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## RESEARCH ARTICLE

### Endothelial Dysfunction, its Relationship with Chronic Periodontal Disease, and other Associated Risk Factors

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#### Abstract:

#### Background:

Chronic periodontitis is related to individual characteristics. However, it is precisely infectious in nature with the possibility of generating a chronic systemic inflammatory response that could favour its association with diseases, such as endothelial dysfunction, hypertension, CVD, and diabetes.

#### Purpose:

The aim of the study was to analyze the relationship of endothelial dysfunction measured by flow-mediated vasodilation in the brachial artery with periodontal disease and other possible factors.

#### Methods:

A case-control study was carried out in which those who had periodontitis were defined as cases, and those who were periodontally healthy or had gingivitis were defined as controls. A clinical history was obtained from all patients, and all patients underwent biofilm control and periodontal examinations. Blood tests were performed to determine CBC, glycaemia, total cholesterol, HDL-C, and LDL-C levels, and standardized procedures were used to measure flow-mediated dilation.

#### Results:

A total of 202 patients were included in this study: 101 controls [healthy/gingivitis] and 101 cases [periodontitis]. Regarding sex, glycaemia [ $p = 0.019$ ] and triglycerides [ $p = 0.001$ ] levels and initial flow-mediated vasodilation [ $p = 0.001$ ] and final flow-mediated vasodilation [ $p = 0.001$ ] values were higher in men, while HDL values were lower [ $p = 0.001$ ]. The average age was higher for those in the group that presented dysfunction than for those in the group without dysfunction [ $p = 0.014$ ]. When analyzing the percentage of patients with endothelial dysfunction in each of the groups, there were very few positive results obtained [5 per group].

#### Conclusion:

Initial and final arterial vasodilation was lower in women than in men. Likewise, there were more cases of endothelial dysfunction in women. In this study, patients with endothelial dysfunction were older. Periodontitis was not associated with endothelial dysfunction.

**Keywords:** Atherosclerosis, Risk factors, Periodontitis, Endothelium, Vasodilation, Gingivitis.

#### Article History

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## 1. INTRODUCTION

Cardiovascular Disease (CVD) is the pathophysiological basis of atherosclerosis, and begins with alterations in vascular homeostasis regulated by the endothelium. A healthy endothelium presents a balance between endothelial vasocon-

striction and vasodilation factors. In contrast, an imbalance among these factors and alterations in endothelial function are harmful and predict or identify the development of CVD. The endothelium lines the internal wall of vessels and has an important role in the regulation of vascular tone, coagulation, inflammatory responses, platelet adhesion and thrombolysis. There are conditions that can alter the function of the endothelium, such as dyslipidaemia, age, sex, family history of atherosclerotic disease, smoking, hypertension and chronic

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infections such as periodontal disease. A reduction in the bioavailability or the increased degradation of Nitric Oxide (NO) are markers of endothelial dysfunction associated with altered Endothelium-Dependent Dilation (EDD), allowing not only the identification of disease but also the prediction of future cardiovascular events [1, 2]

Endothelial dysfunction is defined as vascular alterations generated by an imbalance in the bioavailability of active substances of endothelial origin. This inflammatory situation can lead to vasoconstriction and increased vascular permeability. Researchers have been investigating the role of systemic inflammatory responses in the vascular endothelium because, as an immune response, the vascular endothelium releases biomarkers such as C-Reactive Protein (CRP), IL-6 and TNF- $\alpha$ . These biomarkers decrease the availability of vasodilation factors such as nitric oxide, and increase vasoconstriction factors derived from the endothelium, thus decreasing dilation. A marker of endothelial abnormality established by the international literature is alterations in flow-mediated vasodilation measured in the brachial artery. The normal response of the endothelium to moderate ischaemia is the release of nitric oxide, resulting in vasodilation. Endothelium that is injured by proinflammatory factors, lipid deposits [fatty streak] or atheromatous plaques reacts abnormally and does not vasodilate, serving as a marker of endothelial dysfunction [2 - 5].

Periodontal disease is an infectious disease with a chronic inflammatory response. It commonly occurs in middle-aged adults, with an increased prevalence in older people, and it is one of the most important causes of tooth loss in adults; periodontal disease can also predispose individuals to vascular diseases. Periodontitis causes the destruction of supporting tissues of the tooth. Its primary aetiology is the accumulation of biofilm. Periodontal pathogen biofilms affect local and systemic immune and inflammatory responses; lipopolysaccharides also activate a cascade of systemic inflammatory cytokines, such as tumour necrosis factor TNF $\alpha$  and interleukin (IL)-1, IL-6 and IL-8, that generate vascular and coagulation complications associated with endothelial dysfunction and atherosclerosis [6].

Chronic periodontitis is related to individual characteristics, such as age and sex, and only some individuals experience advanced destruction of the supporting tissues of the tooth. However, it is precisely infectious in nature with the possibility of generating a chronic systemic inflammatory response that could favour its association with diseases such as endothelial dysfunction, hypertension, CVD, and diabetes [7, 8].

Therefore, the objective of this study was to analyze the relationship between endothelial dysfunction measured by flow-mediated vasodilation in the brachial artery and periodontal disease and other possible associated factors.

## 2. MATERIALS AND METHODS

A case-control study was conducted in which cases were defined as those who had stages III and IV (grades A and B) periodontitis, and controls were defined as those who were periodontally healthy or who only had biofilm-induced

gingivitis.

A clinical and medical history was obtained from all patients where the date of birth, age, sex, and the type of exercise performed per week were recorded according to 5 previously established categories (daily exercise of 30 minutes 5 times a week, exercise 1 to 4 times a week, exercise less than 1 time a week on average, no exercise but physical activity, no exercise as well as no physical activity), and all patients underwent biofilm control; also, a periodontogram was carried out using a 15-mm North Carolina probe. The cases involved patients who presented stages III and IV (grades A and B) periodontitis based on the new classification of periodontal disease by Caton 2018 (previously considered advanced chronic periodontitis in the classification by Armitage 1999) [9]. These patients had probings greater than 4 mm, bleeding on probing, insertion level losses, horizontal and vertical bone loss and grades II and III furcation lesion. The control group consisted of healthy patients or those with biofilm-induced gingivitis who had a probing depth of 3 mm or less, the presence or absence of bleeding on probing, and no bone loss or insertion levels.

All patients underwent blood tests (triglycerides, total cholesterol, HDL cholesterol, calculated LDL cholesterol, processed LDL cholesterol, and baseline blood glucose levels) and a flow-mediated vasodilation test (FMV, ultrasound of the brachial artery to determine endothelial function). Before performing the FMV, blood pressure and arterial index were taken. The FMV technique and procedure used was the internationally standardized one [10], and the results were given in terms of millimeters. Ultrasound images were obtained from the predominant brachial artery proximal to the antecubital fossa with 14 MHz linear transducer ultrasound system (Canon Aplio i600®). Initial images were obtained after 10 minutes of resting in the supine position. Flow-mediated dilation was determined by establishing the change in arterial diameter in response to reactive hyperemia (initial image vs. final image). Reactive hyperemia was induced by inflating a pneumatic handle placed around the arm (proximal to the segment to be imaged) until a pressure of 200 mmHg was obtained (5 min). Images were obtained 2 minutes after deflating the handle (final image).

To calculate the sample size, the software TAMAMU 1.1® (Pontificia Universidad Javeriana, Facultad de Medicina, 2001) [11] was used to determine the specific difference between groups (mean), a type I error: 0.05; type II error: 0.2; standard deviation: 4.5% and average difference 3%. The minimum sample size obtained was 142 patients.

A total of 480 patients were screened, of which 202 patients met the inclusion criteria: over 40 years of age, with or without periodontal involvement (depending on whether they were cases or controls). Subjects with diagnosed vascular diseases or who took any drugs that modify endothelial function (aspirin, statins, ACE inhibitors, ARBs, calcium antagonist, sildenafil, L-arginine and antioxidants, corticosteroids or estrogens) and periodontal or antibiotic therapy 3 months before the study, were excluded. The study was evaluated and approved by the Research and Ethics Committee of the Faculty of Dentistry of Pontificia

Universidad Javeriana in Bogotá, Colombia [approval # 005/2009] in accordance with the Declaration of Helsinki, which also approved the informed consent form, which was signed by all patients. Confidentiality of patient data was guaranteed.

**3. ANALYSIS OF THE RESULTS**

The collected information was analyzed, including a description of the demographic characteristics of periodontal evaluations and the FMV, using means, medians, ranges, standard deviations and 95% confidence intervals.

FMV is reported in absolute values, in the percentage of change and in categorical terms as normal or abnormal, using internationally the defined cut-off points of 4%. [12]

For the outcomes analysis, indirect relative risks [odds ratio] were used for the probability of having dysfunction in the case and control groups. Adjustments were made for age and sex.

Student’s t-test or chi-square tests were used for

comparisons between groups. Significant difference was considered at  $p < 0.05$  [2-tailed].

Analyses were performed using Stata IC 14.2 for MAC [StataCorp 2015, College Station, Tx, USA].

**4. RESULTS**

The study sample consisted of 101 controls [healthy/gingivitis] and 101 cases [periodontitis]. Of the 202 patients, 54.9% were female. The average age was 51.7 years [95% CI 50.6 - 52.9]. On average, current smokers smoked approximately 8 cigarettes per day.

Regarding laboratory tests, the average blood glucose level was 97.6 mg/dl [95% CI 94.1 - 101.2], the average total cholesterol level was 204 mg/dl [95% CI 198.8 - 209.1], and the average triglyceride level was 149.1 mg/dl [95% CI 136.6-161.6]. When evaluating FMV, the average initial FMV was 3.9 mm [95% CI 3.8 - 4.0], and the average final FMV was 4.5 mm [95% CI 4.3 - 4.6]. The average percentage of vasodilation was 15.3% [95% CI 14.2 - 16.4] (Table 1).

**Table 1. General characteristics of the sample and analysis by group.**

-	Mean	S.E.	95% CI
Age	51,7	0,59	50,6 – 52,9
Cigarettes per day	7,8	0,41	7,0 – 8,6
Glycaemia	97,6	1,78	94,1 – 101,2
Total Cholesterol	204	2,6	198,8 – 209,1
Triglycerides	149,1	6,3	136,6 – 161,6
cHDL	44,3	0,82	42,6 – 45,9
cLDL	129,9	2,1	125,7 – 134,0
FMV Initial (mm)	3,91	0,59	3,80 – 4,02
FMV Final (mm)	4,49	0,06	4,37 – 4,61
% FMV	15,3	0,57	14,2 – 16,4
Endothelial dysfunction	10	4,95	
Yes	192	95,0	
No			
	<b>Healthy</b>	<b>Periodontitis</b>	
	Mean (S.E.)	Mean (S.E.)	p-value
Age	51,7 (0,88)	51,7 (0,78)	0,966
Cigarettes per day	7,3 [0,52]	8,2 (0,62)	0,278
Glycaemia	96,5 (1,86)	98,8 (3,04)	0,522
Total Cholesterol	205,2 (3,48)	202,7 (3,88)	0,638
Triglycerides	143,7 [7,34]	154,5 (10,35)	0,395
cHDL	45,3 (1,14)	43,2 (1,18)	0,205
cLDL	130,6 (2,98)	129,1 (3,00)	0,712
FMV Initial (mm)	3,8 (0,07)	3,9 (0,07)	0,426
FMV Final (mm)	4,4 (0,08)	4,5 (0,08)	0,395
% FMV	15,5 (0,88)	15 (0,73)	0,659
Exercise 30 minutes a day 5 times per week			
No	96	97	0,733
Yes	5	4	
Exercise 1 to 4 times per week			
No	76	84	0,165
Yes	25	17	
Exercise less than once a week on average			

(Table 1) *contd....*

-	Mean	S.E.	95% CI
No	93	101	0,007*
Yes	8		
No exercise / physical activity			
No	89	62	0,001*
• Yes	12	39	
No exercise / no physical activity			
No	63	74	0,098
• Yes	38	27	
Endothelial dysfunction			
No	96	96	1,0
Yes	5	5	

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; FMV, flow-mediated vasodilation test.

When evaluating the characteristics according to the presence or absence of chronic periodontitis, a statistically significant difference was found between groups for exercise at least once a week ( $p = 0.007$ ) and no exercise but physical activity ( $p < 0.001$ ); the controls exercised more frequently than the cases. The frequency of patients with endothelial dysfunction was the same in the two groups (Table 1).

Regarding sex, glycaemia ( $p = 0.019$ ) and triglyceride ( $p = 0.001$ ) levels and initial FMV ( $p = 0.001$ ) and final FVM [ $p = 0.001$ ] values were higher in men, and HDL levels were lower in men ( $p = 0.001$ ). Endothelial dysfunction was more frequent in women than in men ( $p = 0.022$ ) (Table 2). When analysing the percentage of patients with endothelial dysfunction in each of the groups, there were very few positive results obtained (5 per group).

**Table 2. Bivariate analysis of risk factors by sex.**

	Female (n=111)	Male (n=91)	p-value
	Mean (S.E.)	Mean (S.E.)	
Age	51,6 (0,68)	51,9 (1,01)	0,830
Cigarettes per day	7,5 (0,54)	8,1 (0,62)	0,507
Glycaemia	93,9 (2,44)	102,2 (2,53)	0,019*
Total Cholesterol	207,1 (3,35)	200,2 (4,07)	0,188
Triglycerides	124 (6,15)	179,7 (11,1)	0,001*
cHDL	48,5 (1,07)	39,1 (1,06)	0,001*
cLDL	133 (2,80)	126 (3,17)	0,099
FMV Initial [mm]	3,5 (0,06)	4,3 (0,07)	0,001*
FMV Final[mm]	4,0 (0,06)	4,9 (0,08)	0,001*
% FMV	15,1 (0,77)	15,5 (0,84)	0,714
Endothelial dysfunction			
No	102	90	0,022*
Yes	9	1	

Abbreviations: HDL, high density lipoprotein; LDL low density lipoprotein; FMV, flow-mediated vasodilation test

**Table 3. Analysis of risk factors with endothelial dysfunction.**

	No Endothelial Dysfunction	Endothelial Dysfunction	p-value
	Mean (S.E.)	Mean (S.E.)	
Age	51,4(0,59)	58,1 (2,73)	0,014*
Cigarettes per day	7,7 (0,42)	10,4 (1,65)	0,155
Glycaemia	97,3 (1,84)	103,9 (6,90)	0,427
Total Cholesterol	203,3 (2,68)	216,1 (10,2)	0,291
Triglycerides	149,8 (6,61)	134,6 (17,4)	0,603
cHDL	44,1 (0,84)	46,8 (4,10)	0,492
cLDL	129,2 (2,17)	142,3 (8,46)	0,180
FMV Initial [mm]	3,9 (0,05)	4,2 (0,25)	0,213
FMV Final [mm]	4,5 (0,06)	4,3 (0,26)	0,487
% FMV	15,9 (0,56)	2,7 (0,34)	0,000*

The average age was higher for those in the group with dysfunction than in those in the group without dysfunction ( $p = 0.014$ ). Despite not being statistically significant, patients with dysfunction tended to smoke more than those without dysfunction (Table 3).

In the multivariate analysis establishing an association between having or not having endothelial dysfunction and the other characteristics evaluated, through logistic regression, %FMV was found to be a protective factor for presenting endothelial dysfunction ( $p = 0.01$ ). Additionally, although not statistically significant, being male trended towards being a protective factor (Table 4).

**Table 4. Multivariate analysis of endothelial dysfunction and associated factors.**

Endothelial Dysfunción	OR	95% CI	p-value
Age	1,20	0,93 – 1,56	0,14
Male	0,009	0,00 – 2,12	0,092
%FMV	0,19	0,05 – 0,67	0,01*

When the outcome was evaluated as % FMV and its association with risk factors, age was an associated factor, but in this case, it was a protective factor ( $p = 0.004$ ), indicating that the younger a person is, the greater the % FMV values will be. Being male, despite not being statistically significant, had a protective effect on endothelial function because males had higher % FMV values (Table 5).

**Table 5. Multivariate analysis of FMV % and associated factors.**

%FMV	OR	95% CI	p-value
Chronic Periodontitis	0,89	0,65 – 1,24	0,516
Age	0,97	1,02 – 1,27	0,004*
Male	1,23	0,005 – 1,06	0,056
Cigarettes per day	1,00	0,88 – 1,71	0,212
Total Cholesterol	1,00	0,99 – 1,00	0,865
Triglycerides	0,99	0,99 – 0,99	0,050
No exercise / physical activity	0,98	0,12 – 8,07	0,991

## 5. DISCUSSION

Endothelial dysfunction is considered a predictor of CVD. Endothelial cells play a fundamental role in vascular homeostasis. Chronic inflammation has a negative impact on endothelial function. It has been shown that inflammatory lesions can cause an imbalance in the synthesis/secretion of vasodilators, such as nitric oxide, prostacyclin, and endothelial hyperpolarization factor, and vasoconstrictors, such as endothelin 1, thromboxane and angiotensin II. Vascular endothelial dysfunction has been associated with a variety of conditions and risk factors for atherosclerosis, such as age, hypertension, dyslipidaemia, diabetes, smoking and inflammatory processes, such as periodontal disease [13, 14].

The present research found, when analysing the vasodilation values of women versus men, that the initial FMV values were 3.5 and 4.3 and final FMV values were 4.0 and 4.9, respectively, *i.e.* significantly higher in men. In this sense, the literature has indicated that the prevalence of

atherosclerotic CVD in men is higher than in women until menopause, when the prevalence of CVD increases in women, exceeding that in men. Studies on differences in endothelial function according to sex are contradictory. Some studies show decreases in endothelial function at younger ages in men than in women, while others show similar decreases between sexes related to age. Because the increased risk of CVD coincides with menopause in women, it is generally believed that female hormones, particularly oestrogens, are cardioprotective, while androgens are harmful [15].

Similarly, endothelial dysfunction was found to be more frequent in women than in men. This, in agreement with the results reported above, could also be related to the fact that a decrease in endothelial function begins around the fourth decade of life in men and approximately 10 years later in women. This is the reason why the reduction in endothelial function becomes more evident during the fifth decade of life in women, *i.e.* during menopause, and the average age of the women in the present study was consistent with the age at menopause. This could be justified by the abrupt change in sex hormones, especially oestrogen ( $E_2$ ), with loss of their vasoprotective/vasodilator effects, which leads to a greater decrease in vascular endothelium function, which in turn could favour endothelial dysfunction and the associated increase in CVD after menopause [16, 17].

The average age was higher for participants in the group that presented dysfunction than for those in the group without dysfunction (58.1 years versus 51.4 years, respectively). Likewise, in the multivariate analysis, age was a risk factor for presenting dysfunction. The literature in this sense has mentioned that advanced age, independent of other risk factors, leads to important biochemical, histological and structural vascular alterations that determine a pro-atherogenic environment in which the main cardiovascular risk factors act, favouring the progression and destabilization of stable atherosclerotic plaques [15–17,18–20]. In the relationship between age and endothelial dysfunction, it is also important to highlight that plasma concentrations of inflammatory proteins, including proinflammatory cytokines such as interleukin (IL)-6, tumour necrosis factor alpha (TNF- $\alpha$ ) and monocyte chemoattractant protein-1 (MCP-1), can increase with age in healthy people [21,22].

When evaluating characteristics according to the presence or absence of chronic periodontitis, no significant difference was observed because the frequency of endothelial dysfunction was exactly the same in the two groups. These results are consistent with those reported by Ruiz *et al.* in 2012 [23], who found no relationship between periodontal disease and endothelial dysfunction. The study did show significant differences in final artery diameters after performing the FMV test; the diameters were smaller in patients with periodontal disease. Velosa *et al.*, in 2016 [5], in a study involving a sample of 140 patients, also showed no relationship between endothelial dysfunction and periodontal disease.

Higashi *et al.* [24] conducted an investigation to evaluate endothelial function in patients with periodontitis. They reported higher values in patients with periodontitis than in those who did not have periodontitis. Blum *et al.* [25] reported

that patients with periodontitis had greater dysfunction than those without periodontitis (FMD 4.12 versus 16.60).

Although the evidence leans towards the beneficial effect of periodontal treatment on systemic inflammation, the literature in this regard remains controversial because there is research that contradicts the positive effect of periodontal treatment on the vascular endothelium. Saffi *et al.* [26] found that non-surgical periodontal treatment does not provide better vasodilation in patients with coronary artery disease; however, they did find small benefits in blood vasodilation markers.

## CONCLUSION

Initial and final arterial vasodilation was lower in women than in men. Likewise, there were more cases of endothelial dysfunction in women. These results could be related to menopause, based on the average age of the participants.

The vascular endothelium plays a fundamental role in the pathogenesis of CVD, and it is important to analyze the factors that may alter endothelial function, such as age, sex and chronic infections, for example, periodontal disease. In this study, patients with endothelial dysfunction were older than those without endothelial dysfunction.

The analysis of endothelial dysfunction did not adequately detect statistically significant differences given the sample size (5 cases in the periodontitis group and 5 in the group without periodontitis). In this study, periodontitis was not found to be related to endothelial dysfunction.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was evaluated and approved by the Research and Ethics Committee of the Faculty of Dentistry of Pontificia Universidad Javeriana in Bogotá, Colombia (approval # 005/2009).

## HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT FOR PUBLICATION

All the patients signed an informed consent form. Confidentiality of patient data was guaranteed.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## FUNDING

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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