Mediterranean Journal of Clinical Psychology

ISSN 2282-1619

MJCP

Volume 8, n 2, 2020

Articles

Relationship between Periodontitis and Psychosocial Impact in Patients with Systemic Sclerosis: A Clinical Study

*Alessandro Polizzi [1 § *], Simona Santonocito [1 §], Manuel Vaccaro [1], Grazia Fichera [1], Salvatore Torrisi [1], Vincenzo Ronsivalle [1], Giuseppe Palazzo [1], Federica Sicari [2], Francesco Indelicato [1]*

Abstract

Background: Systemic Sclerosis (SSc) is a multi-system disorder that can have significant adverse effects upon the oral health. The aim of this study was to analyze the associations between SSc, periodontal disease (PD) and tooth loss and oral health-related quality of life (OHRQoL).

Methods: For the study were enrolled 70 patients affected by SSc and 75 non-diseased controls matched for age and gender. SSc was characterized in subtypes and with the mean duration of disease and the Modified Rodnan Skin Score [mRSS]. Patients were surveyed and examined through the evaluation of the periodontal parameters and the number of teeth and OHRQoL scores.

Results: A logistic regression analysis showed that patients with SSc presented a higher number of missing teeth (p=0.001) and a 6.89-fold (95% CI 2.04 to 18.36) increased odds of CAL compared to the control group. Moreover, the less values of PPD was correlated with mRSS in the total SSc group and with the mean duration of disease in patients with limited SSc, even after adjusting this correlation with the presence of the major organ involvement.

The OHIP sub-scale psychosocial impact differed significantly between groups (p= 0.002). The OHIP sum score was also significantly different between groups (p< 0.001).

Conclusions : This study showed that patients with SSc presented an increased odds of PD and tooth loss compared to non-diseased controls. In SSc patients, the magnitude of PD was strongly associated with the mRSS and with the mean duration of the disease.

[1] Department of General Surgery and Surgical-Medical Specialties, University of Catania, Catania, Italy

[2] Department of Cognitive Sciences, Psychology, Educational and Cultural Studies (COSPECS), University of Messina, Italy

§ Alessandro Polizzi and Simona Santonocito contributed equally to this manuscript and share the first authorship.

E-mail corresponding author: alexpoli345@gmail.com

Keywords:
Systemic Sclerosis; Oral Health; Periodontal disease; Psychological well-being.

Received: 16 June 2020
Accepted: 5 August 2020
Published: 13 August 2020

Citation: Polizzi, A., Santonocito, S., Vaccaro, M., Fichera, G., Torrisi, S., Ronsivalle, V., Palazzo, G., Sicari, F., Indelicato, F. (2020). Relationship between Periodontitis and Psychosocial Impact in Patients with Systemic Sclerosis: A Clinical Study. *Mediterranean Journal of Clinical Psychology, 8*(2).
https://doi.org/10.6092/2282-1619/mjcp-2509

1. Introduction

Systemic sclerosis (SSc) is a multi-systemic disorder of connective tissue characterized by the thickening and fibrosis of the skin and the involvement of internal organs (Derk & Jimenez, 2003). Prevalence estimates for SSc are between 240 per million and 276 per million in the US population (Mayes et al., 2003).

Facial manifestations due to fibrosis of the skin and soft tissues are typical in SSc and include amimia, the disappearance of cutaneous wrinkles, vertical furrows around the mouth and nose sharpening (Amin et al., 2011). Oral changes include burning mouth syndrome, reduction of mouth opening and microstomia (Matarese et al., 2016). All of these symptoms, including also the presence of temporomandibular joint (TMJ) disorders (Isola et al., 2017), can influence facial aesthetics and can be correlated with the worsening of the quality of life during SSc (Baron et al., 2014).

The temporomandibular joint in fact allows the mouth to be closed and opened, it is involved in breathing, expressiveness and facial aesthetics. The feedback of the tissues and the thickening of the skin, due to systemic sclerosis, directly involves the joints, muscles and tendons causing pain, reduction of the movements of the jaw and therefore reduced opening of the mouth (Nagy et al., 1994). Such a situation leads to disabilities in chewing, feeding, speaking, difficulties in oral hygiene and dental treatments (Albilia et al., 2007).

The perception of the progressive decay of physical functions and appearance changes in highly visible areas of the body, particularly the face and hands, are common in patients with SSc and contribute to body image distress, which in turn can be associated with neurotic manifestations such as anxiety and depression (Benrud et al., 2002; Beretta et al. 2006; Malcarne et al., 1999; Martino et al., 2018b, 2019a; Matsuura et al., 2003; Rosa et al., 2019; Settineri et al., 2019a, b), which affect the feeling of stability and integrity of the ego (Lorenzi, 2009). However, chronic conditions might have different effects on psychological functioning depending on the maturity of defense mechanisms activated in response to distress (Di Giuseppe et al., 2019; Settineri, Frisone & Merlo, 2019; Settineri et al., 2018, 2019c).

The impairment of the aesthetic of the face, due to the aggressive and evolutionary potential of the disease, therefore entails not only functional but also psychosocial effects: expressiveness will be so compromised as to condition the self-perceived aspect (Claudino & Traebert, 2013), self-esteem, interpersonal skills and the general well-being (De Paula et al., 2009; Kaur et al., 2017; Klages, Esch, & Wehrbein, 2005).

Orality therefore plays an important role in both general and mental health, becoming salient in the clinical setting (Stanciu, 2019), where it is known that psychological factors may influence the psychic integration of disease, adaptation and adherence (Settineri et al., 2019b).

These data support the need for careful evaluation and treatment not only of the medical aspects of the pathology but also of the repercussions on the patient's psychological health (Merlo, 2019b; Thombs et al., 2007), often particularly affected by the presence of chronic conditions (Di Giuseppe, 2020; Martino et al., 2019b; Marchini et al., 2018) such as periodontal disease (PD). It's a common inflammatory disease characterized by the dysregulation of the host immune response induced by the oral bacterial biofilm in soft and hard tissue resulting in periodontal breakdown and tooth loss (Isola et al., 2019b, 2020a, 2020b, 2020). PD, as well as widening of periodontal ligament spaces and abnormalities in periodontal microcirculation have been reported as a frequent finding during SSc as part of the global fibrosing aspects of the disease (Baron et al., 2016; Isola et al., 2019g, 2019h, 2020d; Matarese et al., 2016).

For many years, several health-related quality of life questionnaires have been used to detect the impact of the disease on the daily quality of life and the patient-relevant burden of daily disease in patients affected by SSc and other pathological conditions (Martino et al., 2018a). Moreover, this generation of questionnaire have been confirmed as a useful tool to well assess the impact of oral health in the quality of life of SSc and rheumatoid arthritis patients (Dagenais et al., 2015; Isola et al., 2018a, 2019f). In this sense, we refer to the concept of Oral Health Related Quality of Life (OHRQoL), a multidimensional construct that includes a subjective evaluation of the individual's oral health, functional well-being, emotional well-being, expectations and satisfaction with care, and sense of self (Sischo & Broder, 2011). Recently, several reports have underlined a lower quality of life during SSc (Mitropoulos et al., 2018).

Despite several cases of evidence from literature on the correlation between orofacial manifestation during SSc, only a limited number of studies has examined the periodontal status in patients with SSc, indicating a high prevalence of PD and a high increase in the risk of periodontal attachment loss during SSc (Pischon et al., 2016).

As reported recently, PD possesses a systemic impact during SSc, and it has been shown that periodontal therapy reduces rheumatic disease activity and severity (Al-Katma et al., 2007). However, although a potential association between SSc and PD was indicated, the strength and temporality of this association is still unclear. Analysing the relationship between PD and disease characteristics of SSc, such as the onset time and extension of disease, could be important for providing optimal treatment for patients with SSc. Therefore, the aim of the present study is to examine whether SSc characteristics were associated with an increased prevalence and extent of

PD and tooth loss and to analyse to what extent confounders might potentially influence this association respect to non-diseased controls.

2. Materials and methods

2.1 Procedure and participants

A total of 145 patients, 70 with SSc and 75 controls, were included in the present observational case-control study between January 2011 and October 2019 at the School of Dentistry, University of Catania, Catania, Italy. A written informed consent was acquired by all patient who were informed about the characteristics of the study, in accordance with the Declaration of the World Medical Association 1975 in Helsinki, revised in 2000. Clinical characteristics of the patients were documented by a skilled rheumatologist at each visit.

The exclusion criteria for both groups were a history of periodontal treatment, pregnancy and lactation and use of antibiotics during the previous 6 months. During the first phase of the study, 429 patients (201 man, 228 women), with SSc and healthy controls, were initially enrolled. However, after screening, 284 patients (156 man, 128 women) were excluded because they did not meet the exclusion criteria (n=199), declined to participate (n=46), or were lost during the first visit (n=40). Thus, the final number of patients assessed for eligibility was 145. The SSc group comprised 70 patients, 28 men and 42 women, with a mean age of 53.2 (±6.4) years. SSc was diagnosed by an expert rheumatologist skilled in caring for patients with systemic sclerosis according to the American College of Rheumatology classification criteria as diffuse SSc or limited SSc based on the extent of skin involvement (Masi, 1980). The disease onset was determined by patients recall of the first non-Raynaud symptom clearly attributable to SSc (Masi, 1980).

The control group, similarly matched for age and gender, comprised 75 patients, 36 men and 39 women, with a mean age of 51.4 (±5.1) years old. (Table 1)

Table 1. Characteristics of patients with Systemic Sclerosis [SSc] and non-diseased controls.

Patients characteristics	SSc (n=70)	Controls (n=75)	*p* value
Males, n° and percentage	28 (40)	31 (41.3)	0.22
Age (years), mean ± SD	49.7 (11.4)	48.3 (11.1)	
Educational attainment			0.02
None	30	32	
Trained worker	21	24	
Academic	19	19	
Smoking status			0.07
Never smoker	57	62	
Former smoker	9	8	
Current smoker	4	5	

Alcohol consumption frequency			0.02
None or low	55	63	
Moderately	9	8	
Daily	6	4	
BMI (kg/m²)			0.03
<25 (normal)	54	56	
≥25 to <30 (overweight)	10	14	
≥30 (obese)	6	5	
BMI (kg/m²), mean ± SD	22.9 ± 2.9	24.7 ± 2.7	0.04
Diabetes mellitus	3	2	0.19
Dyslipidemia	11	4	0.13
Coronary heart disease	6	3	0.81
Hypertension	23	12	0.41
Pulmonary ipertension	15	-	
Osteoporosis	8	1	0.66
Number of missing teeth	11.1 ± 1.9	5.9 ± 2.6	0.001
Type of SSc			
Diffuse cutaneous SSc	51 (72.3)	-	
Limited cutaneous SSc	8 (11.4)	-	
Overlap syndrome	5 (7.1)	-	
Sclerosis sine scleroderma	4 (5.7)	-	
Undifferentiated SSc	2 (2.9)	-	
Disease duration (5-year categories)			
≤5	51 (72.9)	-	
>5 to 10	10 (14.3)	-	
>10	9 (12.8)	-	
Disease duration (years), mean ± SD	7.6 ± 3.1	-	
Quality of life			
Oral Pain	1.4 ± 2.8	0.8 ± 1.1	0.04
Orofacial appearance sense of uncertainty with teeth	0.6 ± 1.2	0.7 ± 1.3	0.02
OHIP-14 sum score	8.7 ± 2.3	7.4 ± 2.3	0.03

Variables were compared between cases and controls using the χ^2 test or Fisher exact test (two-tailed) for categorical variables and using Student unpaired t test for continuous variables.

Serological analysis and clinical and oral examinations were performed in both groups. Oral examinations were performed by the same calibrated examiner. Periodontal status of the SSc and non-diseased controls was thoroughly assessed by comprehensive standard periodontal and oral parameters as previously described (Cuzzocrea, 2016; Isola et al., 2018b, 2019a, e) at six sites of each tooth (mesiobuccal, distobuccal, mesiolingual, distolingual and interproximal) using a manual periodontal probe (PCP 15; Hu-Friedy, Chicago, Illinois, USA). Clinical attachment loss (CAL) was defined as the distance from the cementoenamel junction (CEJ) to the bottom of the sulcus or periodontal pocket and was calculated as the sum of pocket probing depth and gingival recession measurements. Pocket probing depth (PPD) was defined as the distance from

the free gingival margin to the bottom of the sulcus or periodontal pocket. Gingival recession was defined as the distance from the CEJ to the free gingival margin. Plaque index (PI) was evaluated according to Silness and Loe (Briguglio et al., 2011; Iorio-Siciliano et al., 2019; Isola et al., 2019d, 2020e; Loe et al., 1976) and Bleeding on Probing (BOP) was evaluated as the presence of bleeding for 10 seconds following probing. In addition to the periodontal status, the number of missing teeth was recorded during clinical examination. In the inter-examiner reliability test, the percent agreement was 84.3% (Kappa = 0.61) for CAL value.

Sociodemographic characteristics, lifestyle factors, and medical history were assessed by a self-administered questionnaire. Anthropometric data (height and weight) was measured. In patients with SSc, telangiectasiae, calcinosis, joint tenderness with synovitis, joint contractures and others major organ system involvement such as lungs or gastrointestinal tract, if present, were recorded. In addition, enlarged capillaries and/or capillary dropout with or without pericapillary hemorrhages at the nailfold as possible prediction of future organ involvement, were also recorded.

Blood plasma was collected and analyzed for antinuclear antibodies and anti-RNA polymerase (Scl-70) antibody by routine laboratory testing from patients with SSc.

Smoking status was classified as never smoker, former smoker, or current smoker. Alcohol consumption was classified based on the reported drinking frequency as seldom (less than or equal to once a month), moderately often (twice a month or several times a week), or daily (daily or even more frequently). BMI (calculated from the body weight in kilogrammes divided by the square of height in metres) was classified as normal weight (<25 kg/m^2), overweight (25 to <30 kg/m^2), or obese (over 30 kg/m^2). In addition, the assessment of their medical history included the recording of the major organ involvement associated with SSc.

Moreover, a calibrated dermatologist skilled in caring for patients with systemic sclerosis evaluated, in the patients of the SSc group, the modified Rodnan skin score (mRSS). This score assessed the patients with the grades of the cutaneous involvement (from grade 0 that was a normal skin condition to grade 3 that represented intense thickness of the skin) at 51 positions in over 17 body regions (Furst et al., 1998).

2.2 Sample size calculation

The sample size was established considering the CAL as primary outcome variable. An effect size of 0.40 with α= 0.050 and a power level of 0.80 was determined, with a minimum sample of 31 patients per group would be needed. Fifty-four and 55 patients were enrolled for the SSc and for the control group, so that the primary variable, CAL, achieved a power value of 0.93, predicting a good sample size.

2.3 Statistical Analysis

Risk factors and dental variables were compared between patients with SSc and controls using the Student unpaired *t* test for continuous normally distributed variables, the Wilcoxon test for continuous variables, or the χ^2 test for the relationship between the clinical findings and mRSS or mean duration of disease. Frequency distributions, mean, standard deviations and confidence interval (CI) were determined to describe the data.

The association between SSc and periodontal status was assessed by linear regression procedures and the association among SSc subtypes (limited and diffuse SSc) with CAL was analysed separately. In a second step, a stepwise multivariable adjusted logistic regression was used with PPD as the dependent variable with the additional inclusion of the other parameters into the model. In a third step, the final multivariable regression model was additionally adjusted for PI to estimate if this potentially variables influenced the association between SSc and PD.

In the SSc group, the Spearman correlation test was applied in order to assess the existence of any significant interdependence between mRSS, mean disease duration versus the other parameters, respectively. Multivariable logistic regression analyses were performed in order to evaluate the association between mRSS and mean disease duration versus the number of missing teeth. The variable was dichotomized because of a bimodal and skewed distribution of the number of missing teeth.

The comparison of the six subgroups regarding their demographic data, disease-specific parameters and OHIP-14 scores, in first step an ANOVA, chi-square or Kruskal–Wallis test was applied. In case of significance, the groups were compared to each other using the Mann–Whitney U test or t test, respectively.

All P values presented are two tailed, and P values <0.05 were considered statistically significant. Analyses were performed using statistical software (SAS v.9.3, Cary, NC).

2.4 Observation instrument

Oral Health Impact Profile (OHIP-14): to assess OHRQoL, all participants were interviewed using a standardized and validated questionnaire, in the Italian version (Corridore et al., 2013). Thus, the form of the Oral Health Impact Profile (OHIP-14) was applied to assess OHRQoL (John et al., 2016).

The OHIP provides information about the occurrence of functional and psychosocial impacts that participants experienced in the previous month as a result of complaints with their teeth, mouth or dentures. For each of the 14 applied questions, a score based on a five-point scale was rated, whereby the following options were available: very often = "4", fairly often = "3", occasionally = "2", hardly ever = "1", and never = "0". The achievable sum score of all

questions ranged between "0" (all questions were answered with "never") and "56" (all questions were answered with "very often"). The main analysis was applied for the OHIP-14 sum score.

The reliability indicators of the alpha scale are as follows: 0.90 for the total scale, 0.90 for difficult pronounce words , 0.90 for worsened taste, 0.90 for Pain, 0.90 for Uncomfortable to eat, 0.89 for Self-conscious, 0.89 for Feel tensed, 0.90 for Diet unsatisfactory, 0.89 for Interrupted meals, 0.92 for Difficult to relax, 0.90 for Embarrassed, 0.90 for Irritable, 0.90 for Difficult to do jobs, 0.89 for Life less satisfying, 0.90 for Totally unable to function.

3. Results

The sociodemographic and rheumatological characteristics, medical history of both groups are shown in Table 1. Patients with SSc presented a slightly lower median BMI than the non-diseased control group (22.9 kg/m^2 versus 24.7 kg/m^2; p=0.04). Among SSc group, 54 patients were of normal weight, 10 were overweight and 6 were obese, while the control group were 56 normal, 14 overweight and 5 obese, respectively. All patients of the SSc group were matched with regards to disease duration, clinical rheumatological data, laboratory measurements as well as medication.

Among major organ involvement, in the total SSc group, 34 patients had a slight or moderate lung involvement measured by pulmonary function test – the forced vital capacity – (FVC) and diffusing capacity of the lungs for carbon monoxide (DICO); Of these, 49% had no minimal restrictive disease and 22% presented a moderate disease. Ever in the total SSc group, 15 patients presented pulmonary hypertension (mean values of 33.6 ± 7.4 mmHg) and 23 patients presented hypertension; Four patients had a myositis/arthritis while digital ulcer and related complications as amputation/gangrene were present in 9 patients. A history of scleroderma renal crisis was reported in 3 patients with arterial hypertension. The history of gastroesophageal reflux was reported in 21 patients. Furthermore, synthomps of constipaion, frequent bloating and flatulence were presente in about 54% of the total SSc group.

Three patients in the diffuse SSc group presented a severe and clinically relevant lung fibrosis requiring oxygen at rest and 2 patients in the limited SSc group presented a severe involvement of the gastrointestinal tract with chronic intestinal pseudo-obstruction and sign of severe anorexia and malabsorption.

The results of OHIP-14, including a comparison of the different questions, sub-scale oral function and psychosocial impact as well as the sum score are presented in Table 2.

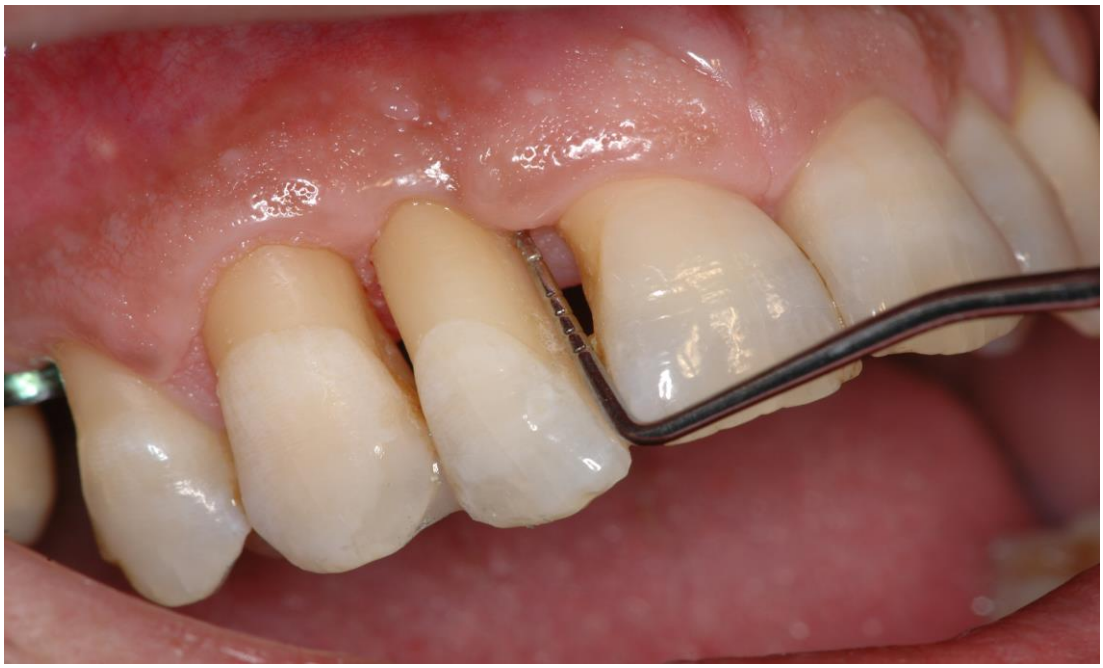
Table 2. Periodontal parameters in patients with Systemic Sclerosis (SSc) and non-diseased controls

Dental Characteristics	SSc (n=70)	Controls (n=75)	95% Confidence Interval			P value
			Diff	Lower	Upper	
CAL (mean mm ± SD)	3.85 ± 0.24	2.66 ± 0.21	1.33	-0.12	0.28	<0.05
PPD (mean mm ± SD)	4.76 ± 0.15	2.84 ± 0.12	1.97	0.35	0.77	<0.05
PI (mean % ± SD)	67.9 ± 10.4	65.6 ± 11.2	0.9	-1.21	8.65	0.125
BOP (mean % ± SD)	72.8 ± 6.6	42.3 ± 6.4	32.9	25.68	33.21	<0.05
Percentage of sites with CAL ≥4 mm (%)	24.9 ± 13.5	16.5 ± 11.9	6.6	9.56	10.25	<0.05
Percentage of sites with PPD ≥4 mm (%)	18.1 ± 8.4	9.1 ± 8	7.1	1.15	2.63	<0.05
Variables were compared between cases and controls using the χ^2 test or Fisher exact test (two-tailed) for categorical variables and using Student unpaired t test for continuous variables.						

Within oral function, neither the total score for the sub-scale, nor the five included questions were significantly different between groups. With the SSc group that presented lower OHRQoL values compared to healthy controls (Table 1). More specifically, the OHIP sub-scale psychosocial impact differed significantly between groups (p= 0.002). The OHIP sum score was also significantly different between groups (p< 0.001).

Table 2 shows dental variables in SSc and control groups. CAL (SSc 3.85 mm versus controls 2.66 mm, p<0.05) and PPD (SSc 4.76 mm versus controls 2.84 mm, p<0.05) were significantly higher in SSc compared to the control group. Significantly higher levels of BOP levels (SSc 72.8% versus controls 42.3%, p<0.05) were significantly elevated in patients with SSc (Figure 1), compared to the levels of the control group. Moreover, patients in the SSc group presented a higher number of missing teeth compared to the control group (p<0.05).

Figure 1. Intraoral images and ortopantomography of a patient of the Systemic Sclerosis [SSc] group



In univariate as well as in multivariable adjusted analyses, the association of SSc and patient's characteristics with the odds of PD was subsequently investigated (Table 3).

Table 3. Association of Systemic Sclerosis (SSc) and patient's characteristics with periodontal attachment loss (CAL)

	Odds ratio (95% CI) for periodontal attachment loss (CAL)		
Patient characteristics	**Univariate**	**Multivariate 1***	**Multivariate 2****
SSc			
No	1 (reference)	1 (reference)	1 (reference)
Yes	2.93 (1.21 to 5.89)	6.89 (2.04 to 18.36)	5.58 (1.23 to 20.44)
Sex			
Male	1 (reference)	-	-
Female	0.77 (0.31 to 1.95)		
Age (per 1 year)	1.08 (1.06 to 1.16)	1.12 (1.05 to 1.18)	1.14 (1.08 to 1.23)
Educational attainment			
None	1 (reference)	1 (reference)	1 (reference)
Trained worker	0.92 (0.22 to 3.58)	0.33 (0.06 to 1.83)	0.16 (0.03 to 1.44)
Academic	0.03 (0.01 to 0.25)	0.02 (0.01 to 0.12)	0.01 (0.00 to 0.07)
Smoking			
Never	1 (reference)	-	-
Ex-smoker	1.62 (0.63 to 4.23)		
Current	2.85 (0.96 to 8.65)		
Alcohol consumption			
None or low	1 (reference)	-	-
Moderate	1.02 (0.43 to 2.47)		
Heavy	1.56 (0.35 to 7.05)		
BMI (per kg/m^2)	1.18 (1.18 to 1.36)		
PI	1.27 (1.12 to 1.52)	-	1.42 (1.13 to 1.74)

*Multivariate model 1 was derived from stepwise logistic regression with inclusion of all variables listed in the table except plaque index (of these variables, only SSc status, age and education remained as significant predictors of periodontal disease in the final logistic regression model). **Multivariate model 2 was derived by forcing SSc status, age, education and plaque index into the logistic regression model. BMI, body mass index; PI, plaque index.

In univariate logistic regression analysis, patients with SSc presented a significant 2.93-fold (95% confidence interval, CI, 1.21 to 5.89) increase in odds of CAL when compared to the control group. Potential risk factors of PD, such as higher age, low education, smoking, alcohol consumption, major organ involvement, Scl-70, higher BMI and high PI were related to higher

odds of PD in a univariate analysis, although only the associations for low education, high BMI and high PI with the odds of PD were statistically significant at a 5% level. A stepwise logistic regression was applied in order to examine the association of SSc with the odds of PD adjusted for potential confounders (Table 3).

In addition to SSc, age, sex, education, smoking, alcohol consumption and BMI were analysed into the logistic regression model. This model revealed that only SSc status, age and education remained as significant predictors of CAL. Thus, adjusted for age and education, patients with SSc presented 6.89-fold (95% CI 2.04 to 18.36) increased odds of CAL compared to the control group (Table 3). In order to examine to what extent PI (as a measure of oral hygiene) may account for the observed association between SSc and PD, a logistic regression model was also performed. The strength of the association of SSc with PPD was attenuated but remained statistically significant after further adjustment for PI. Thus, the odds ratio (OR) for the association of SSc with PD decreased to 5.58 (95% CI 1.23 to 20.44) when adjusted for PI in addition to age.

In the SSc group, the correlation analysis performed showed that mRSS was significantly correlated to PPD (coefficient= −0.521; P= 0.009), CAL (coefficient = 0.422; P= 0.031) and BOP (coefficient = 0.411; P= 0.006) values. The mean duration of disease was significantly correlated only for the PPD values in the total SSc group (coefficient= −0.306; P= 0.028). In the limited SSc group, there was a significant correlation also between mRSS and values such as PD (coefficient= −0.529; P= 0.041) and BOP (coefficient= −0.518; P= 0.039). The correlation of PD and mRSS, in SSc group, remained correlated after adjusting for the presence of major organ involvement and of antibody Scl-70.

Moreover, a statistically significant association between SSc and the number of missing teeth was observed only in the crude model [OR= 1.34 (95% CI: 1.11, 1.66)], but not in the fully adjusted model [OR= 1.16 (95% CI: 0.88, 1.51)]. In gender-stratified analyses, the association between SSc and tooth loss was significant only in male patients [OR= 1.63 (95% CI: 1.24, 2.39)].

4. Discussion

This study systematically assessed the relationship between periodontitis (valued as CAL) and the disease features of SSc. In the present study, patients with SSc had significantly higher odds of PD compared to controls, even after adjustment for age, sex and for the presence of major organ involvement. In order to assess a possible association between PD and SSc, in the cohort of analysed patients, comprehensive standard periodontal measurements were performed

during clinical examinations. PPD and CAL were used as a reproducible, extensively validated measures of PD and was used a mean CAL >3 mm in order to define the periodontal attachment loss.

SSc is a chronic systemic disease, of unknown ethiology, characterized by to an excessive deposition of connective tissue in the involved organs, skin sclerosis and vasculopathy of inner organs and muscles (Juhl et al., 2020). SSc is considered a disabling condition which may determine the presence of craniofacial deformities due to a peripheral arthritis (Dagenais et al., 2015). A common oral complication in SSc is a reduced mouth opening which might contributes to a limited oral hygiene, increased plaque accumulation and, consequently, with an increased risk of oral and periodontal disease and alveolar bone reabsorption (Briguglio et al., 2013; Cannavale et al., 2013; Dagenais et al., 2015; Matarese et al., 2012).

In the present study, the main parameters of periodontitis, such as CAL and PD were significantly higher in SSc compared to the non-diseased controls (PD, 4.76 mm of SSc versus 2.84 mm of controls, $p<0.05$; CAL 3.85 mm of SSc versus 2.66 mm of controls, $p<0.05$).

In accordance with our results, many studies have demonstrated a high prevalence of PD and periodontal ligament (PDL) space widening in SSc patients (~76%) (Baron et al., 2015). Previous investigator have suggested that, during SSc, the increase of bacterial plaque accumulation, which may be due to a reduction of the mouth opening, associated with the chronic fibrosis of the disease, is responsible for an extended periodontal tissue breakdown characteristic of SSc (White et al., 1977), although fewer acute periodontal and salivary inflammatory signs are clinically present. Moreover, it was shown that PD implicates periodontal pathogens as potential triggers of auto-immunity (Monasterio et al., 2019). Recent studies demonstrated that, during rheumatoid arthritis, oral pathogens such as *Aggregatibacter actinomycetemcomitans* may trigger also the production of disease-specific autoantibodies and arthritis in susceptible individuals by the ability to reproduce the repertoire of citrullinated antigens in neutrophils and their presentation to antigen presenting cells, leading to further auto antibody production during disease (Strachan et al., 2019). The hypercitrullination induced by the bacterial load may be primarily relevant for periodontal disease initiation at gingival level (Curro et al., 2014; Ferlazzo et al., 2017; Isola et al., 2015; Matarese et al., 2015) that finally could create positive feedback loops that could sustain inflammation and auto immunity in established rheumatic disease, as SSc is.

In accordance to the results of this study, Baron et al., evaluating the oral conditions of 163 SSc patients by standardized examinations, through a multivariate regression analysis, demonstrated a higher prevalence of PD during the different stages of SSc and confirmed that SSc is a

significant independent predictor of missing teeth and tooth attachment loss (Baron et al., 2014; Matarese et al., 2013). As already highlighted in the introductory section, physical deficits, in this case associated with the oral sphere, have an impact on the patient's psychological level and quality of life; this fact is in contrast to the current tendency of health care to focus exclusively on the patient's physical conditions as if they were separate from the mental ones (Behel & Rybarczyk, 2019; Caputo, 2013; Carr, 2017). Considering for example the role of teeth in the production of language, their loss can cause psychophysical and self-esteem effects (Benyamini, Leventhal, & Leventhal, 2004). Language concerns personal communication and self-representation, therefore together with mechanics and aesthetics, it is a key factor that contributes to personal and interpersonal success (Seehra et al., 2011). These considerations demonstrate how physical illness can affect psychological health as chronic pathologies, such as systemic sclerosis, are often complicated by psychiatric symptoms or emotional / psychological subjective suffering (Conversano, 2019).

Furthermore, as already highlighted, orofacial modifications affect aesthetics and are ranked as the most worrying aspects of SSc (Amin et al., 2011; Van Lankveld et al., 2007).

These modifications may also alter the patient's oral health-related quality of life as they hinder eating and cause difficulty in chewing and speaking. Despite their high frequency, oral manifestations and OHRQoL in SSc patients are underrated and not comprehensively studied, probably because they are overshadowed by concomitant systemic symptoms (Del Rosso & Maddali-Bongi, 2014).

The importance of these factors is demonstrated in our research by the association between the deterioration of oral conditions during SSc and the low OHRQoL score compared to healthy subjects, which underlines the importance of developing targeted interventions to improve oral health in patients with SSc (Baron et al., 2015).

Orthodontic treatment is therefore functional not only for improving facial aesthetics or restoring certain functions but above all to promote OHRQoL and the general well-being of the subject.

Based on the pilot observation by Baron et al. (2014), we designed the current study to analyze the OHRQoL and the relationship between PD and some disease characteristics of SSc, such as mRSS and the mean duration of disease.

The present study showed, through a multivariable logistic correlation analysis, that in SSc patients the main parameters of periodontal tissues breakdown (PPD, CAL and BOP) were significantly correlated with mRSS, while only PPD was significantly correlated with the mean

duration of disease even after adjusting this correlation with the presence of the major organs involvement.

These results support the interestingly hypothesis that the global measures of SSc severity are associated with PD. It also conceivable that tooth loss, previous described in SSc (Pischon et al., 2016), would not be associated with a wide PDL since that the increased width were due to an excess of collagen of the PDL (Baron et al., 2016; Isola et al., 2016). Although it might seem possible that, during SSc, PD might lead to an abnormal stimulation of PDL fibroblasts via local inflammatory mechanisms (Chen et al., 2012; Piancino et al., 2017) that, associated with to the defective vascularity and alterations in the microcirculation of the gingival tissues tipically present during SSc, could finally determines the periodontal tissue breakdown (Scardina, Pizzigatti, & Messina, 2005). In fact, a reduced number of periodontal capillaries and reduced levels of vascular endothelial growth factor (VEGF) expression (Cutroneo et al., 2012), that could limit the angiogenic defense responsiveness to oral bacteria, have been found in periodontal tissues of patients affected by SSc (Ozcelik et al., 2008).

Furthermore, in order to investigate possible bias linked to SSc duration and severity, in the present cohort, patients with varying degrees of SSc duration and severity of disease and of major organ involvement were included in the analysis. The results of the multiple regression analysis demonstrated that in the SSc group, the association between PD and SSc disease characteristics remained significantly after adjusting for the presence of antibody to Scl-70, which predisposes towards a higher skin score (Pugliese et al., 2016).

Concerning the systemic conditions of the SSc patients, over 30% of patients in the total SSc group that presented PD and higher mRSS had a various degree of major organ involvement. This is according with previous reports that showed that the vasculopathy and tissue fibrosis during SSc lead to specific forms of organ damage, skin fibrosis, pulmonary fibrosis or pulmonary arterial hypertension, renal involvement (vasculopathy of renal arteries) and gastrointestinal (GI) involvement with fibrosis and thickening of the gastrointestinal tract (leading to GI dysmotility) (Becker & Riemekasten, 2016) and malocclusions (Cavuoti et al., 2016; Isola et al., 2019c; Lo Giudice et al., 2020; Perillo et al., 2013). Notably, the extent of skin fibrosis in SSc patients was demonstrated to have also a bad impact on patient survival (Domsic et al., 2011).

In conclusion, the present study indicated that patients with SSc presented an increased prevalence of CAL and lower OHRQoL compared to non-diseased controls. In SSc patients, the magnitude of many periodontal parameters was strongly associated with the mRSS and with the mean duration of the disease. Although this relationship needs further investigation, it seems

that the clinicians should be aware of the increased prevalence of PD in patients with SSc as well as the potential systemic health problems related to PD.

Acknowledgements

This work was carried out with funding by Department of General Surgery and Surgical-Medical Specialties, University of Catania, Catania, Italy.

References

1. Albilia, J. B., Lam, D. K., Blanas, N., Clokie, C. M., & Sándor, G. K. (2007). Small mouths… Big problems? A review of scleroderma and its oral health implications. *Journal of the Canadian Dental Association*, *73*(9).
2. Al-Katma, M. K., Bissada, N. F., Bordeaux, J. M., Sue, J., & Askari, A. D. (2007). Control of periodontal infection reduces the severity of active rheumatoid arthritis. *J Clin Rheumatol, 13*(3), 134-137. https://doi.org/10.1097/RHU.0b013e3180690616
3. Amin, K., Clarke, A., Sivakumar, B., Puri, A., Fox, Z., Brough, V., . . . Butler, P. (2011). The psychological impact of facial changes in scleroderma. *Psychol Health Med, 16*(3), 304-312. https://doi.org/10.1080/13548506.2010.540250
4. Baron, M., Hudson, M., Dagenais, M., Macdonald, D., Gyger, G., El Sayegh, T., . . . Gornitsky, M. (2016). Relationship Between Disease Characteristics and Oral Radiologic Findings in Systemic Sclerosis: Results From a Canadian Oral Health Study. *Arthritis Care Res (Hoboken), 68*(5), 673-680. https://doi.org/10.1002/acr.22739
5. Baron, M., Hudson, M., Tatibouet, S., Steele, R., Lo, E., Gravel, S., . . . Gornitsky, M. (2015). Relationship between disease characteristics and orofacial manifestations in systemic sclerosis: Canadian Systemic Sclerosis Oral Health Study III. *Arthritis Care Res (Hoboken), 67*(5), 681-690. https://doi.org/10.1002/acr.22490
6. Baron, M., Hudson, M., Tatibouet, S., Steele, R., Lo, E., Gravel, S., . . . Gornitsky, M. (2014). The Canadian systemic sclerosis oral health study: orofacial manifestations and oral health-related quality of life in systemic sclerosis compared with the general population. *Rheumatology (Oxford), 53*(8), 1386-1394. https://doi.org/10.1093/rheumatology/ket441
7. Becker, M. O., & Riemekasten, G. (2016). Risk factors for severity and manifestations in systemic sclerosis and prediction of disease course. *Expert Rev Clin Immunol, 12*(2), 115-135. https://doi.org/10.1586/1744666X.2016.1115717
8. Behel, J. M., & Rybarczyk, B. (2019). Interviewing in health psychology and medical settings. In Diagnostic interviewing (pp. 481-503). Springer, New York, NY. https://doi.org/10.1007/978-1-4939-9127-3_19
9. Benyamini, Y., Leventhal, H., & Leventhal, E. A. (2004). Self-rated oral health as an independent predictor of self-rated general health, self-esteem and life satisfaction. *Social science & medicine*, *59*(5), 1109-1116. https://doi.org/10.1016/j.socscimed.2003.12.021
10. Benrud-Larson, L. M., Haythornthwaite, J. A., Heinberg, L. J., Boling, C., Reed, J., White, B., & Wigley, F. M. (2002). The impact of pain and symptoms of depression in scleroderma. *Pain*, *95*(3), 267-275. https://doi.org/10.1016/S0304-3959(01)00409-2
11. Beretta, L., Astori, S., Ferrario, E., Caronni, M., Raimondi, M., & Scorza, R. (2006). Determinants of depression in 111 Italian patients with systemic sclerosis. *Reumatismo*, 219-225. https://doi.org/10.4081/reumatismo.2006.219
12. Briguglio, F., Briguglio, E., Briguglio, R., Cafiero, C., & Isola, G. (2013). Treatment of infrabony periodontal defects using a resorbable biopolymer of hyaluronic acid: a randomized clinical trial. *Quintessence Int, 44*(3), 231-240. 10.3290/j.qi.a29054

13. Briguglio, F., Zenobio, E. G., Isola, G., Briguglio, R., Briguglio, E., Farronato, D., & Shibli, J. A. (2011). Complications in surgical removal of impacted mandibular third molars in relation to flap design: Clinical and statistical evaluations. *Quintessence International, 42*(6), 445-453.
14. Cannavale, R., Matarese, G., Isola, G., Grassia, V., & Perillo, L. (2013). Early treatment of an ectopic premolar to prevent molar-premolar transposition. *Am J Orthod Dentofacial Orthop, 143*(4), 559-569. https://doi.org/10.1016/j.ajodo.2012.03.035
15. Caputo, A. (2013). Health demand in primary care context: What do people think about physicians?. *Psychology, health & medicine, 18*(2), 145-154. https://doi.org/10.1080/13548506.2012.687828
16. Claudino, D., & Traebert, J. (2013). Malocclusion, dental aesthetic self-perception and quality of life in a 18 to 21 year-old population: a cross section study. *BMC oral health, 13*(1), 3. https://doi.org/10.1186/1472-6831-13-3
17. Carr, J. E. (2017). Psychology, medicine and collaborative innovation: An appreciative reply to Kirch and Ast. *Journal of clinical psychology in medical settings, 24*(2), 92-95. https://doi.org/10.1007/s10880-016-9466-7
18. Cavuoti, S., Matarese, G., Isola, G., Abdolreza, J., Femiano, F., & Perillo, L. (2016). Combined orthodontic-surgical management of a transmigrated mandibular canine. *Angle Orthod, 86*(4), 681-691. https://doi.org/10.2319/050615-309.1
19. Chen, Y. C., Ninomiya, T., Hosoya, A., Hiraga, T., Miyazawa, H., & Nakamura, H. (2012). 1alpha,25-Dihydroxyvitamin D3 inhibits osteoblastic differentiation of mouse periodontal fibroblasts. *Arch Oral Biol, 57*(5), 453-459. https://doi.org/10.1016/j.archoralbio.2011.10.005
20. Conversano, C. (2019). Psychological common factors in chronic diseases. *Frontiers in Psychology, 10*, 2727. https://doi.org/10.3389/fpsyg.2019.02727
21. Corridore, D., Campus, G., Guerra, F., Ripari, F., Sale, S., & Ottolenghi, L. (2013). Validation of the Italian version of the oral health impact profile-14 (IOHIP-14). *Annali di stomatologia, 4*(3-4), 239.
22. Curro, M., Matarese, G., Isola, G., Caccamo, D., Ventura, V. P., Cornelius, C., . . . Ientile, R. (2014). Differential expression of transglutaminase genes in patients with chronic periodontitis. *Oral Dis, 20*(6), 616-623. https://doi.org/10.1111/odi.12180
23. Cutroneo, G., Piancino, M. G., Ramieri, G., Bracco, P., Vita, G., Isola, G., . . . Trimarchi, F. (2012). Expression of muscle-specific integrins in masseter muscle fibers during malocclusion disease. *Int J Mol Med, 30*(2), 235-242. https://doi.org/10.3892/ijmm.2012.986
24. Cuzzocrea, F., Costa, S., Gugliandolo, M. C., & Larcan, R. (2016). Psychologists in preoperative programmes for children undergoing surgery. *Journal of Child Health Care, 20*(2), 164-173. https://doi.org/10.1177/1367493514557726
25. Dagenais, M., MacDonald, D., Baron, M., Hudson, M., Tatibouet, S., Steele, R., . . . Gornitsky, M. (2015). The Canadian Systemic Sclerosis Oral Health Study IV: oral radiographic manifestations in systemic sclerosis compared with the general population. *Oral Surg Oral Med Oral Pathol Oral Radiol, 120*(2), 104-111. https://doi.org/10.1016/j.oooo.2015.03.002

26. De Paula, J., Delcides, F., Santos, N., da Silva, É. T., Nunes, M. F., & Leles, C. R. (2009). Psychosocial Impact of Dental Esthetics on Quality of Life in Adolescents Association with Malocclusion, Self-Image, and Oral Health–Related Issues. *The Angle Orthodontist, 79*(6), 1188-1193. 10.2319/082608-452R.1
27. Del Rosso, A., & Maddali-Bongi, S. (2014). Oral health in patients with systemic sclerosis. *Rheumatology (Oxford, England)*, *53*(8), 1355. https://doi.org/10.1093/rheumatology/keu179
28. Derk, C. T., & Jimenez, S. A. (2003). Systemic sclerosis: current views of its pathogenesis. *Autoimmun Rev, 2*(4), 181-191. https://doi.org/10.1016/S1568-9972(03)00005-3
29. Di Giuseppe, M., Ciacchini, R., Piarulli, A., Nepa, G., & Conversano, C. (2019). Mindfulness dispositions and defense style as positive responses to psychological distress in oncology professionals. *European Journal of Oncology Nursing, 40*, 104-110. https://doi.org/10.1016/j.ejon.2019.04.003
30. Di Giuseppe, M., Miniati, M., Miccoli, M., Ciacchini, R., Orrù, G., Sterzo, R. L., ... & Conversano, C. (2020). Defensive responses to stressful life events associated with cancer diagnosis. *Mediterranean Journal of Clinical Psychology, 8*(1). https://doi.org/10.6092/2282-1619/mjcp-2384
31. Domsic, R. T., Rodriguez-Reyna, T., Lucas, M., Fertig, N., & Medsger, T. A., Jr. (2011). Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. *Ann Rheum Dis, 70*(1), 104-109. https://doi.org/10.1136/ard.2009.127621
32. Ferlazzo, N., Curro, M., Zinellu, A., Caccamo, D., Isola, G., Ventura, V., . . . Ientile, R. (2017). Influence of MTHFR Genetic Background on p16 and MGMT Methylation in Oral Squamous Cell Cancer. *Int J Mol Sci, 18*(4). https://doi.org/10.3390/ijms18040724
33. Furst, D. E., Clements, P. J., Steen, V. D., Medsger, T. A., Jr., Masi, A. T., D'Angelo, W. A., . . . Seibold, J. R. (1998). The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. *J Rheumatol, 25*(1), 84-88.
34. Iorio-Siciliano, V., Blasi, A., Nuzzolo, P., Matarasso, M., Isola, G., & Ramaglia, L. (2019). Treatment of Periodontal Intrabony Defects Using Enamel Matrix Derivative: Surgical Reentry After an Observation Period of at Least 5 Years. *Int J Periodontics Restorative Dent, 39*(4), 537-543. https://doi.org/10.11607/prd.4148
35. Isola, G., Alibrandi, A., Curro, M., Matarese, M., Ricca, S., Matarese, G., . . . Kocher, T. (2020a). Evaluation of salivary and serum ADMA levels in patients with periodontal and cardiovascular disease as subclinical marker of cardiovascular risk. *J Periodontol*. https://doi.org/10.1002/JPER.19-0446
36. Isola, G., Alibrandi, A., Pedulla, E., Grassia, V., Ferlito, S., Perillo, L., & Rapisarda, E. (2019a). Analysis of the Effectiveness of Lornoxicam and Flurbiprofen on Management of Pain and Sequelae Following Third Molar Surgery: A Randomized, Controlled, Clinical Trial. *J Clin Med, 8*(3). https://doi.org/10.3390/jcm8030325
37. Isola, G., Alibrandi, A., Rapisarda, E., Matarese, G., Williams, R. C., & Leonardi, R. (2020b). Association of vitamin D in patients with periodontitis: A cross-sectional study. *J Periodontal Res*. https://doi.org/10.1111/jre.12746
38. Isola, G., Anastasi, G. P., Matarese, G., Williams, R. C., Cutroneo, G., Bracco, P., & Piancino, M. G. (2018a). Functional and molecular outcomes of the human masticatory muscles. *Oral Dis, 24*(8), 1428-1441. https://doi.org/10.1111/odi.12806

39. Isola, G., Giudice, A. L., Polizzi, A., Alibrandi, A., Patini, R., & Ferlito, S. (2019b). Periodontitis and Tooth Loss Have Negative Systemic Impact on Circulating Progenitor Cell Levels: A Clinical Study. *Genes (Basel), 10*(12). https://doi.org/10.3390/genes10121022
40. Isola, G., Matarese, G., Cordasco, G., Rotondo, F., Crupi, A., & Ramaglia, L. (2015). Anticoagulant therapy in patients undergoing dental interventions: a critical review of the literature and current perspectives. *Minerva Stomatol, 64*(1), 21-46.
41. Isola, G., Matarese, G., Ramaglia, L., Pedulla, E., Rapisarda, E., & Iorio-Siciliano, V. (2020c). Association between periodontitis and glycosylated haemoglobin before diabetes onset: a cross-sectional study. *Clin Oral Investig. 24*(8), 2799-2808. https://doi.org/10.1007/s00784-019-03143-0
42. Isola, G., Matarese, G., Williams, R. C., Siciliano, V. I., Alibrandi, A., Cordasco, G., & Ramaglia, L. (2018b). The effects of a desiccant agent in the treatment of chronic periodontitis: a randomized, controlled clinical trial. *Clin Oral Investig, 22*(2), 791-800. https://doi.org/10.1007/s00784-017-2154-7
43. Isola, G., Matarese, M., Briguglio, F., Grassia, V., Picciolo, G., Fiorillo, L., & Matarese, G. (2019c). Effectiveness of Low-Level Laser Therapy during Tooth Movement: A Randomized Clinical Trial. *Materials (Basel), 12*(13). https://doi.org/10.3390/ma12132187
44. Isola, G., Matarese, G., Cordasco, G., Perillo, L., & Ramaglia, L. Mechanobiology of the tooth movement during the orthodontic treatment: a literature review. (2016). *Minerva Stomatol. 65*(5), 299-327.
45. Isola, G., Matarese, M., Ramaglia, L., Cicciu, M., & Matarese, G. (2019d). Evaluation of the efficacy of celecoxib and ibuprofen on postoperative pain, swelling, and mouth opening after surgical removal of impacted third molars: a randomized, controlled clinical trial. *Int J Oral Maxillofac Surg, 48*(10), 1348-1354. https://doi.org/10.1016/j.ijom.2019.02.006
46. Isola, G., Matarese, M., Ramaglia, L., Iorio-Siciliano, V., Cordasco, G., & Matarese, G. (2019e). Efficacy of a drug composed of herbal extracts on postoperative discomfort after surgical removal of impacted mandibular third molar: a randomized, triple-blind, controlled clinical trial. *Clin Oral Investig, 23*(5), 2443-2453. https://doi.org/10.1007/s00784-018-2690-9
47. Isola, G., Perillo, L., Migliorati, M., Matarese, M., Dalessandri, D., Grassia, V., . . . Matarese, G. (2019f). The impact of temporomandibular joint arthritis on functional disability and global health in patients with juvenile idiopathic arthritis. *Eur J Orthod, 41*(2), 117-124. https://doi.org/10.1093/ejo/cjy034
48. Isola, G., Polizzi, A., Alibrandi, A., Indelicato, F., & Ferlito, S. (2020d). Analysis of Endothelin-1 Concentrations in Individuals with Periodontitis. *Sci Rep, 10*(1), 1652. https://doi.org/10.1038/s41598-020-58585-4
49. Isola, G., Polizzi, A., Iorio-Siciliano, V., Alibrandi, A., Ramaglia, L., & Leonardi, R. (2020e). Effectiveness of a nutraceutical agent in the non-surgical periodontal therapy: a randomized, controlled clinical trial. *Clin Oral Investig.* https://doi.org/10.1007/s00784-020-03397-z
50. Isola, G., Polizzi, A., Muraglie, S., Leonardi, R., & Lo Giudice, A. (2019g). Assessment of Vitamin C and Antioxidant Profiles in Saliva and Serum in Patients with Periodontitis and Ischemic Heart Disease. *Nutrients, 11*(12). https://doi.org/10.3390/nu11122956

51. Isola, G., Polizzi, A., Santonocito, S., Alibrandi, A., & Ferlito, S. (2019h). Expression of Salivary and Serum Malondialdehyde and Lipid Profile of Patients with Periodontitis and Coronary Heart Disease. *Int J Mol Sci, 20*(23). https://doi.org/10.3390/ijms20236061
52. Isola, G., Ramaglia, L., Cordasco, G., Lucchese, A., Fiorillo, L., & Matarese, G. (2017). The effect of a functional appliance in the management of temporomandibular joint disorders in patients with juvenile idiopathic arthritis. *Minerva Stomatol, 66*(1), 1-8. :10.23736/S0926-4970.16.03995-3
53. John, M. T., Rener-Sitar, K., Baba, K., Celebic, A., Larsson, P., Szabo, G., . . . Reissmann, D. R. (2016). Patterns of impaired oral health-related quality of life dimensions. *J Oral Rehabil, 43*(7), 519-527. https://doi.org/10.1111/joor.12396
54. Juhl, P., Bay-Jensen, A. C., Hesselstrand, R., Siebuhr, A. S., & Wuttge, D. M. (2020). Type III, IV, and VI Collagens Turnover in Systemic Sclerosis - a Longitudinal Study. *Sci rep, 10*(1), 7145. https://doi.org/10.1038/s41598-020-64233-8
55. Kaur, P., Singh, S., Mathur, A., Makkar, D. K., Aggarwal, V. P., Batra, M., ... & Goyal, N. (2017). Impact of dental disorders and its influence on self esteem levels among adolescents. Journal of clinical and diagnostic research: JCDR, 11(4), ZC05. https://doi.org/10.7860/JCDR/2017/23362.9515
56. Klages, U., Esch, M., & Wehrbein, H. (2005). Oral health impact in patients wearing removable prostheses: relations to somatization, pain sensitivity, and body consciousness. International Journal of Prosthodontics, 18(2). 10.1007/s11136-006-9122-z
57. Lo Giudice, A., Ortensi, L., Farronato, M., Lucchese, A., Lo Castro, E., & Isola, G. (2020). The step further smile virtual planning: milled versus prototyped mock-ups for the evaluation of the designed smile characteristics. *BMC Oral Health, 20*(1), 165. https://doi.org/10.1186/s12903-020-01145-z
58. Loe, H., Schiott, C. R., Karring, G., & Karring, T. (1976). Two years oral use of chlorhexidine in man. I. General design and clinical effects. *J Periodontal Res, 11*(3), 135-144. https://doi.org/10.1111/j.1600-0765.1976.tb00061.x
59. Lorenzi, P. (2009). *Il corpo vissuto: Psicopatologia e clinica*. SEID.
60. Matsuura, E., Ohta, A., Kanegae, F., Haruda, Y., Ushiyama, O., Koarada, S., ... & Nagasawa, K. (2003). Frequency and analysis of factors closely associated with the development of depressive symptoms in patients with scleroderma. *The Journal of rheumatology, 30(8), 1782-1787.*
61. Malcarne, V. L., Hansdottir, I., Greenbergs, H. L., Clements, P. J., & Weisman, M. H. (1999). Appearance self-esteem in systemic sclerosis. *Cognitive Therapy and Research*, *23*(2), 197-208. https://doi.org/10.1023/A:1018783329341
62. Martino, G., Catalano, A., Bellone, F., Langher, V., Lasco, C., Penna, A., ... & Morabito, N. (2018a). Quality of life in postmenopausal women: which role for vitamin D?. *Mediterranean Journal of Clinical Psychology, 6*(2). Doi: https://doi.org/10.6092/2282-1619/2018.6.1875
63. Marchini, F., Caputo, A., Napoli, A., Balonan, J. T., Martino, G., Nannini, V., & Langher, V. (2018). Chronic illness as loss of good self: underlying mechanisms affecting diabetes adaptation. *Mediterranean Journal of Clinical Psychology, 6*(3). https://doi.org/10.6092/2282-1619/2018.6.1981

64. Martino, G., Catalano, A., Bellone, F., Sardella, A., Lasco, C., Caprì, T., ... & Morabito, N. (2018b). Vitamin D status is associated with anxiety levels in postmenopausal women evaluated for osteoporosis. *Mediterranean Journal of Clinical Psychology, 6*(1). https://doi.org/10.6092/2282-1619/2018.6.1740

65. Martino. G., Sardella, A., Bellone, F., Lasco, C., Langher, V., Cazzato, V., ... & Catalano, A. (2019a). Executive functions and bone health: a focus on cognitive impulsivity and bone mineral density. *Mediterranean Journal of Clinical Psychology, 7*(2). https://doi.org/10.6092/2282-1619/2019.7.2167

66. Martino, G., Langher, V., Cazzato, V., & Vicario, C. M. (2019b). Psychological factors as determinants of medical conditions. *Frontiers in psychology, 10*, 2502. https://doi.org/10.3389/fpsyg.2019.02502

67. Masi, A. T. (1980). Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum, 23*(5), 581-590. https://doi.org/10.1002/art.1780230510

68. Matarese, G., Curro, M., Isola, G., Caccamo, D., Vecchio, M., Giunta, M. L., . . . Ientile, R. (2015). Transglutaminase 2 up-regulation is associated with RANKL/OPG pathway in cultured HPDL cells and THP-1-differentiated macrophages. *Amino Acids, 47*(11), 2447-2455. https://doi.org/10.1007/s00726-015-2039-5

69. Matarese, G., Isola, G., Alibrandi, A., Lo Gullo, A., Bagnato, G., Cordasco, G., & Perillo, L. (2016). Occlusal and MRI characterizations in systemic sclerosis patients: A prospective study from Southern Italian cohort. *Joint Bone Spine, 83*(1), 57-62. https://doi.org/10.1016/j.jbspin.2015.04.014

70. Matarese, G., Isola, G., Anastasi, G. P., Cutroneo, G., Cordasco, G., Favaloro, A., . . . Perillo, L. (2013). Transforming Growth Factor Beta 1 and Vascular Endothelial Growth Factor Levels in the Pathogenesis of Periodontal Disease. *European Journal of Inflammation, 11*(2), 479-488. https://doi.org/10.1177/1721727X1301100217

71. Matarese, G., Isola, G., Anastasi, G. P., Favaloro, A., Milardi, D., Vermiglio, G., . . . Cutroneo, G. (2012). Immunohistochemical analysis of TGF-beta1 and VEGF in gingival and periodontal tissues: a role of these biomarkers in the pathogenesis of scleroderma and periodontal disease. *Int J Mol Med, 30*(3), 502-508. https://doi.org/10.3892/ijmm.2012.1024

72. Mayes, M. D., Lacey, J. V., Jr., Beebe-Dimmer, J., Gillespie, B. W., Cooper, B., Laing, T. J., & Schottenfeld, D. (2003). Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum, 48*(8), 2246-2255. https://doi.org/10.1002/art.11073

73. Merlo, E. M. (2019a). Adolescent phobia as a "mask object". *Mediterranean Journal of Clinical Psychology*, *7*(1). https://doi.org/10.6092/2282-1619/2019.7.2241

74. Merlo, E. M. (2019b). Opinion Article: The role of psychological features in chronic diseases, advancements and perspectives. *Mediterranean Journal of Clinical Psychology, 7*(3). https://doi.org/10.6092/2282-1619/2019.7.2341

75. Mitropoulos, A., Gumber, A., Crank, H., Akil, M., & Klonizakis, M. (2018). Investigating the effectiveness and feasibility of exercise on microvascular reactivity and quality of life in systemic sclerosis patients: study protocol for a feasibility study. *Trials, 19*(1), 647. https://doi.org/10.1186/s13063-018-2980-1

76. Monasterio, G., Guevara, J., Ibarra, J. P., Castillo, F., Diaz-Zuniga, J., Alvarez, C., . . . Vernal, R. (2019). Immunostimulatory activity of low-molecular-weight hyaluronan on dendritic cells stimulated with Aggregatibacter actinomycetemcomitans or Porphyromonas gingivalis. *Clin Oral Investig, 23*(4), 1887-1894.. https://doi.org/10.1007/s00784-018-2641-5

77. Nagy, G., Kovács, J., Zeher, M., & Czirják, L. (1994). Analysis of the oral manifestations of systemic sclerosis. *Oral surgery, oral medicine, oral pathology, 77*(2), 141-146. https://doi.org/10.1016/0030-4220(94)90276-3

78. Ozcelik, O., Haytac, M. C., Ergin, M., Antmen, B., & Seydaoglu, G. (2008). The immunohistochemical analysis of vascular endothelial growth factors A and C and microvessel density in gingival tissues of systemic sclerosis patients: their possible effects on gingival inflammation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 105*(4), 481-485. https://doi.org/10.1016/j.tripleo.2007.07.021

79. Perillo, L., Isola, G., Esercizio, D., Iovane, M., Triolo, G., & Matarese, G. (2013). Differences in craniofacial characteristics in Southern Italian children from Naples: a retrospective study by cephalometric analysis. *Eur J Paediatr Dent, 14*(3), 195-198. https://doi.org/10.1007/s40368-013-0074-z

80. Perillo, L., Padricelli, G., Isola, G., Femiano, F., Chiodini, P., & Matarese, G. (2012). Class II malocclusion division 1: a new classification method by cephalometric analysis. *Eur J Paediatr Dent, 13*(3), 192-196.

81. Piancino, M. G., Isola, G., Cannavale, R., Cutroneo, G., Vermiglio, G., Bracco, P., & Anastasi, G. P. (2017). From periodontal mechanoreceptors to chewing motor control: A systematic review. *Arch Oral Biol, 78*, 109-121. https://doi.org/10.1016/j.archoralbio.2017.02.010

82. Pischon, N., Hoedke, D., Kurth, S., Lee, P., Dommisch, H., Steinbrecher, A., . . . Riemekasten, G. (2016). Increased Periodontal Attachment Loss in Patients With Systemic Sclerosis. *J Periodontol, 87*(7), 763-771. https://doi.org/10.1902/jop.2016.150475

83. Pugliese, C., van der Vinne, R. T., Campos, L. M., Guardieiro, P. R., Saviolli, C., Bonfa, E., . . Silva, C. A. (2016). Juvenile idiopathic arthritis activity and function ability: deleterious effects in periodontal disease? *Clin Rheumatol, 35*(1), 81-91. https://doi.org/10.1007/s10067-015-3125-5

84. Rosa, V., Tomai, M., Lauriola, M., & Martino, G. (2019). Body mass index, personality traits, and body image in Italian pre-adolescents: An opportunity for overweight prevention. *psihologija, 52*(4), 379-393. https://doi.org/10.2298/PSI181121009R

85. Scardina, G. A., Pizzigatti, M. E., & Messina, P. (2005). Periodontal microcirculatory abnormalities in patients with systemic sclerosis. *J Periodontol, 76*(11), 1991-1995. https://doi.org/10.1902/jop.2005.76.11.1991

86. Seehra, J., Fleming, P. S., Newton, T., & DiBiase, A. T. (2011). Bullying in orthodontic patients and its relationship to malocclusion, self-esteem and oral health-related quality of life. *Journal of orthodontics, 38*(4), 247-256. https://doi.org/10.1179/14653121141641

87. Settineri, S., Frisone, F., Alibrandi, A., & Merlo, E. M. (2019a). Emotional suppression and oneiric expression in psychosomatic disorders: early manifestations in emerging adulthood and young patients. *Frontiers in psychology*, 10, 1897. https://doi.org/10.3389/fpsyg.2019.01897

88. Settineri, S., Frisone, F., Alibrandi, A., Pino, G., Lupo, N. J., & Merlo, E. M. (2018). Psychological Types and Learning Styles. *Mediterranean Journal of Clinical Psychology, 6*(3). https://doi.org/10.6092/2282-1619/2018.6.2005

89. Settineri, S., Frisone, F., & Merlo, E. M. (2019). The Mask object in psychotherapy: Presentation and Representation. *Mediterranean Journal of Clinical Psychology, 7*(1). https://doi.org/10.6092/2282-1619/2019.7.2232

90. Settineri, S., Frisone, F., Merlo, E. M., Geraci, D., & Martino, G. (2019b). Compliance, adherence, concordance, empowerment, and self-management: five words to manifest a relational maladjustment in diabetes. *Journal of multidisciplinary healthcare*, 12, 299. https://doi.org/10.2147/JMDH.S193752

91. Settineri, S., Merlo, E. M., Frisone, F., Alibrandi, A., Carrozzino, D., Diaconu, C. C., & Pappalardo, S. M. (2019c). Suppression Mental Questionnaire App: a mobile web service-based application for automated real-time evaluation of adolescent and adult suppression. *Mediterranean Journal of Clinical Psychology, 7*(1). https://doi.org/10.6092/2282-1619/2019.7.2056

92. Sischo, L., & Broder, H. (2011). Oral health-related quality of life: what, why, how, and future implications. *Journal of dental research*, *90*(11), 1264-1270. https://doi.org/10.1177/0022034511399918

93. Stanciu, D. (2019). When the fear of dentist is relevant for more than one's oral health. A structural equation model of dental fear, self-esteem, oral-health-related well-being, and general wellbeing. Patient Preference and Adherence, 13, 1229-1240. https://doi.org/10.2147/PPA.S209068

94. Strachan, A., Harrington, Z., McIlwaine, C., Jerreat, M., Belfield, L. A., Kilar, A., . . . Zaric, S. (2019). Subgingival lipid A profile and endotoxin activity in periodontal health and disease. *Clin Oral Investig, 23*(9), 3527-3534. https://doi.org/10.1007/s00784-018-2771-9

95. Thombs, B. D., Taillefer, S. S., Hudson, M., & Baron, M. (2007). Depression in patients with systemic sclerosis: a systematic review of the evidence. *Arthritis Care & Research*, *57*(6), 1089-1097. https://doi.org/10.1002/art.22910

96. Van Lankveld, W. G. J. M., Vonk, M. C., Teunissen, H., & Van den Hoogen, F. H. J. (2007). Appearance self-esteem in systemic sclerosis—subjective experience of skin deformity and its relationship with physician-assessed skin involvement, disease status and psychological variables. *Rheumatology*, *46*(5), 872-876. https://doi.org/10.1093/rheumatology/kem008

97. White, S. C., Frey, N. W., Blaschke, D. D., Ross, M. D., Clements, P. J., Furst, D. E., & Paulus, H. E. (1977). Oral radiographic changes in patients with progressive systemic sclerosis (scleroderma). *J Am Dent Assoc, 94*(6), 1178-1182. https://doi.org/10.14219/jada.archive.1977.0367

DOI: 10.6092/2282-1619/mjcp-2509