Impact of Periodontal Therapy and Adjunctive Omega-3 plus Aspirin on Quality of Life in Patients with Periodontitis and Type 2 Diabetes

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Abstract

Aims: To investigate the impact of periodontal therapy on oral health-related quality of life (QoL) measures (OHRQoL) in patients with periodontitis and diabetes.

Materials and methods: Patients with stages III and IV, generalized, grades B and C periodontitis and diabetes were assessed for OHRQoL using the Oral Health Impact Profile (OHIP)-14 at baseline and after 6 months of periodontal therapy. The patients were randomly selected to receive placebo after periodontal debridement (n=29), omega (ω)-3 polyunsaturated fatty acids (PUFA) and aspirin (ASA) after periodontal debridement (n=25), or ω-3 PUFA and ASA before periodontal debridement (n=24). Mean OHIP-14 scores and prevalence of answers were compared, and stepwise logistic regression was used to measure the relationship between OHIP-14 scores and covariables.

Results: OHIP-14 significantly decreased after therapy indicating improved QoL. Logistic regression revealed that the covariables "treatment protocol" (placebo), "number of pockets with probing depth ≥5mm" (>14), and "mean PD" (>3.3mm) were significant predictors of higher OHIP-14 scores at 6 months after periodontal therapy. Periodontal therapy improved OHRQoL for patients with periodontitis and diabetes after 6 months. The presence of periodontal pockets at 6 months post-therapy was associated with reduced QoL.

Conclusions: These findings show the positive impact of periodontal treatment on QoL of people with diabetes.

Keywords: Quality of life, periodontitis, diabetes, omega-3 fatty acids, aspirin.

Introduction

The World Health Organization defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO, 1946). This social concept has been widely applied to dentistry. The FDI World Dental Federation states that "Oral health is multifaceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey a range of emotions through facial expressions with confidence and without pain, discomfort, and disease of the craniofacial complex" (Glick *et al.*, 2016). Thus, assessment of an oral health-related quality of life (OHRQoL) from the patient's perspective is an important tool for the diagnosis and characterization of oral diseases. The perception of OHRQoL is significant to different oral conditions, such as tooth decay (Ramos-Jorge *et al.*, 2014), gingival recessions (Sangiorgio *et al.*, 2017), tooth loss (Kato *et al.*, 2018), and periodontal disease (Kato *et al.*, 2018; Masood *et al.*, 2019).

Periodontitis is an infectious and inflammatory disease that leads to the destruction of periodontal tissues and its course may be modified by multiple host

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response features in combination with lifestyle and environmental factors (Bartold and Van Dyke, 2013; Papapanou *et al.,* 2018). It is considered a worldwide health problem (WHO, 2003) that over the years has demanded global health policies and programs that can assist in its prevention and treatment (Petersen and Ogawa, 2005). Severe periodontitis is the sixth most prevalent disease in the world, and it is estimated that 11% of the world's population is affected by periodontitis (Kassebaum *et al.*, 2014). Periodontal diseases negatively impact quality of life, with greater severity of disease related to greater impact (Ferreira *et al.*, 2017). Since it has been suggested that periodontitis may decrease life expectancy (Buset *et al.*, 2016), many studies have focused on the influence of this disease on quality of life and systemic health of individuals, including cardiovascular disease (Dietrich, 2008; Tonetti and Van Dyke, 2013), pregnancy complications (Armitage, 2013), neurological diseases (Hellvard *et al.*, 2019) and diabetes (Taylor, 2001; Casanova *et al.*, 2014).

Diabetes is considered one of the largest global health problems of the 21st century. The International Diabetes Federation (IDF) estimates that 463 million people live with diabetes and that 374 million adults have impaired glucose intolerance, putting them at risk for developing diabetes (IDF, 2019). Brazil is currently the 5th country in the number of people with diabetes, with 16.8 million people diagnosed with the disease, and the country with the highest annual health expenditure per patient with diabetes (US$ 3,117) (IDF, 2019). Complications of diabetes, such as cardiovascular disease, nephropathy, retinopathy, and periodontitis, are major causes of reduced quality of life, disability, and loss of productivity. Evidence shows that appropriate management of the disease improves quality of life in people with diabetes. However, even though periodontitis is one of the most frequent diabetes complications, the global guideline for the management of type 2 diabetes does not include oral health care (IDF, 2012). Also, no previous studies have assessed the impact of adjunctive immune modulation therapy with omega (ω)-3 polyunsaturated fatty acids (ω-3 PUFA) and aspirin (ASA) for the concomitant occurrence of periodontitis and diabetes on patients' quality of life. Thus, this study aimed to investigate the impact of periodontal therapy on oral health-related quality of life measures (OHRQoL) in patients with periodontitis and diabetes.

Materials and methods

Study population, Inclusion and Exclusion Criteria

The present study is a retrospective analysis derived from a randomized clinical trial (RCT) conducted in Brazil (Castro dos Santos *et al.*, 2020). Volunteers presenting periodontitis and diabetes mellitus were recruited at São Paulo State University (Unesp) (São José dos Campos, SP). Detailed dental and medical records were obtained. Patients who fulfilled the inclusion criteria were invited to participate in the study. Inclusion criteria were as follows: stages III and IV, generalized, grades B and C periodontitis (Papapanou *et al.*, 2018) with at least 6 sites with PD and clinical attachment level (CAL) ≥5 mm and bleeding on probing (BoP) (Andere *et al.*, 2017; Araujo *et al.*, 2019); ≥15 teeth; aged ≥35; diagnosis of type 2 diabetes for ≥5 years; under treatment for diabetes; presenting glycated hemoglobin (HbA1c) levels ≥6.5% to ≤11%. Exclusion criteria were as follows: need for prophylactic antimicrobial coverage; scaling and root planing (SRP) in the previous 6 months; antimicrobial therapy in the previous 6 months; systemic conditions that could affect the progression of periodontitis, except for diabetes; long-term use of medication that could interfere with periodontal response; pregnancy or lactation; smoking. Informed consent was provided by each volunteer after a thorough explanation of the nature, risks, and benefits of the clinical investigations. The study protocols were approved by Unesp Institutional Review Board (CAAE: 51626115.5.0000.0077). The RCT was registered in ClinicalTrials.gov (NCT02800252).

Clinical Examination

Periodontal measurements were performed by a calibrated examiner (CFA). Clinical evaluations were performed at baseline and 6 months after periodontal therapy. The evaluated parameters were: number of teeth, PD (mm), CAL (mm), BoP (0/1), and Plaque Index (PI) (0/1) (Ainamo and Bay, 1976). All clinical measures were assessed at 6 sites per tooth (mesiobuccal, buccal, distobuccal, distolingual/palatal, lingual/palatal, and mesiolingual/palatal) on all teeth, excluding third molars, using a manual probe (University of North Carolina Probe PCPUNC-BR 15, Hu-Friedy, Chicago, IL, USA). Peripheral blood was collected to evaluate HbA1c levels at baseline and 6 months; anthropometric measures including weight and height were recorded at baseline and body mass index (BMI) was calculated as the weight divided by the square of height (kg/m^2).

Interventions and Treatment Protocol

A computer-generated blocking sequence (3, 6, 9) was used to randomly allocate the selected patients to one of the following groups: (i) periodontal debridement and placebo [Control Group (CG)], (ii) ω-3 PUFA and ASA daily for 2 months *after* periodontal debridement [Test Group (TG)1], or (iii) ω-3 PUFA and ASA daily for 2 months *before* periodontal debridement (TG2). All patients received instructions about the relationship between periodontitis and type 2 diabetes, oral hygiene instructions, supragingival biofilm and calculus removal, extraction of hopeless teeth, dental decay removal and provisional restoration, and removal of overhanging restorations. Prosthetic rehabilitations

were performed after the study follow-up. After local anesthesia, all patients received full-mouth subgingival SRP in one session using an ultrasonic device (Cavitron Select, Dentsply, York, PA, USA) with subgingival inserts and manual curettes (Gracey curettes, Hu-Friedy, Chicago, IL, USA). The endpoint for this procedure was the smoothness of the scaled roots. Randomization was stratified in blocks of 3, 6, and 9. Patients in the CG received placebo capsules for 2 months after periodontal debridement. Patients in the TG1 received 3g fish oil with ω-3 PUFA (Catarinense Pharma, Joinville, SC, Brazil) and 100mg ASA (Bayer, São Paulo, SP, Brazil) daily for 2 months after periodontal debridement. Patients in the TG2 received 3g of fish oil with ω-3 PUFA plus 100mg ASA daily for 2 months before periodontal debridement (Castro dos Santos *et al.*, 2020).

Oral Health-Related Quality of Life

The Oral Health Impact Profile (OHIP)-14 was applied to measure oral health-reported quality of life (OHRQoL) (Slade, 1997). The questionnaire was conducted in Portuguese according to the validated Brazilian version of the OHIP- short form (Oliveira and Nadanovsky, 2005). The OHIP-14 comprises a questionnaire with 14 questions that measure 7 domains (2 questions in each domain) namely functional limitation, physical pain, psychological discomfort, physical disability, psychological disability social disability, and handicap. All patients completed the questionnaire by answering "Never"=0, "Hardly ever"=1, "Occasionally"=2, "Fairly often"=3, or "Very often"=4. Quality of life reduces as the scores increase. At baseline, the questionnaire was applied after the volunteer agreed to participate in the study and signed the informed consent and before any dental treatment was carried out. At 6 months, the questionnaire was applied after all clinical data were collected.

Data Collection and Statistical Analysis

Clinical and OHIP data were entered directly onto electronic spreadsheets at the time of clinical examination by a single investigator. The data were analyzed for all patients at baseline and 6 months. Mean and standard deviations were calculated for each parameter. Normal distribution was tested by Shapiro-Wilk. Demographic data were assessed using one-way ANOVA test. Gender, obesity [body mass index (BMI) >30 kg/m^2], and control of diabetes (HbA1c <7%) distribution differences among groups were assessed using Chi-square test. Mean OHIP-14 comparison before and after therapy was assessed using Kruskal-Wallis test. The percentage of answers according to sub-domains were compared using Chi-square test. Stepwise logistic regression models were used to look at parameters that could have influenced patients' perception of OHRQoL according to OHIP-14 scores. The dependent variables were different cutoffs for OHIP-14 scores: >7, >14, >21, >28, >35, and >42 (binary state). The covariables were quantitative/qualitative parameters (considering quartiles as cutoffs). Multicollinearity was assessed for the variables in the models and no high intercorrelations were detected. All data analyses were performed using IBM SPSS Statistics. The significance level applied was 5%.

Results

Demographic Data

A total of 117 patients were assessed for eligibility. Seventy-six volunteers meeting the inclusion and exclusion criteria were recruited at baseline. One volunteer decided not to go through the treatment for personal reasons. Twenty-five patients received the treatment and were followed up to 3 months after periodontal debridement. Two patients (1 in the CG and 1 in the TG2) were lost to follow-up at 6 months and were excluded from this retrospective analysis. Three additional patients who had received periodontal treatment followed by placebo and had answered the OHIP-14 at baseline and 6 months were included in this analysis. All individuals presented generalized stages III and IV, grades B and C periodontitis (Papapanou *et al.*, 2018). The distribution of female patients was 65.5% in the CG, 64% in the TG1, and 54.2% in the TG2 ($P > 0.05$). Patients presenting obesity represented 69% of the CG, 60% of the TG1, and 40.9% of TG2 ($P > 0.05$). Patients with controlled diabetes (HbA1c < 7.0%) were 32.0% in the CG, 29.2% in the TG1 and 31.0% in the TG2 ($P > 0.05$). Mean age and mean number of teeth did not differ among the study groups ($P > 0.05$). The evaluated periodontal clinical parameters (PD, CAL, BoP, PI) did not present statistically significant differences among the treatment groups ($P > 0.05$) (Table 1).

OHIP-14

The mean score of OHIP-14 was significantly lower after 6 months of periodontal therapy for all study groups ($P < 0.05$). When all patients were analyzed as one group, the percentage of answers according to the sub-domains "psychological discomfort" and "physical inability" decreased 6 months post-therapy ($P < 0.05$) (Figure 1).

A stepwise logistic regression was performed to assess if periodontal parameters were predictors of OHIP-14 after 6 months of periodontal therapy. The use of placebo was a significant predictor for OHIP >21 (OR 4.51, 95% CI 1.41-14.43), >28 (OR 7.71, 95% CI 1.90-31.31), >35 (OR 7.80, 95% CI 1.61-37.91), and >42 (OR 12.71, 95% CI 1.29-124.90) ($P <0.05$). The number of sites with PD ≥5 mm (>14 sites) was a predictor for OHIP >28 (OR 4.34, 95% CI 1.02-18.74) and mean PD

Table 1. Demographic and clinical data at baseline for control, test 1 and test 2 groups

Variables	Control Group (n=29)	Test Group 1 (n=25)	Test Group 2 (n=24)	P value
Female (%)	65.5	64.0	54.2	0.67
Obese (%)	69.0	60.0	40.9	0.13
Controlled diabetes (%)	32.0	29.2	31.0	0.98
Age (years)	54.6 ± 9.2	55.6 ± 8.3	55.4 ± 9.9	0.97
Number of teeth	20.8 ± 3.5	20.8 ± 4.6	22.0 ± 4.0	0.45
PD (mm)	3.3 ± 0.4	3.3 ± 0.6	3.2 ± 0.5	0.10
CAL (mm)	3.9 ± 0.7	3.9 ± 0.8	3.7 ± 0.8	0.11
BoP (%)	52.3 ± 22.5	46.1 ± 20.2	44.4 ± 17.7	0.34
PI (%)	59.4 ± 22.2	52.6 ± 16.0	55.6 ± 13.5	0.16

BoP, bleeding on probing; CAL, clinical attachment level; PD, probing depth; PI, plaque index. Gender, obesity, and control of diabetes were assessed using Chi-square Test; $P < 0.05$. Differences in age, number of teeth, PD, CAL, BoP, and PI were assessed using one-way ANOVA Test; $P < 0.05$.

(>3.3 mm) was a predictor for OHIP >35 (OR 6.96, 95% CI 1.39-34.79) and >42 (OR 6.97, 95% CI 1.08-44.94) (P <0.05) (Table 2).

To analyze the associations between the control group and each test group separately, two stepwise logistic regressions were performed. For CG and TG1, placebo was a predictor for OHIP >28 (OR 10.03, 95% CI 1.43-70.33) and >35 (OR 7.51, 95% CI 1.03-54.64) (P <0.05). The number of sites with PD ≥5 mm (>14 sites) was a predictor for OHIP >28 (OR 7.00, 95% CI 1.18-41.59) and mean PD (>3.3 mm) was a predictor for OHIP >35 (OR 8.03, 95% CI 1.31-49.34) and >42 (OR 14.00, 95% CI 1.47-133.23) (P <0.05) (Table 3). For CG and TG2, placebo was a predictor for OHIP >14 (OR 7.18, 95% CI 1.32-39.11), >21 (OR 7.47, 95% CI 1.87-29.88), >28 (OR 8.50, 95% CI 1.57-45.91) and >35 (OR 12.46, 95% CI 1.40-110.87) (P <0.05). BoP (>30%) was a predictor for OHIP >14 (OR 6.30, 95% CI 1.17-34.90) and mean PD (>3.3mm) was a predictor for OHIP >42 (OR 13.78, 95% CI 2.04-92.97) (P <0.05) (Table 4).

Table 5 presents the analysis of patients with uncontrolled diabetes. Placebo was a predictor for OHIP >21 (OR 4.50, 95% CI 1.12-17.99) and >28 (OR 5.70, 95% CI 1.20-27.12) (P <0.05). Mean PD (>3.3 mm) was a predictor for OHIP >35 (OR 10.00, 95% CI 1.61-62.00) and >42 (OR 9.30, 95% CI 1.23-70.33) (P <0.05). For patients with obesity, (Table 6) placebo was a predictor for OHIP >28 (OR 6.29, 95% CI 1.03-38.45) and number of sites with PD ≥5 mm was a predictor for OHIP >28 (OR 8.30, 95% CI 1.32-52.23) and >35 (OR 5.50, 95% CI 1.07-28.20) (P <0.05).

Discussion

This study compared the impact of periodontal therapy on OHRQoL of patients with generalized stages III and IV, generalized, grades B and C periodontitis and type 2 diabetes mellitus. OHIP-14 scores decreased after 6 months of periodontal therapy for all treatment groups. The percentage of answers according to the sub-domains "psychological discomfort" and "physical inability" were lower at 6 months post-therapy. These findings suggest that periodontal treatment has a positive impact on OHRQoL for individuals with periodontitis and diabetes.

OHIP-14 comprises 14 questions to assess 7 different sub-domains. Periodontal therapy had a positive impact on the following sub-domains: psychological discomfort and physical inability. These sub-domains were assessed through questions related to self-esteem, aesthetics, pronunciation, and social interaction. Psychological factors, such as depression and lack of social support, are believed to be both cause and consequence of how an individual manages diabetes (Rubin and Peyrot, 1992; Walker *et al*., 2014; Walker *et al*., 2016), with social support being robustly more associated with diabetes control than stressful events or stress-prone personality (Chida and Hamer, 2008). Thus, periodontitis negative impact on psychological factors that are related to self-perception and social interaction may indirectly interfere with diabetes control, which could be ameliorated after periodontal therapy. Periodontitis is commonly regarded as a silent disease since patients often live with no or few symptoms for years before seeking professional care (Buset *et al*., 2016). Although individuals with periodontitis do not report severe pain, other symptoms, such as bleeding, swelling, tooth mobility, and halitosis, are frequently reported. However, the OHIP-14 questionnaire does not directly approach these specific characteristics of periodontitis.

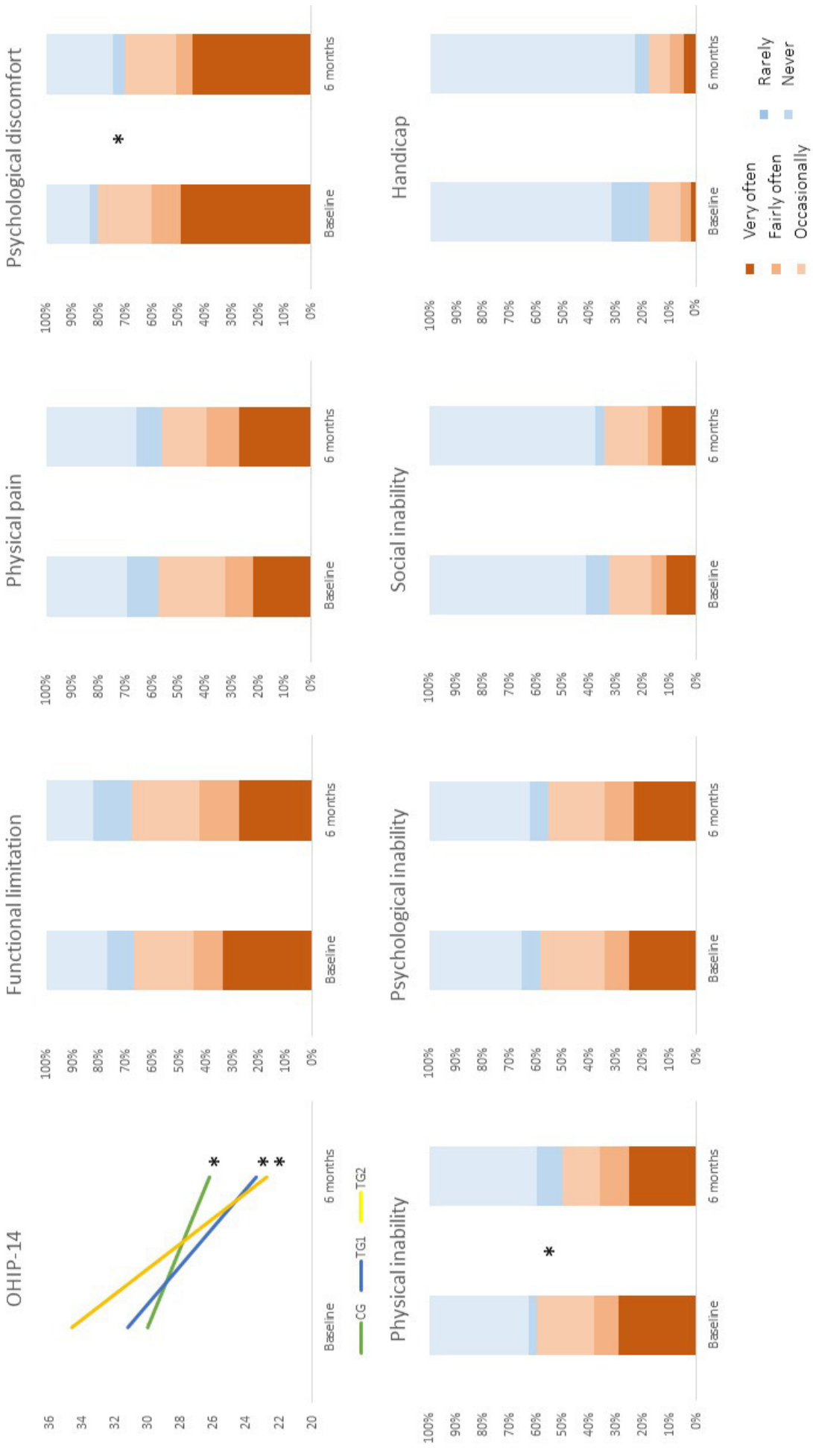

Figure 1. OHIP-14 for rthe Control, Test 1, and Test 2 groups at baseline and 6 months, and percentage of answers according to OHIP-14 sub-domains at baseline and 6 months post-therapy.

Table 2. Stepwise logistic regression considering Oral Health Impact Profile (OHIP) >21, >28, >35, and >42 as outcome variables for all treatment groups 6 months after periodontal therapy. Covariables included are treatment protocol, control of diabetes, obesity, bleeding on probing, probing depth (PD), clinical attachment level and number of sites with PD ≥5mm.

	OHIP >21			OHIP >28			OHIP >35			OHIP >42		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Treatment												
ω-3 + ASA	1.00			1.00			1.00			1.00		
Placebo	4.51	1.41-14.43	0.008	7.71	1.90-31.31	0.004	7.80	1.61-37.91	0.011	12.71	1.29-124.90	0.029
Number of sites with PD ≥5mm												
≤14				1.00								
>14	--	--	--	4.34	1.02-18.74	0.049	--	--	--	--	--	--
Mean PD												
≤3.3mm							1.00			1.00		
>3.3mm	--	--	--	--	--	--	6.96	1.39-34.79	0.018	6.97	1.08-44.94	0.041

ASA, aspirin; CI, confidence interval; OHIP, Oral Health Impact Profile; OR, odds ratio; PD, probing depth.
OHIP >21 Nagelkerke R^2=0.155, OHIP >28 Nagelkerke R^2=0.324,. OHIP >35 Nagelkerke R^2=0.346, OHIP >42 Nagelkerke R^2=0.359

Table 3. Stepwise logistic regression considering Oral Health Impact Profile (OHIP) >28, >35, and >42 as outcome variables for the Control and Test 1 groups 6 months after periodontal therapy. Covariables included are treatment protocol, control of diabetes, obesity, bleeding on probing, probing depth (PD), clinical attachment level and number of sites with PD ≥5mm.

	OHIP >28			OHIP >35			OHIP >42		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Treatment									
ω-3 + ASA (TG1)	1.00			1.00					
Placebo	10.03	1.43-70.33	0.020	7.51	1.03-54.64	0.046	--	--	--
Number of sites with PD ≥5mm									
≤14	1.00								
>14	7.00	1.18-41.59	0.032	--	--	--	--	--	--
Mean PD									
≤3.3mm				1.00			1.00		
>3.3mm	--	--	--	8.03	1.31-49.34	0.025	14.00	1.47-133.23	0.022

ASA, aspirin; CI, confidence interval; OHIP, Oral Health Impact Profile; OR, odds ratio; PD, probing depth.
OHIP >28 Nagelkerke R^2=0.364, OHIP >35 Nagelkerke R^2=0.324, OHIP >42 Nagelkerke R^2=0.512

Table 4. Stepwise logistic regression considering Oral Health Impact Profile (OHIP) >14, >21, >28, >35, and >42 as outcome variables for the Control and Test 2 groups 6 months after periodontal therapy. Covariables included are treatment protocol, control of diabetes, obesity, bleeding on probing, probing depth (PD), clinical attachment level and number of sites with PD ≥5mm.

	OHIP >14			OHIP >21			OHIP >28			OHIP >35			OHIP >42		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Treatment															
ω-3 + ASA (TG2)	1.00			1.00			1.00			1.00					
Placebo	7.18	1.32-39.11	0.023	7.47	1.87-29.88	0.004	8.50	1.57-45.91	0.013	12.46	1.40-110.87	0.024	--	--	--
BoP															
≤30%	1.00														
>30	6.30	1.17-34.90	0.035	--	--	--	--	--	--	--	--	--	--	--	--
Mean PD															
≤3.3mm													1.00		
>3.3mm	--	--	--	--	--	--	--	--	--	--	--	--	13.78	2.04-92.97	0.007

ASA, aspirin; BoP, bleeding on probing; CI, confidence interval; OHIP, Oral Health Impact Profile; OR, odds ratio; PD, probing depth.
OHIP >14 Nagelkerke R^2=0.279, OHIP >21 Nagelkerke R^2=0.266, OHIP >28 Nagelkerke R^2=0.247, OHIP >35 Nagelkerke R^2=0.263, OHIP >42 Nagelkerke R^2=0.283

Table 5. Stepwise logistic regression considering Oral Health Impact Profile (OHIP) >21, >28, >35, and >42 as outcome variables for the patients with uncontrolled diabetes 6 months after periodontal therapy. Covariables included are treatment protocol, obesity, bleeding on probing, probing depth (PD), clinical attachment level and number of sites with PD ≥5mm.

	OHIP >21			OHIP >28			OHIP >35			OHIP >42		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Treatment												
ω-3 + ASA	1.00			1.00								
Placebo	4.50	1.12-17.99	0.033	5.70	1.20-27.12	0.029	--	--	--	--	--	--
Mean PD												
≤3.3mm										1.00		
>3.3mm	--	--	--	--	--	--	10.00	1.61-62.00	0.013	9.30	1.23-70.33	0.031

ASA, aspirin; CI, confidence interval; OHIP, Oral Health Impact Profile; OR, odds ratio; PD, probing depth.
OHIP >21 Nagelkerke R^2=0.153, OHIP >28 Nagelkerke R^2=0.180, OHIP >35 Nagelkerke R^2=0.237, OHIP >42 Nagelkerke R^2=0.208

Table 6. Stepwise logistic regression considering Oral Health Impact Profile (OHIP) >28 and >35 as outcome variables for the obese patients 6 months after periodontal therapy. Covariables included are treatment protocol, control of diabetes, bleeding on probing, probing depth (PD), clinical attachment level and number of sites with PD ≥5mm.

	OHIP >28			OHIP >35		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Treatment						
ω-3 + ASA	1.00					
Placebo	6.29	1.03-38.43	0.046	--	--	--
Number of sites with PD ≥5mm						
≤14	1.00			1.00		
>14	8.30	1.32-52.23	0.024	5.50	1.07-28.20	0.041

ASA, aspirin; CI, confidence interval; OHIP, Oral Health Impact Profile; OR, odds ratio; PD, probing depth. OHIP >28 Nagelkerke R^2=0.345, OHIP >35 Nagelkerke R^2=0.167

After 6 months of periodontal therapy, the covariable "treatment protocol" was a significant factor to predict higher OHIP-14 scores in diabetic patients. The variable "placebo" increased the risk of reporting higher OHIP-14 scores (OR 4.51 for OHIP >21, OR 7.71 for OHIP >28, OR 7.80 for OHIP >35, and OR 12.71 for OHIP >42). The relevance of this variable in predicting higher OHIP scores was observed in the stratified analyses for patients in TG1 and CG, TG2 and CG, patients with uncontrolled diabetes, and with obesity. In addition, the variables "number of sites with PD ≥5 mm", "mean PD", and "BoP" were predictors for increased OHIP-14. These findings suggest that the presence of fewer residual sites with PD ≥5 mm post-treatment, overall deep pockets, and signs of inflammation were perceived by the patients and reflected on the self-reported improvement of OHRQoL. Moreover, evidence suggests that supplementation with ω-3 PUFA may improve quality of life due to beneficial effects of ω-3 PUFA on the brain, by controlling serotonergic and dopaminergic function, modulating brain-derived neurotrophic factor in the hippocampus, regulating the hypothalamic-pituitary-adrenal axis, and modulating neuroinflammation (Lin *et al*., 2010; Rondanelli *et al*., 2010; Levant, 2013). Additionally, a recent systematic review and meta-analysis demonstrated that there is an association of ω-3 PUFA treatment with clinical changes in the severity of anxiety symptoms (Su *et al*., 2018).

This was a retrospective analysis derived from an RCT that evaluated clinical and immunological effects of ω-3 PUFA and ASA as adjuncts to periodontal debridement. Two different protocols, with changes in the time of administration (TG1 and TG2), were compared to a placebo group. Whilst TG1 received ω-3 PUFA and ASA after periodontal debridement, TG2 received ω-3 PUFA and ASA after initial dental therapy, before periodontal debridement. The authors proposed this new protocol to evaluate the effects of ω-3 PUFA and ASA alone, with no subgingival instrumentation. The results showed that a greater percentage of patients in both test groups achieved the clinical endpoint for periodontal treatment (≤4 sites with PD ≥5 mm) 6 months after periodontal debridement when compared to the placebo group (Castro dos Santos *et al*., 2020). In the present study, ω-3 PUFA and ASA were associated with a positive impact on OHRQoL in both test groups, which indicates that the differences in the time of administration did not change the patients' perception of quality of life.

Regulatory agencies, including the Food and Drug Administration (FDA), have suggested that clinically meaningful (or direct) outcomes should be able to directly measure how a patient feels (e.g. disease symptoms, quality of life), functions, or survives (Sullivan, 2012; Feres *et al*., 2020). The findings of the present study support the notion that the presence/absence of residual pockets with PD ≥5 mm and mean PD post-treatment could be considered in future studies that aim to evaluate periodontal parameters and quality of life in patient-reported outcome measures (PROMs) specially designed for periodontal patients. These data are following the study of Sharma *et al*. (2016) that demonstrated an association between a composite outcome (including the presence of deep pockets, bone loss, and BoP) and patient-reported outcomes of "discomfort", "restricted eating" and "unhappiness with appearance", in a robust evaluation including over 14,000 patients. Interestingly, a recent proposal of clinical endpoint for periodontal treatment was also based primarily on the presence of at most 4 sites with PD ≥5 mm and less than 20% of sites with BoP post-treatment (Feres *et al*., 2020).

Although mean CAL (>3.9 mm) was assessed as a covariable in the logistic regression, this variable was not relevant in the equations to predict OHIP scores. For individuals with periodontitis, CAL would be expected

to be associated with the perception of decreased quality of life, mainly due to its relationship with function and esthetics (Ferreira *et al.*, 2017). However, OHIP-14 comprises questions related to general oral health and lacks detailed evaluations of specific characteristics of the teeth and the periodontium. A questionnaire that evaluates periodontal conditions should elucidate the association between CAL and OHRQoL in patients with periodontitis and diabetes.

According to the study protocol, periodontal debridement was performed in one session by a trained periodontist. Previous studies have demonstrated that one-session full-mouth debridement and quadrant-wise scaling have equivalent clinical results with similar adverse effects (Wennström *et al.*, 2005; Farman and Joshi, 2008; Koshy *et al.*, 2005; Fang *et al.*, 2016). Herein, it is not possible to evaluate if performing a single-session treatment could have interfered with the results of OHIP-14 in the present study, as all treatment groups received the same protocol for subgingival instrumentation. Future studies should compare these protocols regarding the psychological effects for the patient and the operator.

The main strength of this study is to be the first one to evaluate the impact of periodontal therapy on OHRQoL for patients diagnosed with generalized periodontitis and type 2 diabetes mellitus who had been selected for a periodontal RCT following inclusion and exclusion criteria. Additionally, it is the first study to evaluate the impact of ω-3 PUFA and ASA as adjuncts to periodontal debridement on OHRQoL. The few previous publications focusing on patients with diabetes were case-control studies and did not differentiate gingivitis and periodontitis or the extent/severity of disease (Irani *et al.*, 2015; Mourão *et al.*, 2016; Hsu *et al.*, 2019). Investigations that assess quality of life in populations with specific periodontal diagnosis pre and post-treatment can contribute to the development of patient-reported outcome measures to be used in future clinical trials in the treatment of periodontal patients. The main limitation of the present study is that OHIP-14 is a tool that aims at assessing general oral health, not periodontal conditions. Questions concerning distinctive periodontal symptoms, such as bleeding and tooth mobility, are not directly approached. A tool that assesses OHRQoL in periodontal patients and allows comparisons between periodontal treatment outcomes is yet to be validated. The findings of the present study may contribute to the development of such a tool.

In conclusion, periodontal treatment improved OHRQoL for patients with generalized periodontitis and type 2 diabetes mellitus after 6 months of therapy. Adjunctive ω-3 PUFA and ASA lowered OHIP-14 scores. Presence of sites with PD≥ 5mm and mean PD 6 months post-therapy showed an association with reduced quality of life for patients with periodontitis and diabetes.

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Conflicts of interest

The authors declare no conflicts of interest.

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