

## Periodontal inflammation correlates with systemic inflammation and insulin resistance in patients with recent diagnosis of type 2 diabetes

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### Abstract

**Background:** diabetes and periodontitis are common comorbidities; however, the clinical implications of this association remain only partially known. This study was aimed to characterize the periodontal status of type 2 diabetic (T2D) patients and its correlation with metabolic and inflammatory parameters. **Methods:** patients (n = 30) with 5 or less years since the diagnosis of T2D (18 – 65 years old) were recruited. Anthropometric (Body Mass Index, BMI), metabolic (fasting glucose, glycated hemoglobin, insulin, HOMA-IR, HDL, LDL and total cholesterol, triglycerides) and inflammatory parameters (ultrasensitive C reactive protein, usCRP) were quantified. Periodontal evaluation included clinical attachment level (CAL), probing depth (PD), gingival level (GL) and bleeding on probing (BOP) average. Statistical significance was assessed by Mann-Whitney and Spearman correlation tests. **Results:** mean values of BOP, CAL, PD and GL were 39.3, 2.8, 2.8, and 0.1, respectively. BOP significantly correlated with BMI and HOMA-IR and was higher in patients with elevated usCRP >3 mg/L (p<0.05). Age and duration of T2D directly and inversely correlated with CAL and GL, respectively. BOP correlated with HOMA-IR and usCRP but not with patients' age, duration of T2D or BMI. **Conclusions:** in patients with recent diagnosis of T2D, BOP is associated with usCRP and HOMA-IR levels, suggesting that periodontal inflammation promotes insulin resistance possibly by increasing systemic inflammation.

**Keywords:** diabetes; periodontitis; C reactive protein; insulin resistance, inflammation; chronic disease

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### Introduction

Type 2 diabetes (T2D) is a worldwide public health problem (Petersen & Ogawa, 2012). In Chile, ~9-12% of the adult population is estimated to be diabetic (Ministerio de Salud de Chile, 2010). Periodontitis is also a prevalent condition (Schatzle *et al.*, 2003; Hajishengallis, 2015) that is associated with decreased quality of life (Gamonal *et al.*, 2010). T2D is a recognized risk factor for periodontitis across different populations (Nelson *et al.*, 1990; Genco & Borgnakke, 2013). Furthermore, the prevalence of periodontitis in diabetic patients is extremely high, such as it has been considered a diabetic complication by itself (Löe, 1993; Preshaw *et al.*, 2012).

Pathophysiologically, periodontitis and diabetes may influence each other in bidirectional ways (Mealey, 2006; Preshaw *et al.*, 2012). Diabetic complications are the result of micro and macrovascular abnormalities. In addition, chronic hyperglycemia impairs immunological function and tissue reparation, leading to chronic tissue inflammation and damage. These might be the underlying mechanisms for accelerated periodontal destruction in diabetic patients and animal models (Pickup, 2004; Lakschevitz *et al.*, 2011).

By other hand, there is still no agreement in scientific community that treatment of periodontitis improves the glycaemic control in this type of patients. A randomized study of 512 patients with DM2 from five medical centers in New York City identified that there is no relationship between the decrease in blood glucose levels among diabetic patients receiving periodontal treatment for a period of six months versus diabetic controls who did not receive it (Engelbreton *et al.*, 2013). While other authors recognize that the treatment has a positive impact on the improvement of blood sugar levels (Borgnakke *et al.*, 2013; Engelbreton & Kocher, 2013; Casanova *et al.*, 2014). A last meta-analysis shows that there was no evidence to support that one periodontal therapy was more effective than another in improving glycaemic control in people with diabetes mellitus (Simpson *et al.*, 2015).

Systemic low grade inflammation is a common finding in T2D and it has been associated with increased insulin resistance (Colombo *et al.*, 2012). Circulating levels of ultrasensitive C reactive protein (usCRP), a marker of subclinical inflammation, are increased in patients with periodontal disease, possibly as a consequence

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of periodontal bacterial translocation to systemic circulation (Gomes-Filho *et al.*, 2011; Pejcic *et al.*, 2011).

Obesity is a major risk factor for T2D and appears to be an independent determinant of periodontitis (Saito *et al.*, 2001; Chaffee & Weston, 2010). Recently, was reported that body mass index (BMI) and waist circumference (WC) to height ratio are significantly associated with periodontal progression (Gorman *et al.*, 2012).

Finally, although the duration of T2D determines the risk for micro and macrovascular complications its influence on the prevalence and severity of destructive periodontal disease remains controversial (Cerdeira *et al.*, 1994; Sandberg *et al.*, 2000; Pranckeviciene *et al.*, 2014).

The aims of this study were to quantify clinical parameters of periodontal inflammation and destruction in patients with recent diagnosis of T2D and to determine the relationship between periodontitis and the duration of diabetes as well as indicators of insulin resistance, systemic inflammation and nutritional status.

## Materials and methods

### Patients

T2D patients were recruited from Pontifical Catholic University of Chile outpatient diabetes and odontology clinics. Inclusion criteria were: T2D with five years or less of formal diagnosis, age between 18 and 65 years and preservation of at least 20 teeth. Exclusion criteria were: use of antibiotics or periodontal treatment in the last six-month, concurrent acute infectious diseases, primary or secondary immunodeficiency unrelated to diabetes, active smoking and severe oral infection. Thirty-nine (39) patients were initially screened but only 9 men and 21 women completed the full series of clinical, anthropometric and laboratory determinations. Study design and informed consent document were approved by Pontifical Catholic University of Chile institutional ethical committee for clinical research. All participants signed informed consent.

### Periodontal evaluation

Periodontal determinations were performed by a single and trained periodontist that was blind for the metabolic and inflammatory status of the patients. Periodontal disease diagnosis and severity classification were based on American Academy of Periodontology guidelines (American Academy of Periodontology, 2000). The periodontal parameters assessed were probing depth (PD), gingival level (GL) measured from cemento-enamel junction, clinical attachment level (CAL) and bleeding on probing (BOP).

### Anthropometric determinations

Body weight (BW), height, waist circumference (WC) and body mass index (BMI) were determined by a single investigator.

### Laboratory determinations

Fasting glucose, insulin, glycated hemoglobin fraction C (HbA1c), insulin resistance (HOMA\_IR), total cholesterol (TC), low density lipoprotein cholesterol (C-LDL), high density lipoprotein cholesterol (C-HDL), triglycerides (TG) and usCRP were determined in the central laboratory of Pontifical Catholic University of Chile Health Network.

### Statistical analysis

Statistical significance of associations was determined with Mann-Whitney and Spearman correlation test using SPSS version 22.0 (IBM Corp. Released 2013) and GraphPad Prism version 7.0 (GraphPad Software, s.f.).

## Results

Thirty patients were included in this study (21 women, 9 men). The age of the subjects was  $48 \pm 10.4$  years (mean  $\pm$  S.D.) and the known duration of T2D was  $2.1 \pm 1.3$  (mean  $\pm$  S.D.). Anthropometric, metabolic, periodontal and dental characteristics of the subjects are shown in table 1. All the patients included in this study had periodontitis and ~15% had the most severe form of the disease (mean CAL 5-6 mm) (table 2).

The age of patients directly correlated with clinical attachment level (CAL) (figure 1A) and inversely with gingival level (GL) (figure 1B). Equivalent associations were found with the duration of T2D (figure 1C-D). By contrast, patients age or duration of T2D did not correlate with BOP, PD or metabolic parameters (table 3).

Obesity has been previously associated with periodontal disease (Saito *et al.*, 2001) however, the impact of diabetes on periodontitis in obese patients remains uncertain. In our group of T2D patients, we found no association between BMI or waist circumference (WC) with periodontal indicators GL, CAL and BOP (table 3).

Combined, these data suggest that, in recently diagnosed patients with T2D, both age and duration of diabetes are determinants of gingival recession, indicated by lower GL, and interproximal loss of attachment indicated by elevated CAL.

The association between gingival inflammation and circulating levels of usCRP is shown in figure 2A. We found a direct correlation between usCRP and BOP levels in diabetic patients ( $r=0.515$ ;  $p<0.004$ ). Concordantly, the median BOP was significantly higher in patients with usCRP  $\geq 3$  mg/L (figure 2B).

**Table 1:** Anthropometric, metabolic and clinical periodontal characteristics of subjects included in the study.

Parameter	Average	SD	Media	Rank
Age (years)	48.4	10.4	49.5	23 - 65
T2D time (years)	2.1	1.3	2.0	0-5
Weight (Kg)	80.6	14.6	78.0	57 - 113
Height (m)	1.6	0.1	1.6	1.5 - 1.8
BMI (Kg/m <sup>2</sup> )	31.5	5.1	30.8	24.4 - 44.1
WC (cm)	104.5	11.3	102.5	87 - 129
Blood sugar (mg/dL)	137.2	67.1	114.5	74 - 377
Insulin (μUI/mL)	17.5	9.0	14.8	4.8 - 35.3
HOMA-IR	6.1	3.9	5.9	1.2 - 13.9
HbA1c (%)	7.2	1.8	6.5	5.3 - 11.8
TC (mg/dL)	167.4	34.4	162.5	114 - 237
TG (mg/dL)	167.2	109.2	131.0	40 - 590
C-HDL (mg/dL)	44.0	11.6	41.0	27 - 76
C-LDL (mg/dL)	89.8	24.4	85.5	45 - 143
usPCR (mg/L)	3.8	3.5	2.4	0.2 - 13.9
BOP (%)	39.3	23.7	34.5	8 - 80
CAL (mm)	2.6	1.2	2.3	1.0 - 5.8
PD (mm)	2.8	0.6	2.6	2 - 4.5
GL (mm)	0.1	1.0	0.2	-1.6 - 1.9

SD, Standard Deviation; BMI, Body Mass Index; WC, Waist Circumference;

HbA1c, Glycated Hemoglobin; TC, Total Cholesterol; TG, Triglycerides; C-HDL, High density lipoproteins cholesterol; C-LDL, Low density lipoprotein cholesterol ; BOP, Bleeding on probing; CAL, Clinical Attachment level; PD, Probing Depth; GL, Gingival Level.

**Table 2:** BOP (%) in T2D patients according to US-CRP level

	usCRP < 3 mg/L	usCRP ≥ 3 mg/L
N	18	12
Median	31.2	50.1
SD	22.4	22.2
Median	25	50*
Rank	8 - 80	12 - 80

Mann-Whitney U Test,\*p< 0.05. BOP, bleeding on probing; usCRP, ultrasensitive C-reactive protein.

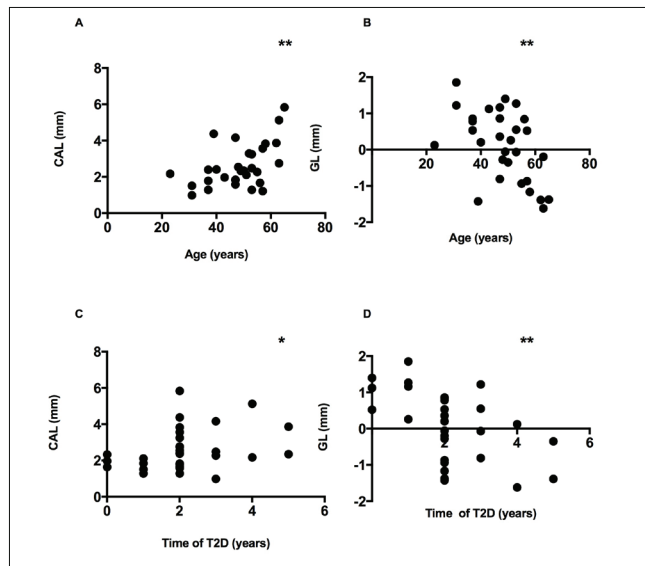
The impact of periodontitis on insulin resistance we assessed with the relationship between gingival inflammation and HOMA-IR. As shown in figure 2C, BOP was positively correlated with HOMA-IR (R=0.4; p = 0.036), suggesting a clinical relationship between local periodontal inflammation and systemic insulin resistance.

Since periodontitis is a site-specific disease, with an heterogeneous intrapersonal distribution of its severity, we clustered the number of periodontitis sites at the individual level. For this purpose, only the sites with probing depth ≥4 mm was analyzed. We found no correlation between the proportion of periodontal pockets larger than 4 mm and usCRP or HOMA-IR (figure 3).

**Discussion**

Herein we report that periodontitis was present in all the middle-aged T2D patients studied and that 15% of them had severe periodontal inflammation and destruction. These findings agree with previous reports showing that periodontitis is significantly more frequent in diabetic patients than non-diabetic individuals of same age and sex ( Tsai *et al.*, 2002; Lakschevitz *et al.*, 2011; Colombo *et al.*, 2012)

Nonetheless, our main finding was that in patients with recent diagnosis of T2D (5 or less years), AL and GL positively correlate with the duration of diabetes. Cerda *et al.* (1994), reported a positive correlation between the time since diagnosis and the size of periodontal pockets and gingival recession, but in patients with duration of diabetes longer than 5 years. Therefore, our results suggest that T2D has a rapid deleterious influence on periodontal tissue which is, fastest that in other classically targeted tissues.



**Figure 1:** Correlation between periodontal parameters (CAL, GL) with age and time of T2D.

- A. Correlation between CAL (mm) and age (years)
- B. Correlation between GL (mm) and age (years)
- C. Correlation between CAL (mm) and time of T2D (years)
- D. Correlation between GL (mm) and time of T2D (years)

\* p<0.05, \*\*p < 0.005 (Spearman)

**Table 3:** Correlation between age, T2D time, BMI and WC with metabolic and periodontal parameters

\* Significance < 0.01. \*\* Significance < 0.05.

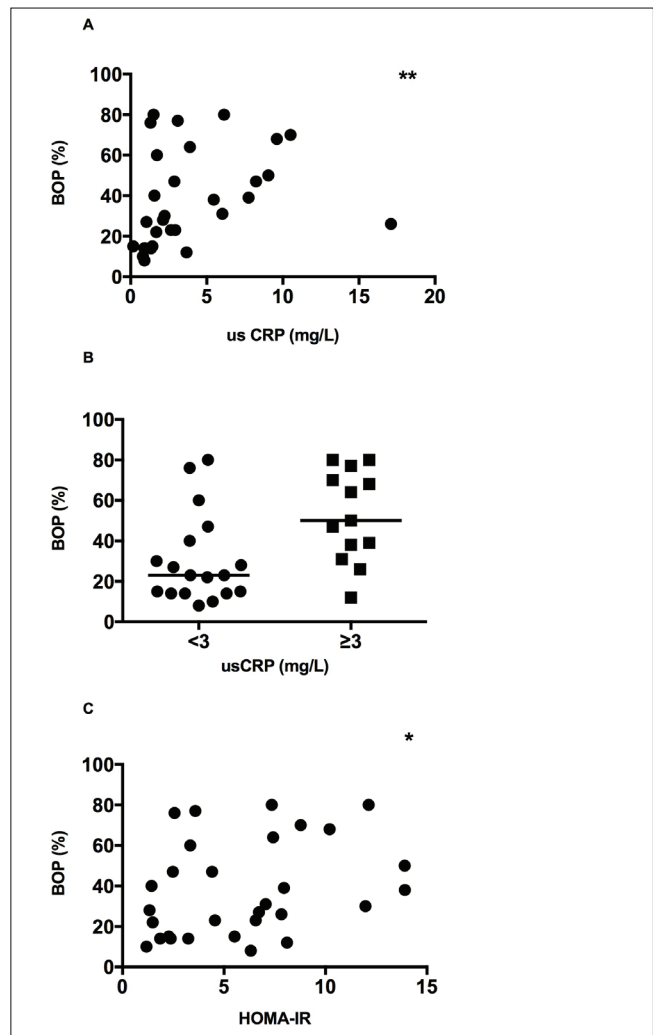
Parameter	Correlation coefficient and p value	Homa-IR	PCR	C-LDL	C-HDL	GL	CAL	BOP	PD
Age	R	-0.322	-0.374	-0.061	0,425	-0.517	0.469	-0.286	0.169
	G	0.082	0.042	0.393	0.019	0.003**	0.008**	0.126	0.371
T2D time	R	0.015	0.08	0.069	0.274	-0.535	0.379	0.033	-0.219
	p	0.938	0.673	0.716	0.143	0.002**	0.039	0.863	0.244
BMI	R	0.331	0.218	0.085	0.088	0.197	-0.029	0.307	0.239
	p	0.074	0.248	0.654	0.642	0.297	0.878	0.099	0.203
WC	R	0.315	0.258	0.011	-0.019	0.203	0.006	0.307	0.332
	p	0.09	0.168	0.955	0.919	0.283	0.976	0.098	0.073

GL (gingival level) and CAL (clinical attachment level) correlates with Age  
 GL correlates with Time of Diabetes type 2

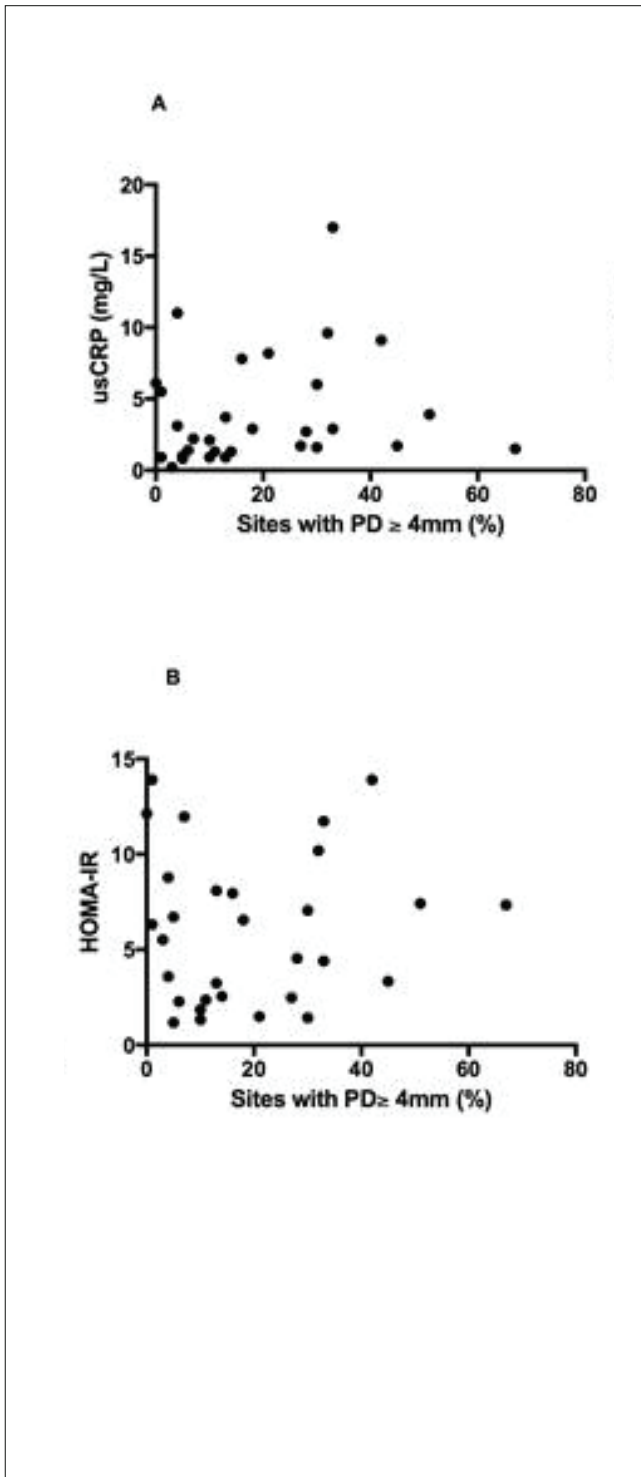
Obesity has been recently proposed as an independent risk factor for periodontitis (Gorman *et al.*, 2012; Papageorgiou *et al.*, 2015). Herein, we found that BOP, a clinical indicator of local periodontal inflammation, was directly correlated with BMI in patients with T2D. Previously, Saito *et al.* (2001) reported that probing depth and BMI are associated in a population of young Japanese patients, whereas Gorman *et al.* (2012) found that white obese male individuals have increased risk for moderate and severe periodontal disease. We did not observe correlations between CAL or GL with BMI or WC in our group of T2D patients.

Another important finding of our study was the direct correlation between BOP and usCRP. It is currently accepted that periodontitis determines low grade systemic inflammation (Gurav, 2012; Hajishengallis, 2015) and this has been implicated in the progression of chronic metabolic conditions like atherosclerotic coronary artery disease (D’Aiuto *et al.*, 2004). The mechanisms of periodontitis-associated systemic inflammation are partially understood but is possible that gingival ulceration at periodontal pockets facilitates the translocation of bacteria into the systemic circulation. In addition, locally generated pro-inflammatory cytokines, such as tumor necrosis factor, interleukin-1 $\beta$  and interleukin-6, enter the circulation and promote systemic inflammatory responses (Hajishengallis, 2015).

Currently, it is proposed that both metabolic (lipotoxicity, mitochondrial dysfunction) and inflammatory determinants play pathogenic roles in insulin resistance (Samuel & Shulman, 2016). In non-diabetic subjects, HOMA-IR has been correlated with periodontitis severity Pejic, suggesting that local periodontal inflammation influence systemic insulin sensitivity (Demmer *et al.*, 2012). A pathophysiological link for this association might be systemic inflammation, as indicated by elevated inflammatory cytokine in patients with periodontitis (Loos, 2005).



**Figure 2:**  
 A. Correlation between BOP and us CRP  
 B. Correlation between BOP and us CRP  $\geq$  or < 3 mg/L ( $p < 0.01$ ; Man Whitney)  
 C. Correlation between BOP and HOMA-IR.  
 \*  $p < 0.05$ , \*\*  $p < 0.01$  (Spearman)



**Figure 3:**

A. Correlation between percentage of sites equal or larger than 4 mm with us CRP and HOMA-IR

B. Correlation between percentage (%) of sites  $\geq$  4mm of each patient and us CRP ( $p = 0.109$ , Spearman)

C. Correlation between percentage (%) of sites  $\geq$  4mm of each patient and HOMA-OR. Not significant ( $p = 0.901$ , Spearman)

Conventional periodontal therapy has beneficial impacts on insulin resistance and systemic inflammation in T2D patients (Sun *et al.*, 2011; Sgolastra *et al.*, 2013). In our study, we found that BOP directly correlated with HOMA-IR, independent of the number or percentage of sites  $\geq$  4mm, suggesting that periodontitis-associated insulin resistance is not related with the extension or severity of periodontal disease. Further studies are required to disclose the biological relationships between periodontitis and insulin resistance.

It has been proposed that the metabolic control of diabetes positively influence periodontitis progression (Chapple & Genco, 2013). In our study, we found no correlations between various periodontitis parameters and HbA1C levels, an indicator of glycemic control, possibly because the limited value of isolated HbA1c determinations to estimate the long-term glycemic control in diabetic patients.

### Conclusion

The main limitation of this study was the small number of patients studied and lack of a control group. In spite of that, we were able to find that in recently diagnosed patients with T2D, age and time since T2D diagnosis correlate with GL and CAL, and that HOMA-IR and usCRP are directly correlated with gingival inflammation (BOP).

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The authors report no conflicts of interest related to this study.

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