the cognitive domains with their respective scores[19].

Biochemical determinations

Serum VCAM-1 levels were determined for a random sample of 37 of 91 patients. Concentrations of soluble vascular cell adhesion molecule VCAM-1 (CD106) in serum were measured by Enzyme-Linked Immunosorbent Assay (abcam187393, UK). It employs an affinity tag labeled capture antibody and a reporter conjugated detector antibody which capture the sample analyte in solution. Signal is

generated proportionally to the amount of bound analyte and the intensity is measured at 450 nm. The assay has a sensitivity of 637pg/ml and specificity of 97%. The results were expressed in ng/ml.

Statistical analysis

Statistical analyses were performed using the statistic program SPSS, version 24.0 IBM Corp., Armonk, NY, USA. Descriptive statistics and frequency distribution were performed for each variable according to type of variable. Demographic, vascular risk factors and SPD characteristics were compared between groups using independent Student's t test or Chi square test, as appropriate. Significant associations were investigated using multivariate logistic regression analysis. The magnitude of association was expressed using odds ratios (ORs) and 95% confidence intervals (95% CI) obtained from the multivariate logistic regression analysis.

Analyses were adjusted for the following groups of potential confounders: i. demographic conditions (age and gender) and ii. vascular risk factors (diabetes, cholesterolemia, hypertension, heart failure and ischemia heart disease).

Pearson's coefficient correlation analyses were conducted between the following continuous variables: MMSE vs. CAL%, MMSE vs. PWV and PWV vs. CAL%.

p value of less than 0.05 was considered statistically significant.

RESULTS

The characteristics of the patients studied according to the presence or absence of CI are shown in Table 1. There were 26 patients with MMSE scores, < 27 (28.6%) and 65 with MMSE ≥ 27 (71.4%). There were no significant differences in average age of patients between groups (Table 1). There were more women (53.8%) among the patients with MMSE < 27 scores as compared to women (36.9%) in the MMSE ≥ 27 group. No differences were observed in the percentage of men and women between groups (Chi square=1.546; p = 0.214). Mean age of women in the MMSE < 27 group was 75 ± 7 years, as compared to a mean age of 72 ± 7 years observed in the women in the MMSE ≥ 27 group; this three-year difference was not significant.

There were no significant differences among the two MMSE score groups and the atherogenic risk factors or CVD types (Table 1). The prevalence of cognitive decline in patients with arteriopathy (ischemia heart disease and peripheral arteriopathy) was 73% with MMSE score < 27 and 50.79 % with MMSE score ≥ 27, differences were not significant.

Patients with MMSE < 27 had higher prevalence of SPD than those with MMSE ≥ 27 (n=23, 88.5% vs. n=31, 47.7 %; Chi square = 30.012; p =0.008). Only three of the 26 patients with MMSE < 27 (11.5%) did not have PD, whereas 34 of the 65 patients with MMSE ≥ 27 (52.3%), had noPD. Distribution of scores in the MMSE <27 group showed that 6 (23.07%) subjects scored between 26 and 25, 15 (57.70%) subjects scored 24 to 21, and 5 (19.23%) subjects scored 20 or < 20. The MMSE negatively correlated with CAL% (Fig. 1A). There was a significant difference in CAL% > 5, (5.8 ± 0.42 vs.1.94 ± 0.20m/sec; p=0.001) between case and control groups.

The associations between CI, PWV and SPD are shown in Table 2. The multivariate logistic regression analysis for MMSE < 27 showed that PWV and SPD had significant and independent effects on development CI. After adjustment for PWV, the presence of SPD was associated with increased risk of having MMSE < 27 by an average 5.39 times. Meanwhile, after adjustment for SPD, the risk of having MMSE < 27 increased an average of 2.404-fold for each 1-unit increase in PWV. After adjustment for CAL% > 5, the risk for MMSE < 27 increased an average of 2.44 and 2.60 for 1-unit increase in PWV (Model 2 and Model 3), respectively. However, MMSE < 27 associations with demographics (age and gender) (Model 2) or vascular risk factors (diabetes, total serum cholesterol, hypertension, heart failure and ischemia heart disease) (Model 3) were not significant.

AS determined by elevated PWV rates was significantly higher in patients with SPD than in those with NoPD (11.72 ± 0.76 vs. 10.63 ± 0.85m/sec, respectively; p= 0.001; 95% CI, 1.59- 0.57). PWV was positively correlated with CAL% (p = 0.001) (Fig. 1B). MMSE score was negatively correlated with AS measured by the PWV (Fig. 1C, p=0.01). Lower MMSE scores were found in patients with SPD (27.53±3.18 vs. 30.68±2.12 p = 0.003 [đ 3.15; 95% CI 1.14 - 5.16]).

The VCAM-1 levels in patients with MMSE < 27 (2385 ± 468pg/ml, n=10) were similar to those with MMSE ≥ 27 (2219 ± 462pg/ml, n=27; p=0.17).

Table 1. Characteristics of the study population

Variables	MMSE < 27 (n=26)	MMSE ≥ 27 (n=65)	p
Age (years) [a]	73 ± 8	73 ± 7	0.73
Male [b]	12 (46)	41 (63)	0.21
Hypertension [b]	18 (69)	42 (65)	0.92
Total cholesterol (mg/dl) [a]	229 ±18	232 ± 22	0.67
LDL cholesterol > 130 (mg/dl)[b]	16 (62)	42 (65)	0.97
Diabetes [b]	7 (27)	18 (28)	0.99
Smoking [b]	2 (8)	4 (6)	0.84
Heart failure [b]	17 (65)	47 (72)	0.69
Ischemia heart disease [b]	14 (54)	28 (43)	0.48
Heart conducted block [b]	3 (12)	4 (6)	0.66
Valvular disease [b]	8 (31)	21 (32)	0.91
Peripheral arteriopathy [b]	5 (19)	5 (8)	0.22
Other pathologies [b]	1 (4)	4 (6)	0.94
Severe Periodontal Disease [b]	23 (88)	31 (48)	0.008

MMSE, Mini Mental State Examination. MMSE < 27 = cases.
MMSE ≥ 27 = controls.
a Values are Means ± Standard Deviation
b Number of patients; in brackets, number of patients/total number of patients of each group, expressed as percentage.
p-value for the comparison between groups. p < 0.05 was considered significant.

However, serum VCAM-1 concentrations were higher among patients with SPD who had MMSE < 27 versus those with SPD and MMSE ≥ 27 (2385 ± 468pg/ml, n=10 vs. 2024 ± 457pg/ml, n=12; p= 0.02).

DISCUSSION

This study showed that CVD patients who had SPD were also likely to present AS and CI. The patients with SPD showed increased arterial stiffness as measured by PWV, and poorer cognitive function as detected by lower MMSE scores. The current study contributes to the body of literature by focusing on CVD patients with SPD. The study is important since the data denote a significant opportunity to improve periodontal health in order to decrease some of the very negative consequences of SPD by adopting simple oral hygiene measures. Regular tooth brushing plus other modifiable risk factors such as minimizing sugary food intake may reduce the risk of SPD and of developing AS and/or CI.

In real life, risk factors coexist and interact with one another, significantly increasing the chance of developing other alterations. SPD has also been known to affect other structures, including the cardiovascular[20] and nervous systems[3]. The inflammatory processes that occur with SPD could account for the alterations found in distal areas of the dental and buccal regions. Several systematic reviews have supported the contribution risk of SPD

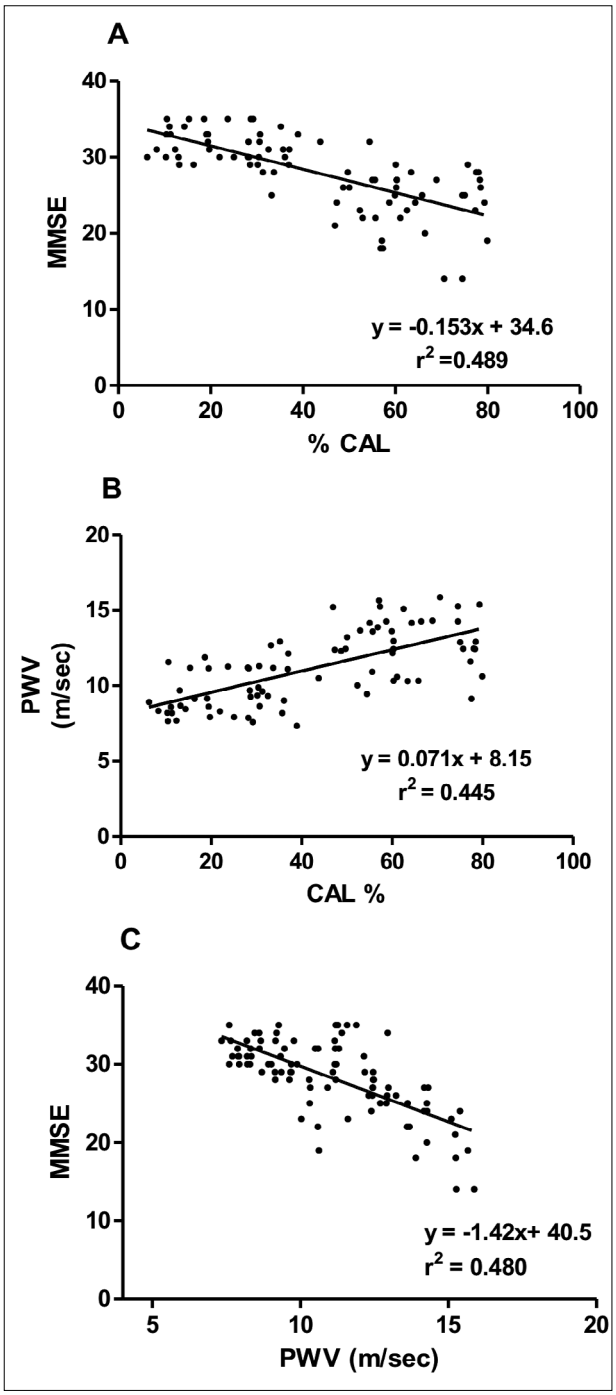

Fig. 1: Correlations between A: MMSE vs. CAL%; B: PWV vs. CAL% and C: PWV vs. MMSE.
MMSE: Mini Mental State Examination; PWV: Pulse wave velocity; CAL %: Mean Clinical attachment level %.

Table 2. Multivariate logistic regression analyses for MMSE < 27

	Model 1			Model 2			Model 3		
Factors	**OR**	**95%CI**		**OR**	**95%CI**		**OR**	**95%CI**	
PWV	2.404 **	1.509	3.829	2.447 **	1.473	4.066	2.605 **	1.486	4.567
SPD	5.397 **	1.084	26.856	0.944	0.044	20.103	1.002	0.043	23.312
CAL >5%				1.066	0.985	1.153	1.062	0.979	1.153
Demographics									
Age (years)				0.965	0.862	1.080	0.965	0.850	1.096
Sex (female/male)				0.167	0.031	0.890	0.191	0.033	1.104
Vascular risk factors									
Diabetes mellitus (yes/no)							1.332	0.205	8.652
Cholesterolemia (mg/dl)							0.881	0.146	5.323
Hypertension (yes/no)							0.505	0.075	3.391
Heart Failure (yes/no)							0.663	0.103	4.265
Ischemia heart disease (yes/no)							0.882	0.162	4.788

A total three models were run (Table 2). These models included: PWV and SPD (Model 1); PWV, SPD and CAL >5% in addition to demographics (Model 2) and PWV, SPD and CAL >5% in addition to demographics and vascular risk factors (Model 3).
PWV, Pulse Wave Velocity; SPD, Severe Periodontal Disease; CAL, Clinical Attachment Level; MMSE, Mini Mental State Examination; OR: odds ratio; CI confidence interval - ** $p < 0.01$

in the development of dementia[21]. Furthermore, SPD has also been associated with increased brain amyloid-β load[22], while lipopolysaccharides from periodontal bacteria have been demonstrated in Alzheimer disease brain specimens[23]. Peripheral infectious diseases and low-level systemic inflammation have also been proposed as potential etiological factors involved in dementia[24].

Recent studies have reported that PD and infection with *Porphyromonas gingivalis* constitute significant risk factors for developing amyloid-β plaques, dementia and Alzheimer's disease[25]. Patients with Alzheimer's disease also had neuroinflammation consistent with infection by *P.gingivalis,* DNA and gingipains antigens in the brain. It has been postulated that blocking the gingipains diminishes neurodegeneration and the host response to *P. gingivalis* infection. Other authors reported that patients with CVD had 100% arterial colonization by *P. gingivalis*[26], whereas *P. gingivalis* is usually found at low levels in healthy individuals without periodontitis[27]. Oral bacteria may escape into the bloodstream to other tissues, reaching arteries during and after brushing, chewing or dental interventions. The link between periodontitis and CVD is also well established. An association between childhood periodontitis with CVD risk factors and subclinical atherosclerosis in adulthood has been documented[28]. Observational studies showed periodontitis to be a risk indicator for myocardial infarction and stroke[29]. As periodontitis and CI share risk factors, it raises the possibility of a causal biological path linking both disorders. A pro-inflammatory phenotype most likely constitutes a common factor that links PD and CI[30]. However, there are studies suggesting that these diseases are the independent result of the atherogenic process[31].

Our data are consistent with recent findings from a systematic review and meta-analyses[32]. They demonstrated that independently of the heterogeneity of the patients with severe periodontitis, they exhibited higher AS assessed by PWV, a cardiovascular risk factor that cannot be underestimated[9]. The abnormal PWV in patients with SPD was likely due to endothelium dysfunction in response to a chronic inflammatory disease, which can be detected before the occurrence of clinically apparent CVD. Endothelial dysfunction induces an imbalance between vasodilator and vasoconstrictor synthesis that may trigger structural and functional vascular remodeling[6]. A systematic review undertaken by Paraskevas et al.[33] provided additional evidence that PD induces an elevation of plasma C-reactive protein (CRP) levels; this acute-phase response reactant may also be a marker of predisposition to a higher risk for CVD.

It is clear that AS is determined by the proportion of elastin and collagen that form the extracellular matrix of the artery. The inflammatory response to a fibro-

proliferative response is associated with breakdown of elastin and increases in collagen. This mechanism is superimposed on the decrease of nitric oxide (NO), a powerful regulator of AS which enhances hemodynamic imbalance; the bioavailability of NO contributes to the physiological regulation of arterial elasticity. The loss of endothelial NO produces a detrimental effect on clearance of the major cytotoxic peptides and amyloid-β which are responsible for the initiation and progression of cognitive decline[34].

The increase in AS denoted by PWV and the % CAL could lead to a rise in brain central pulse pressure and impact large and small vessels, blood pressure and flow dynamics[32]. The brain is rich in vascularization and has low resistance to blood flow; thus, it is particularly susceptible to hemodynamic changes, generating greater arterial stiffness from the direct transmission of the pulse wave. As a result, cerebral microvascular disease may result from the damaging forces of abnormal flow pulsations extending into small cerebral arteries. CI may also be the direct consequence of an ischemic brain. Altogether, the data are consistent with the association of AS and CI observed in the current study.

As a result of the inflammatory response, the vascular wall is remodeled, with increased AS and VCAM-1 serum level changes. The expression of adhesion molecules, such as VCAM-1 and ICAM-1, reduce the permeability of the microvasculature by interaction with leucocytes, diminish vasodilation and exacerbate cytokines production with increased production of reactive oxygen that lead to the development of oxidative stress status[35]. In our study, there were higher serum VCAM-1 concentrations in patients with CI.

Other authors have shown that even in non-inflamed tissues, the level of VCAM-1 on a given endothelial cell in brain micro-vessels was greater than in other tissues[36]. Thus, we could infer that elevated serum VCAM-1 levels in patients with MMSE scores below normal may be more representative of a cerebral inflammatory state with an impaired microvascular endothelium[37]. Elevated VCAM-1 might reflect defects of the vascular system as reported by Zuliani et al.[38], who found elevated plasma VCAM-1 in patients with dementia. VCAM-1 may thus reflect cerebral endothelial inflammation, and may be a suitable marker for the detection of early cognitive decline.

Finally, the present study has limitations. For example, folic acid intake and folic acid levels were not measured, although folate deficiency has been associated with increased oxidative stress, endothelial dysfunction and progression of dementia[39]. Additionally, the MMSE was the tool used to assess CI; this test has been validated as an accurate instrument for screening, and it facilitates an early detection of CI. However, other methods with high specificity and sensitivity were not used in our study[40].

Although the sample size potentially constituted a limitation for carrying out some specific statistical analyses, the CI observed in CVD patients with SPD in the current study represents an improvement over other studies. Extension of the study time should be considered in future research to replicate these data.

CONCLUSIONS

The current study showed that AS in CVD patients increased the risk of CI. The presence of SPD, in addition to atherogenic risk factors, probably contributes to the increase in AS. The inflammatory process induced by SPD and detected by the increase in serum VCAM-1 levels, could contribute to the progression of endothelial dysfunction and arterial stiffness, as a substrate for CI. The presence of severe periodontal disease in CVD patients needs to be considered as a contributing factor to CI. These findings highlight the need to promote oral health assessment in order to prevent CI in CVD patients with SPD.

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