

Chronic Periodontitis in Patients with Type 2 Diabetes: Analysis of the FokI Polymorphism and Perception of Quality of Life

Romário Correia dos Santos¹, Roberto Carlos Mourão Pinho², Renata Cimões²

¹Instituto Aggeu Magalhães, Fiocruz, Recife, PE, Brazil.

²Department of Prosthesis and Oral and Maxillofacial Surgery, Federal University of Pernambuco, Recife, PE, Brazil.

Author to whom correspondence should be addressed: Renata Cimões, Av Prof. Moraes Rego, s/n, Cidade Universitária, Recife, PE, Brazil. 50670-901. Phone: +55 8121268817. E-mail: renata.cimoes@globo.com.

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Abstract

Objective: To analyze whether the FokI polymorphism (rs228570) present in the vitamin D receptor gene in type 2 diabetics is related to chronic periodontitis's clinical status and evaluates the influence of chronic periodontitis on the perception of quality of life. **Material and Methods:** It is a clinical and laboratory study, composed of a sample of 59 individuals with previous diagnosis of type 2 Diabetes Mellitus and chronic periodontitis, of both sexes. On clinical examination, socio-epidemiological data and quality of life of patients with the Oral Health Impact Profile (OHIP-14) were recorded and a periogram was performed. Subsequently, saliva was collected spontaneously in sterile Falcon tubes (15 ml) and stored in the freezer at -20 °C. The purification of the genetic material was done with a PROMEGA kit (Wizard®), and the polymorphism studied was FokI (rs228570), found in the vitamin D receptor promoting region, with rs: 228570. After extraction of saliva DNA and purification, genotyping was performed by real-time PCR using specific allele probes (TaqMan® System). **Results:** The polymorphism of the vitamin D receptor gene was not positively associated with the severity and clinical characteristics of periodontitis, but suggested a relationship with the extent of the disease. Periodontitis also had no positive association with patients' perception of quality of life. **Conclusion:** The perception of quality of life of patients with chronic periodontitis and type 2 diabetes mellitus was compromised by the systemic condition, secondary to oral health, although some dimensions of OHIP-14 have been more frequently mentioned, such as psychological discomfort, physical pain and physical disability.

Keywords: Diabetes Mellitus, Type 2; Chronic Periodontitis; Polymorphism, Genetic.

Introduction

Diabetes mellitus is a group of chronic metabolic diseases in which insulin production by pancreatic beta cells is deficient or the non-beneficial use of this hormone leads to hyperglycemia. It is estimated that the number of people in the world affected with diabetes may increase from 382 million to 592 million between 2013 and 2035. There are several types of diabetes mellitus, being classified into two main types: type 1 (DM1) and type 2 (DM2) [1].

The causal origin of DM2 is related to several factors such as physical inactivity, excess body weight and poor eating habits, characterized by systemic inflammation and poor regulation of glucose levels [2]. Individuals with DM2 constitute 90% of all diabetic patients [3], and this chronic condition is recognized as an important risk factor for the prevalence and severity of periodontal disease (DP) [4].

Periodontitis develops due to an imbalance between the bacterial challenge and the host's immune response, which generates inflammation, destruction of connective tissue, and bone tissue remodeling. It has a multifactorial etiology; however, recent findings suggest that genetic factors [5] and vitamin D [6] influence their disposition.

In recent years, it has been discovered that vitamin D can affect periodontal status since it acts on bone homeostasis of calcium and is an anti-inflammatory agent that inhibits the expression of immune cell cytokines causing monocytes / macrophages to secrete molecules that have a strong antibiotic effect [6]. For all these reasons, this vitamin affects directly the pathogenesis induced by *Porphyromonas gingivalis* [7], becoming a protective factor against DP progression [8].

Vitamin D is known to express its genomic action through its receptor (VDR), which shows numerous polymorphisms rs731236 (TaqI), rs7975232 (ApaI), rs1544410 (BsmI) and rs2228570 (FokI) that affect the functional activity of the VDR protein in PD [9].

However, of all these polymorphisms, only one specific can result in differences in the amino acid sequence of the VDR protein, changing its structure, FokI [10], and its research may perhaps serve in the future as a genetic biomarker of periodontitis [11]. Thus, the early identification of these risk indicators for the development of DP may prove to be essential to signal the individuals most predisposed to their development and institute personalized therapies and more effective preventive strategies [12].

However, the epidemiological evidence on the relationship between VDR, its polymorphisms, especially FokI, and periodontitis are inconsistent, requiring more detailed work, which could bring important contributions to its understanding [13].

Periodontitis, too, is often related to tooth mobility and gingival recession, which can alter the smile's aesthetics and, negatively, affect self-esteem, decreasing quality of life. However, there is no significant data regarding this perception in Brazilian patients with diabetes [14].

It is essential to understand how people perceive their oral health and the implications for everyday life [15] and one of the most used indexes to assess the impact of oral health on quality of life is the Oral Health Impact Profile (OHIP-14), which was developed to obtain information about the nature and extent of the functional, social and psychological impact on dental research [16]. The higher the total OHIP-14 score, the greater the oral problems perceived by the patient and the greater their reflexes on quality of life [14].

From this perspective, this study investigated whether the FokI polymorphism (rs2228570) present in the vitamin D receptor (VDR) gene in type 2 diabetics is related to the clinical status of chronic periodontitis in these patients and to evaluate the influence of periodontitis on perception of quality of life.

Material and Methods

Study Design and Sample

This is a clinical and laboratory study, composed of a sample of 59 individuals with DM2 following the parameters of the Brazilian Diabetes Society: (1) Symptoms of polyuria, polydipsia and weight loss plus casual blood glucose ≥ 200 mg/d; (2) Fasting blood glucose ≥ 126 mg/d (7 mmol/l); (3) Blood glucose after overloading 75 g of glucose in 2 hours ≥ 200 (A) 1.2 mg / d; (4) Glycosylated Hemoglobin (HbA1C) greater than or equal to 6.5% and insulin resistance) [17].

The parameters of chronic periodontitis followed the guidelines of the American Academy of Periodontics (periodontal pocket, bleeding and clinical insertion level greater than 3mm) [18], for both sexes. The individuals' data collection was carried out in the post-graduate dental clinic of the Dentistry Course of the Federal University of Pernambuco (UFPE) and the Endocrinology Clinic of the Hospital Agamenon Magalhães (HAM), both located in the city of Recife, Brazil.

The sample selection followed the following inclusion criteria: having DM2, having a clinical diagnosis of chronic periodontitis, having at least 8 (eight) natural teeth, accepting to participate in the research by signing the informed consent form and being at least 35 years old [19]. The exclusion criteria were: being a smoker, being pregnant or breastfeeding, having undergone periodontal treatment or using antibiotics in the last 6 months, using anti-inflammatory drugs in a chronic way.

Clinical Examination

Before starting the clinical examination, socio-epidemiological data on age, sex, income, education, marital status, smoking, type of diabetes, use of medications (including insulin) and time with diabetes were recorded, as well as data on the quality of life of patients using the OHIP-14.

A periogram containing data on probing depth (PD) and Clinical attachment level (CAL) was filled out. Data on visible plaque and bleeding on probing were also collected to verify the respective indices. Six sites were probed for each tooth: mesio-vestibular, mid-vestibular, disto-vestibular, mesio-lingual, mid-lingual and disto-lingual. This examination was carried out with artificial light and using as instruments: odontoscope and millimeter-periodontal probe of the North Carolina University type and Trinity® brand, in addition to personal protective equipment (hat, mask, gloves, glasses, lab coat).

Collection of Biological Material and DNA Isolation

After the clinical examination, saliva was collected in sterile Falcon tubes (15 ml), asking the individual to spit for three minutes [20]. The collected material was placed in a thermal box with recyclable ice and taken to the Laboratory of Molecular Biology of the Graduate School of Dentistry at UFPE for storage in a freezer at a temperature of -20°C , for subsequent isolation of the genetic material. The isolation of deoxyribonucleic acid (DNA) was performed using the PROMEGA genomic DNA purification kit (Wizard®, Promega Corporation, Madison, WI, USA), following the manufacturer's protocol for blood samples. The material was quantified using nanodrop (Thermo Fisher Scientific Inc., Waltham, MA, USA), and kept at -20°C until the realization of the Polymerase Chain Reaction (PCR) in real-time.

SNPS Selection and Real-Time PCR Genotyping

The selection of SNPs for the study was based on the following criteria: MAF (Minor Allele Frequency) values, functional impact of the variant and previous associations of the variants with periodontitis,

DM2 and/or inflammatory diseases in other populations. Variants with MAF values greater than 0.1 (10%) were selected in the Caucasian (Utah Residents with Northern and Western European Ancestry - CEU) and African (Yoruba in Ibadan, Nigeria - YRI) populations, which contributed to the formation of the Brazilian population. The MAF values for the different polymorphisms in the population were obtained from public databases such as: HapMap [21] and 1000 genomes project [22]. For the VDR gene, the selected variant was: rs2228570 G/A (FOK 1), located in the coding promoter region of chromosome 12q13.1, at position 4787912 [23]. Genotyping was performed by real-time PCR using specific allele probes (TaqMan®, Applied Biosystems, Foster City, CA, USA) and the ABI 7500 thermocycler (Applied Biosystems, Foster City, CA, USA) [24]. To detect the genotypes of each SNPs of the studied genes, a reaction with a total volume of 5 µl was used for each variant, containing approximately 1µl of template DNA per reaction (with a concentration of 25ng/µl), 1.25µl of water, 2.5µl of TaqMan® Universal PCR Master Mix (Applied Biosystems, Foster City, CA, USA) and 0.25µl of each probe diluted to 20x (Applied Biosystems, Foster City, CA, USA). A negative control (water) was included in each analysis and the thermal cycler was programmed to perform 50 cycles.

Statistical Analysis

The data were expressed in descriptive measures (average and standard deviation, minimum and maximum) and absolute and relative frequency distributions. The probing depth (PD), Clinical attachment level (CAL), bleeding on probing, plaque index, age, income and time with diabetes were applied to the Mann-Whitney non-parametric test to verify associations with the VDR genotype and OHIP. The likelihood ratio test was applied for categorical variables when Pearson's chi-square test and Fisher's exact test could not be applied to check variable dependencies. The level of significance adopted was 5%. The software used was SPSS 20.0.

Ethical Aspects

The present research was carried out in accordance with the ethical norms established by the Brazilian legislation and obtained a favorable verdict for its execution by the Research Ethics Committee of the Federal University of Pernambuco and the Hospital Agamenon Magalhães, being registered in the CAAE: 49166415.0.0000.5208 and the CAAE: 49166415.0.3001.5197, respectively.

Results

Table 1 describes the clinical-epidemiological profile of the sample studied and its relationship with the VDR genotypes. The only variable to have a positive association between genotypes was the mean PD for individuals with GG and GA (p=0.023).

Table 1. Descriptive measures of some epidemiological variables and clinical characteristics according to the genotypes of VDR (Fok I) rs229570.

Variables	VDR	N	Mean	SD	Minimum	Maximum	p-value
Age	GG	30	60.4	9.6	44.0	80.0	Reference
	GA	25	56.9	10.7	20.0	70.0	0.374
	AA	3	55.7	7.1	48.0	62.0	0.346
	Total	58	58.6	10.1	20.0	80.0	
Income (Wages)	GG	28	1.2	0.6	0.0	2.2	Reference
	GA	23	1.2	0.4	0.5	2.0	0.830
	AA	3	2.4	1.7	1.0	4.3	0.134
	Total	54	1.3	0.7	0.0	4.3	

How Long Diabetic	GG	26	10.8	8.4	0.0	37.0	Reference
	GA	23	13.4	8.2	3.0	30.0	0.227
	AA	3	19.0	6.1	12.0	23.0	0.056
	Total	52	12.4	8.3	0.0	37.0	
Mean PD	GG	30	2.7	0.9	1.4	5.2	Reference
	GA	25	2.2	0.4	1.3	2.9	0.023*
	AA	3	2.2	0.7	1.7	3.0	0.316
	Total	58	2.5	0.7	1.3	5.2	
Mean CAL	GG	30	4.6	2.0	1.6	10.2	Reference
	GA	25	3.9	1.6	1.8	7.8	0.250
	AA	3	4.1	1.6	2.4	5.3	0.802
	Total	58	4.3	1.8	1.6	10.2	
Bleeding Index (%)	GG	30	15.9	16.0	0.0	50.0	Reference
	GA	25	11.6	9.1	0.0	28.1	0.709
	AA	3	9.3	9.2	2.3	19.7	0.637
	Total	58	13.7	13.2	0.0	50.0	
Plaque Index (%)	GG	30	25.7	28.4	0.0	100.0	Reference
	GA	25	26.5	26.4	0.0	100.0	0.641
	AA	3	57.1	37.4	31.8	100.0	0.077
	Total	58	27.7	28.3	0.0	100.0	

Mann-Whitney non-parametric test; *Statistically significant; p-value comparing each genotype with the reference value in the groups.

Table 2 compares the severity of the periodontal condition in relation to the VDR (Fok I) rs229570 genotypes, indicating that these genotypes have no positive association with severity ($p=0.810$). However, the data suggests that there is a relationship between genotypes and the extent of periodontitis ($p=0.012$). While in the genotypes GG (96.7%) and GA (80%) the majority had an extension of generalized periodontitis, in genotype AA, only 33.3% of the sample demonstrated this clinical characteristic.

Table 2. Absolute and relative frequency of the severity of the periodontal condition in relation to the VDR (Fok I) rs229570 genotypes.

Severity of Periodontal Condition	VDR (Fok I) rs229570						Total		p-value
	GG		GA		AA		N	%	
	N	%	N	%	N	%			
Severity of Periodontitis									
Light	4	13.3	6	24.0	1	33.3	11	19.0	0.810
Moderate	12	40.0	10	40.0	1	33.3	23	39.7	
Severe	14	46.7	9	36.0	1	33.3	24	41.4	
Periodontitis Extension									
Localized	1	3.3	5	20.0	2	66.7	8	13.8	0.012*
Generalized	29	96.7	20	80.0	1	33.3	50	86.2	
Total	30	100	25	100	3	100	58	100	

Likelihood Ratio Test, *Statistically Significant.

In Table 3, the dimensions of OHIP-14 did not show a positive association with the severity of periodontitis ($p>0.05$).

Table 3. Absolute and relative frequency of OHIP-14 dimensions to periodontitis severity.

OHIP	Severity of Periodontitis						Total		p-value
	Light		Moderate		Severe		N	%	
	N	%	N	%	N	%			
Functional Limitation									
No	8	66.7	21	91.3	20	83.3	49	83.1	0.201 ¹

Yes	4	33.3	2	8.7	4	16.7	10	16.9	
Physical Pain									
No	5	41.7	19	82.6	16	66.7	40	67.8	0.048 ^{1*}
Yes	7	58.3	4	17.4	8	33.3	19	32.2	
Psychological Discomfort									
No	7	58.3	18	78.3	14	58.3	39	66.1	0.288 ¹
Yes	5	41.7	5	21.7	10	41.7	20	33.9	
Physical Disability									
No	8	66.7	18	78.3	17	70.8	43	72.9	0.733 ¹
Yes	4	33.3	5	21.7	7	29.2	16	27.1	
Psychological Disability									
No	7	58.3	19	82.6	18	75.0	44	74.6	0.293 ¹
Yes	5	41.7	4	17.4	6	25.0	15	25.4	
Social Disability									
No	10	83.3	23	100.0	22	91.7	55	93.2	0.097 ²
Yes	2	16.7	0	0.0	2	8.3	4	6.8	
Handcap									
No	9	75.0	21	91.3	20	83.3	50	84.7	0.431 ²
Yes	3	25.0	2	8.7	4	16.7	9	15.3	
Total	12	100.0	23	100.0	24	100.0	59	100.0	

¹Pearson's chi-square test; ²Likelihood Ratio Test, *Statistically Significant.

About the OHIP-14 questionnaire, 55.9% of the interviewees had some impact on quality of life, in which the dimensions most frequently were: OHIP3 (Psychological Discomfort) and OHIP2 (Physical Pain), as shown in Figure 1.

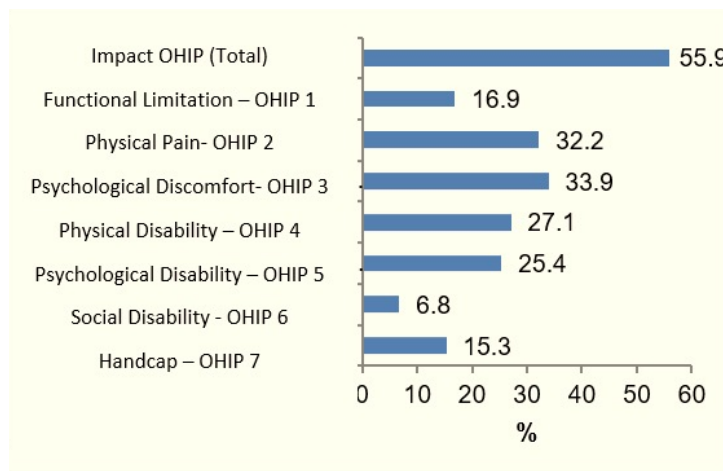


Figure 1. Percentage of the presence of impact on OHIP and its 7 dimensions.

Table 4 shows no positive association between the dimensions of the OHIP-14 and the severity of the periodontal condition, as well as the genotypes of the VDR.

Table 4. Absolute and relative frequency of variables: periodontal condition severity and VDR (FokI) to the total OHIP-14 impact.

Variables	Total OHIP				Total		p-value
	No Impact		With Impact		N	%	
	N	%	N	%			
Severity of Periodontitis							
Light	3	11.5	9	27.3	12	20.3	0.090 ¹
Moderate	14	53.8	9	27.3	23	39.0	

Severe	9	34.6	15	45.5	24	40.7	
Total	26	100.0	33	100.0	59	100.0	
Periodontitis Extension							
Localized	3	11.5	6	18.2	9	15.3	0.718 ²
Generalized	23	88.5	27	81.8	50	84.7	
Total	26	100.0	33	100.0	59	100.0	
VDR							
GG	12	46.2	18	56.3	30	51.7	0.617 ³
GA	13	50.0	12	37.5	25	43.1	
AA	1	3.8	2	6.3	3	5.2	
Total	26	100.0	32	100.0	58	100.0	

¹Pearson's chi-square test; ²Fisher's exact test; ³Likelihood Ratio Test.

Discussion

DM2 was cataloged as the first epidemic of the 21st century [2]. The prevalence, progression and severity of DP have been reported as bidirectional and influenced by DM2, which shows an interrelation between the two diseases [25].

The VDR gene polymorphisms are members of the nuclear receptor superfamily and act as a ligand-dependent transcription factor [26]. Its alterations in the signaling pathways can lead to different cellular defects that are important in the activation of genes, such as the increase or decrease in the transcription of calcium metabolism, cell proliferation and immune response [27].

The VDR gene is located on chromosome 12q13.11 and is composed of 11 exons [28]. There are numerous nucleotide polymorphisms (SNPs) in the VDR gene. BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236) and FokI (rs2228570), are the SNPs most frequently investigated, being associated with susceptibility to many cardiovascular diseases, metabolic disorders, cancer, infectious, autoimmune diseases and diabetes [29].

Despite the previous associations for FokI variants with the risk of developing PD in other populations [30,31], increasing its frequency according to the severity of the periodontal condition [32], no significant differences were observed between the groups of our sample. Our results corroborate with other findings in the literature [9,13] where there was no influence of the FokI polymorphism (rs2228570) on chronic periodontitis among the different frequencies of genotypes, alleles, haplotypes and in most clinical characteristics. However, there is a statistical difference found in our study regarding the extent of DP and the different associated genotypes.

It is now known that FOKI genotypic variations interact differently with immunospecific transcription factors reflecting a variable immune behavior of macrophages, cytokines, dendritic cells and lymphocytes [33]. Thus, it is likely that individuals with a VDR FokI polymorphism and different genotypes may have different risks for developing autoimmune disorders, which may explain our findings about the difference in the extent of periodontitis in the GG, GA and AA genotypes [5]. PD being the result not only of an imbalance between the load of periodontopathic bacteria in the subgingival microenvironment and the host's immunological potential [34], but a genetic susceptibility determined by the genotypes [35].

The different associations about the influence of FokI on clinical characteristics and severity in previous studies can be explained by the genetic configuration of the population sample, where a high degree of miscegenation will imply genetic heterogeneity, leading to negative or positive results from the FokI interrelation and chronic periodontitis [36].

The dimensions of OHIP-14 in this study did not show positive associations with the severity of periodontitis, contrary to other findings [37,38]. And, although patients have reported some impact on quality of life, this perception can be explained by the fact that the oral condition is secondary in detriment of the systemic, and this fact is evidenced by another study [39].

In our study, the dimensions of the OHIP-14 most cited were psychological discomfort, physical pain, and physical disability, which, in turn, converges with other studies [38,40], significantly impacting individuals' functional limitation [14].




The results discussed so far reveal the need to understand the degree of dissatisfaction with the oral health of patients with DM2 and chronic periodontitis through OHIP-14, as self-perception in oral health is a measure that contributes to the evaluation of care in health generating subsidies to intervene in the health-disease process [15].

The limitations identified in this study were the small sample size and the convenience sampling method used, which may present a sampling bias that may not be valid to represent the general study population.

Conclusion

The VDR polymorphism in this study had no positive association with the severity and clinical characteristics of periodontal disease, but suggested a relationship with the disease's extent. The perception of the quality of life of patients with chronic periodontitis and DM2 was compromised by the systemic condition, while oral health was secondary, although some dimensions of OHIP-14 have been mentioned more, such as psychological discomfort, physical pain and physical disability. Further studies on FokI need to be carried out to better clarify its influence on the extent of periodontitis and clinical variables.

Authors' Contributions

RCS	 0000-0002-4973-123X	Conceptualization, Methodology, Investigation, Formal Analysis, Writing – Original Draft Preparation and Writing – Review and Editing.
RCMP	 0000-0002-2831-2722	Conceptualization, Methodology, Investigation, Formal Analysis, Writing – Original Draft Preparation and Writing – Review and Editing.
RC	 0000-0003-3673-8739	Conceptualization, Methodology, Investigation, Formal Analysis, Writing – Original Draft Preparation and Writing – Review and Editing.

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

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