



The tendency of reduced periodontal destruction in acromegalic patients showing similar inflammatory status with periodontitis patients

Yesim Ozdemir¹ · H. Gencay Keceli¹ · Nafiye Helvacı² · Tomris Erbas² · Rahime M. Nohutcu¹

Received: 17 June 2019 / Accepted: 14 August 2019 / Published online: 2 September 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Purpose Evaluate periodontal status of acromegalics through clinical and biochemical variables.

Methods Demographics, hormone and metabolic variables, periodontal variables, gingival crevicular fluid (GCF) volume, and content data were collected from 30 patients with acromegaly, 30 patients with periodontitis, and 20 healthy subjects and comparatively analyzed.

Results GH differences between acromegaly (2.56 ± 4.86) and periodontitis (0.53 ± 0.95) ($p < 0.001$) were statistically significant. IGF-1 was lowest at periodontitis (113.31 ± 45.01) and lower (152.11 ± 45.56) at healthy group compared with acromegalics (220.38 ± 167.62) ($p < 0.05$). GH and IGF-1 had positive correlation ($p < 0.05$). IGF-1 and CAL had negative ($p < 0.01$) correlation except healthy group that showed the same correlation at the opposite direction ($p < 0.05$). Besides similar plaque and gingival indices with periodontitis, acromegalics showed relatively less CAL and GCF volume but except CAL, all their periodontal variables were higher than healthy subjects. GCF GH and prolactin showed higher values in acromegalics while healthy subjects showed relatively high interleukin-1, -10 and carboxyterminal telopeptide of type I collagen compared with others.

Conclusion Acromegalics have a tendency of slowed periodontal destruction with an influence of GH and IGF-1 to the inflammation- and collagen metabolism-related mechanisms rather than bone-associated ones. However, this information must be confirmed with further studies exploring the mechanisms possibly bonded to others.

Keywords Acromegaly · Periodontal · Bone loss · Gingival crevicular fluid · Growth hormone · Insulin-like growth factor-1

Introduction

Acromegaly is a rare disease (30–130 cases/million prevalence,) [1] mostly (around 95%) caused by a benign pituitary adenoma originating from somatotrophic cells that leads to increase in growth hormone (GH) and insulin-like growth factor-I (IGF-I) secretion [2–4]. In addition to its most significant signs seen in face and extremities as progressive somatic deformities, many other systems

(metabolic, cardiovascular, and respiratory) can be affected [5, 6]. While the most prevalent comorbidities (reported to contribute 23–50% of deaths) are associated with cardiovascular system (arterial hypertension, cardiomyopathy, rhythm disorders, valve diseases, and progressive systolic dysfunction) [7–9] malignancies still remain in the forefront due to their effect amplitude [10, 11]. Respiratory complications such as sleep breathing disorders may also occur and give 25% contribution to mortality rates [9]. Metabolic complications are mainly associated with lipid (decrease in high-density lipoprotein (HDL), hypertriglyceridemia, hypercholesterolemia) [12] and glucose (impaired glucose tolerance, diabetes mellitus) metabolism [13].

Gingiva, alveolar bone, periodontal ligament, and root cementum are the components of the periodontium that covers and supports the teeth for mastication and several other functions. Periodontal tissues have their own microbial flora that lives in a defined homeostasis [14]. In

✉ H. Gencay Keceli
monsieur_gencay@yahoo.com

¹ Hacettepe University Faculty of Dentistry, Periodontology Department, Ankara, Turkey

² Hacettepe University Medical School, Department of Endocrinology and Metabolism, Ankara, Turkey

consequence of biofilm formation and dysbiosis on the tooth surface, immune response causing a clinical inflammatory state called ‘periodontal disease’ might occur in susceptible cases [15]. Periodontal diseases, that considered as the most common infection in adults emerge due to this host-organism interaction is staged as gingivitis and periodontitis. While only gingiva is involved in gingivitis, periodontitis also affects the remaining parts of the periodontium resulting in tissue degeneration and bone resorption [16]. Inside the population aged >40 years, periodontitis is known as the most frequent reason of tooth loss whereas some cases may onset relatively earlier (<25 years) and show a rapid destruction with higher rate of genetic susceptibility whereas a relatively slow progress with the influence of predisposing factors such as smoking, malocclusion, incompatible restorations is more common [16, 17]. In addition to biofilm and predisposing local factors, several systemic conditions involving diabetes, cardiovascular diseases, obesity/metabolic syndrome, rheumatoid arthritis have been found to be associated with periodontal diseases [15].

Besides most frequent extra- and intra-oral findings such as frontal bulge, nasal, and labial changes, increased mandibular growth and prognathism, diastemas, malocclusion, increased arch width, tongue enlargement [18, 19], tooth mobility and gingival overgrowth are the earliest detected periodontal findings in acromegaly patients. Clinicians often diagnose acromegaly relatively late due to its slowly progressing course and late emergence of the symptoms [6]. Like other symptoms, slowed periodontal destruction is a remarkable finding in those patients and supported with some papers [20, 21]. Previous studies attribute this finding to the underlying mechanism associated with increased secretion [22, 23] and binding of IGF-1 to IGFBP-3 [24] that mediates GH stimulation and related anabolic activities inside the body [25]. Accordingly, a slowed periodontal tissue destruction process is expected due to this mechanism [26, 27]. Hence, the association between higher IGFBP-3 levels and less periodontal disease in the general population may support this phenomenon [23].

The first case reports speculating a possible relationship between acromegaly and periodontal conditions mainly focused on gingival inflammation and hyperplasia [28]. In 2007, Japanese authors reported a periodontitis case treated by bromocriptine in an acromegalic patient [29]. Two years after, Lima et al. [21] decided to investigate the periodontal status of 16 acromegalic subjects by comparing with 20 healthy controls and claimed that acromegaly patients might be less prone to periodontal destruction. Recently, three comparative cross-sectional trials evaluated the prevalence of periodontitis in acromegaly patients by periodontally examining 23 [30], 47 [20], and 32 [23] cases. While lower periodontitis frequency was present in first two of those

trials, the last one reported similar disease severity. According to their interpretations, the low prevalence of periodontitis was mainly attributed to the protective effect of GH and abovementioned interaction between IGF-1 and GH. However, considering the complexity of periodontal disease pathogenesis [31], the existing data regarding to periodontal findings in acromegaly is scant and the mechanisms underlying the less tendency of periodontal destruction and bone resorption in those patients still needs to be highlighted. From this point of view, the present comparative cross-sectional study aims to evaluate the periodontal status of acromegalic individuals through clinical and biochemical parameters.

Materials and methods

Patient selection

The study was designed as comparative cross sectional and conducted between December 2015 and April 2017. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Hacettepe University Local Ethics Committee, date: Mar 04, 2015; no: GO15/173-08) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Thirty acromegaly patients (17 female, 13 male) treated for GH excess (GH > 1 ng/mL in oral glucose tolerance test and increased IGF-1) referred from Hacettepe University Medical School, Department of Endocrinology and Metabolism participated in the study [32]. The participants that gave consent to take place aged between 35 and 60 years and did not have history of radiotherapy, pregnancy or lactation that can influence periodontal status and/or bone/tissue metabolism. From nonsmoking individuals, 30 periodontitis, 20 periodontally healthy subjects that applied to Hacettepe University, Faculty of Dentistry, Periodontology Department for periodontal treatment, or routine follow-up were also included. The decision for diagnosis of periodontitis was made according to the classification of Armitage [33] and defined as >30% periodontal bone loss at more than seven teeth whereas periodontally health was defined as no sign of inflammation and bone loss.

Demographic and systemic data

Age, gender, and education status of the participants were collected. After their physical examination, information of the date of acromegaly diagnosis, history of surgical operations, presence/absence of hypogonadism and somatostatin analogues use information were obtained. In addition to their dentate status [34], presence/absence of

macroglossia and gingival hyperplasia were also identified by intraoral examination.

Blood cell, hormone, and metabolic variables

After collecting fasting venous blood samples between 8.00 and 9.00 a.m.; complete blood count and hormone variables involving GH, IGF-1, prolactin, free T3, free T4, TSH, total cholesterol, HDL, low-density lipoprotein, triglyceride, HbA1c, and glucose were measured. Moreover bone metabolism-related variables including parathormone (PTH), Vit D, bone alkaline phosphatase (B-ALP), calcium, phosphorus, and magnesium levels were measured.

Periodontal variables

A PhD student, at her second year of education, accomplished the examination of the participants. She was calibrated by measuring attachment levels of 50 subjects not associated with the trial and 0.88 intraexaminer calibration value was achieved. The following indices were recorded by using standardized periodontal probe (Michigan O Color-Coded Probe, Hu-Friedy, Chicago, IL) for the assessment of the periodontal status; plaque index (PI) [35], gingival index (GI) [36], clinical attachment level (CAL), and probing depth (PD). PI is the most preferred index giving the plaque deposit level around the teeth. It was detected by circulating the periodontal probe around the neck of the tooth and giving the following scores according to the amount of soft deposits; 0-no plaque, 1-plaque as a thin biofilm in gingival margin, 2-visible plaque inside the sulcus and gingival margin, 3-intense plaque inside the sulcus and gingival margin. GI was determined with the following scores and shows the level of gingival inflammation; 0-no inflammation, 1-slight gingival inflammation, color change and edema, no bleeding on probing, 2-moderate gingival inflammation, color change and edema, bleeding on probing. 3-advanced gingival inflammation, color change and edema, spontaneous bleeding and/or bleeding on probing. CAL was measured as the distance from the junction of crown and the root surface (cement-enamel junction) to the deepest end of the gingival collar finishes in the sulcus base. PD was measured from the most coronal point of the gingival collar to the deepest end of the collar endpoint in the sulcus base. All measurements were made from six tooth surfaces (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual, and distolingual) and the scores were divided into number of regions after having their sum. During those measurements, the presence of bleeding at any region 10–15 s after probing was recorded as BOP (+). After recording, PD data were exhibited as PD and proximal (prox.) PD.

Gingival crevicular fluid sampling and storage

Before achievement of clinical recordings, gingival crevicular fluid (GCF) sampling was carried out according to well-known procedures [37] to identify levels of markers specifically associated with inflammation and bone resorption. In order to keep the samples from GCF flow stimulation and blood contamination, GCF was collected 1 day after periodontal variable measurements. The deepest periodontal pockets were chosen for collecting GCF with standardized paper strips (Periopaper®, Interstate Drug Exchange, Amityville, NY, USA). Just before sampling, supragingival plaque was removed from the respective region. Then, the area was isolated with cotton rolls and gently air-dried during 5 s. Mesiobuccal, mid-buccal, distobuccal, and mid-palatinal/lingual sites were sampled with the strips inserted from the pocket orifice of the teeth and the strips were kept in place for 30 s until taking the slight resistance from the base of the pocket and kept inside for 30 s. The visibly blood contaminated samples were discarded. After taking out the strips, they were placed into the holder of Periotron 8000® (Oraflow Inc., Plainview, NY, USA) and digital measurement of the liquid volume on the strips was recorded into the database of the connected computer. Then, the strips were transferred into the Eppendorf tubes and stored at -80°C until further analyses. The values were then converted to actual volume (microliters) by using this formula: $\text{ELISA} \times 0.2 / \text{GCF volume (pg}/\mu\text{L)}$

Biochemical analysis of GCF samples

Following completion of the sampling process from all patients, the stored Eppendorf tubes were transferred to Biochemistry Department in Hacettepe University Faculty of Medicine inside dry ice protected packages. The frozen samples were dissolved at room temperature and then pertaining ELISA kits (Eastbiopharm, Hangzhou, Republic of China), including measurement of GH, IGF-1, prolactin PTH, Vit D, B-ALP, receptor activator of NF- κ B ligand (RANKL), carboxyterminal telopeptide of type I collagen (ICTP), IL-1 β , IL-4, IL-6, and IL-10 amounts, were used to identify the protein levels. In brief, paper strips were placed into the standard ELISA buffer solutions for dilution and ELISA reactions were started inside the microtiter plates according to each manufacturer's recommendations. Following color change that shows the completion of the reaction, absorbance values at 450 nm wavelengths were detected by using spectrophotometer. Then, analyzers were benefited from standardized curves to calculate GCF protein levels as pg/ μL .

Statistical analysis

IBM SPSS Statistics v.22.0 software program was used for statistical tests. To measure intergroup differences, one-way ANOVA test was performed. Before making comparisons, the distribution of the data was assumed as consistent with normality. According to the results, the threshold value for p was approved as 0.05 for intergroup differences. The homogeneity of the variances was also tested with Levene's Test for Equality of Variances and $p < 0.05$ showed non-homogenous variances. In such cases, Tamhane's T2 statistics method was used for multiple comparisons. If $p > 0.05$, the variances were defined as homogenous and to determine the origin of the difference, Tukey's HSD post hoc test was applied.

Results

Demographic and systemic data

The data associated with age, gender, accompanying systemic diseases, the date of acromegaly diagnosis and initiation of complaints, history of surgical operations, medical treatment status, presence/absence of hypogonadism and use of somatostatin analogues are given in Table 1.

Accordingly, the age, gender, and education distribution of the patients were homogenous. Most of the acromegalic individuals had hypertension as accompanying systemic disease. A total of 93.7% of them took active medical treatment with/without surgical therapy for acromegaly. Although the complaints of the population usually started 10–20 years before, their diagnosis of acromegaly could be made in the last 5–10 years. Except five persons, all participant acromegalics were exposed to a surgical acromegaly treatment. None of the participants was completely edentulous. Only one case demonstrated high number of tooth loss in acromegaly group due to caries and caries was reported as the main reason for the loss. Except this case, none of the acromegaly patients showed more than three teeth loss and most of them kept all their natural teeth. Twelve acromegaly patients had macroglossia whereas none of the participants in periodontitis and healthy groups showed any finding of an enlarged tongue. In total, four participants had gingival hyperplasia and divided into two equal shares for periodontitis and acromegaly groups.

Serum, hormone, and metabolic variables

When the serum samples were evaluated in terms of blood cell variables, healthy patients showed statistically higher MPV but reached to statistical difference at the comparison

only with periodontitis group ($p < 0.05$). Number of leukocytes exhibited lower values for healthy patients compared with other groups ($p < 0.05$). Acromegaly group did not reveal any remarkable and specific complete blood cell count findings (data not shown).

The mean GH was 2.56 ± 4.86 ng/mL, 2.50 ± 3.09 ng/mL, and 0.53 ± 0.95 ng/mL for the acromegaly, healthy and periodontitis groups, respectively. According to the intergroup comparisons, periodontitis had the lowest amount and the difference was statistically significant ($p < 0.05$) whereas acromegalics demonstrated similar GH with healthy patients. Another important marker IGF-1 revealed following 220.38 ± 167.62 ng/mL, 152.11 ± 45.56 ng/mL, and 113.31 ± 45.01 ng/mL for acromegaly, healthy, and periodontitis patients, respectively. The differences between acromegaly and periodontitis ($p < 0.001$) and between acromegaly and healthy ($p < 0.05$) were statistically significant. Although ACTH exhibited lower values for healthy patients compared with others ($p < 0.05$), its range was within the normal values for all groups. Cortisol levels did not differ among the study groups ($p > 0.05$). Free T3 expressing thyroid functions was remarkably low in acromegaly patients and the difference was valid for both comparisons with periodontitis and healthy groups ($p < 0.05$) (Table 2).

Among cholesterol markers, only HDL was significantly higher in healthy group ($p < 0.05$). Bone and bone metabolism markers including Vit D, B-ALP, Ca, P, and Mg did not show remarkable intergroup difference ($p > 0.05$) (Table 3).

Periodontal variables

Remarkably high PI, GI, CAL, and GCF volume was seen in periodontal variable evaluation in periodontitis group. When hygiene and inflammation-related variables were considered, in addition to highest mean PI for periodontitis group (2.00 ± 0.45), acromegaly group showed significantly higher PI (1.36 ± 0.91) compared with healthy patients (0.55 ± 0.35) ($p < 0.001$). GI also showed similar intergroup differences with following mean values; 1.01 ± 0.78 , 0.15 ± 0.23 , and 1.61 ± 0.52 that are consecutive for acromegaly, healthy, and periodontitis ($p < 0.001$). Mean CAL was 1.66 ± 0.66 mm in acromegaly group, slightly less than healthy group showing corresponding value of 1.82 ± 0.62 mm. Although this difference was not statistically significant, values in both healthy and acromegaly groups defined lower numbers of CAL compared with periodontitis ($p < 0.001$). Mean PD and prox. PD also indicated the similar intergroup relationship with CAL ($p < 0.001$). Higher mean GCF volume existed in both periodontitis (112.58 ± 24.88 mL) and acromegaly (56.39 ± 26.14 mL) patients compared with healthy group (22.85 ± 10.66 mL)

Table 1 Demographic and systemic information of the patients

	Acromegaly	Healthy	Periodontitis	Total
Age	44.83 ± 10.94	38.50 ± 8.58	48.93 ± 9.83	44.79 ± 10.67
Gender				
Female	17 (56.6%)	16 (80.0%)	18 (60.0%)	51 (63.8%)
Male	13 (43.4%)	4 (20.0%)	12 (40.0%)	29 (36.2%)
Education status				
less than high school	21 (70.0%)	8 (40.0%)	18 (60.0%)	47 (58.8%)
high school	9 (30.0%)	10 (50.0%)	9 (30.0%)	28 (35.0%)
more than high school	0 (0.0%)	2 (10.0%)	3 (10.0%)	5 (6.2%)
Accompanying diseases				
None	9 (30.0%)	20 (100.0%)	30 (100.0%)	59 (73.7%)
Diabetes	5 (16.6%)	–	–	5 (6.2%)
Hypertension	14 (46.6%)	–	–	14 (17.5%)
Sleep apnea	1 (3.3%)	–	–	1 (1.3%)
Osteoporosis	1 (3.3%)	–	–	1 (1.3%)
Medical treatment				
No therapy	2 (6.6%)	20 (100.0%)	30 (100.0%)	52 (65.0%)
Active	10 (33.3%)	–	–	10 (12.5%)
Previous	18 (60.0%)	–	–	18 (22.5%)
Diagnosis				
None	–	20 (100.0%)	30 (100.0%)	50 (62.5%)
Last 5 years	10 (33.3%)	–	–	10 (12.5%)
5–10 years	9 (30.0%)	–	–	9 (11.3%)
10–20 years	9 (30.0%)	–	–	9 (11.3%)
≥20 years	2 (6.6%)	–	–	2 (2.5%)
Initiation of complaints				
None	–	20 (100.0%)	30 (100.0%)	50 (62.5%)
Last 5 years	5 (16.6%)	–	–	5 (6.2%)
5–10 years	10 (33.3%)	–	–	10 (12.5%)
10–20 years	13 (43.3%)	–	–	13 (16.3%)
≥20 years	2 (6.6%)	–	–	2 (2.5%)
History of pituitary surgery				
No surgery	5 (16.6%)	20 (100.0%)	30 (100.0%)	55 (68.8%)
Last 5 years	12 (40.0%)	–	–	12 (15.0%)
5–10 years	5 (16.6%)	–	–	5 (6.2%)
10–20 years	6 (20.0%)	–	–	6 (7.5%)
≥20 years	2 (6.6%)	–	–	2 (2.5%)
Dentate status				
Completely edentulous	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Edentulous in one arch	1 (3.3%)	0 (0.0%)	5 (16.7%)	6 (7.5%)
Some natural teeth present	5 (16.6%)	0 (0.0%)	7 (23.3%)	12 (15.0%)
All natural teeth present	24 (80.0%)	20 (100.0%)	18 (60.0%)	62 (77.5%)
Macroglossia				
Present	12 (40.0%)	0 (0.0%)	0 (0.0%)	12 (15.0%)
Absent	18 (60.0%)	20 (100.0%)	30 (100.0%)	68 (85.0%)
Gingival hyperplasia				
Present	2 (6.6%)	0 (0.0%)	2 (6.7%)	4 (5.0%)
Absent	28 (93.4%)	20 (100.0%)	28 (93.3%)	76 (95.0%)

Values are given as mean ± SD and N (%)

Table 2 Hormone variables

	Acromegaly (N = 30)	Healthy (N = 20)	Periodontitis (N = 30)	Total
GH (ng/mL)	2.56 ± 4.86	2.50 ± 3.09 ^a	0.53 ± 0.95 ^c	1.75 ± 3.36
IGF-1 (ng/mL)	220.38 ± 167.62 ^b	152.11 ± 45.56 ^a	113.31 ± 45.01	163.16 ± 118.41
ACTH (pg/mL)	25.00 ± 11.14	15.53 ± 8.61 ^a	27.71 ± 18.09 ^c	22.97 ± 14.69
Cortisol (µg/dL)	11.11 ± 2.17	11.83 ± 4.68	12.71 ± 3.34	12.04 ± 3.64
Prolactin (ng/mL)	17.23 ± 26.63	10.44 ± 5.43	9.84 ± 4.77	12.61 ± 16.46
Free T3 (pmol/L)	4.54 ± 0.66 ^{b, c}	5.09 ± 0.71 ^d	5.19 ± 0.71 ^e	4.94 ± 0.74
Free T4 (pmol/L)	11.80 ± 2.93	11.03 ± 1.16	10.94 ± 1.07	11.26 ± 1.94
TSH (µIU/mL)	1.15 ± 1.08 ^c	2.06 ± 1.04 ^d	1.84 ± 1.07	1.67 ± 1.12

Values are given as mean ± SD

GH growth hormone, IGF-1 insulin-like growth factor-1, ACTH adrenocorticotrophic hormone, TSH thyrotrophin stimulating hormone

^aSignificantly different from healthy ($p < 0.05$)

^bSignificantly different from periodontitis ($p < 0.001$)

^cSignificantly different from healthy ($p < 0.05$)

^dSignificantly different from acromegaly ($p < 0.05$)

^eSignificantly different from acromegaly ($p < 0.001$)

Table 3 Bone and metabolic variables

	Acromegaly (N = 30)	Healthy (N = 20)	Periodontitis (N = 30)	Total
Ca (mg/dL)	9.69 ± 0.38	9.61 ± 0.28	9.56 ± 0.33	9.61 ± 0.33
P (mg/dL)	3.63 ± 0.66	3.54 ± 0.53	3.26 ± 0.45	3.46 ± 0.56
Mg (mg/dL)	2.05 ± 0.20	2.13 ± 0.12	2.03 ± 0.15	2.07 ± 0.16
B-ALP (U/L)	0.62 ± 0.24	0.73 ± 0.32	0.64 ± 0.26	0.66 ± 0.27
Vit D (µg/L)	19.68 ± 10.57	16.02 ± 6.59	19.41 ± 6.16	18.35 ± 7.89
PTH (pg/ml)	60.92 ± 30.37	51.32 ± 13.82	59.99 ± 18.16	57.20 ± 20.69
Glucose (mg/dL)	102.34 ± 17.16	91.19 ± 23.25	102.00 ± 6.69	98.60 ± 17.37
HbA1c (%)	5.63 ± 0.57	5.28 ± 0.53	5.45 ± 0.35	5.45 ± 0.50
Total cholesterol (mg/dL)	199.44 ± 38.67	213.73 ± 48.02	198.55 ± 47.83	203.88 ± 44.46
HDL (mg/dL)	50.16 ± 9.95	61.21 ± 12.93 ^{a, c}	48.89 ± 10.51 ^b	53.45 ± 12.29
LDL (mg/dL)	138.25 ± 31.22	142.65 ± 37.11	131.73 ± 36.59	137.93 ± 34.47
Triglyceride (mg/dL)	145.75 ± 89.66	105.21 ± 57.75	144.84 ± 79.42	132.18 ± 78.84

Values are given as mean ± SD

PTH parathormone, HDL high-density lipoprotein, LDL low-density lipoprotein, B-ALP bone alkaline phosphatase, P phosphorus, Ca calcium, Mg magnesium, Hb hemoglobin

^aSignificantly different from periodontitis ($p < 0.001$)

^bSignificantly different from healthy ($p < 0.001$)

^cSignificantly different from acromegaly ($p < 0.001$)

and the difference was statistically significant ($p < 0.001$) (Table 4).

Correlations among serum GH, IGF-1, and CAL

In general, GH and IGF-1 showed positive correlation ($p < 0.05$). The mean values of all participants revealed a strong negative correlation between IGF-1 and CAL ($p <$

0.01), while the same correlation was at the opposite direction in healthy group ($p < 0.05$) (Table 5).

Biochemical analysis of GCF samples

The values measured by ELISA after GCF sampling revealed significant differences for GH, Prolactin, IL-1 β , IL-10, and ICTP. While the highest mean value was

Table 4 Periodontal variables

	Acromegaly (N = 30)	Healthy (N = 20)	Periodontitis (N = 30)	Total
PI	1.36 ± 0.91 ^{a, c}	0.55 ± 0.35 ^{b, e}	2.00 ± 0.45 ^{c, d}	1.40 ± 0.85
GI	1.01 ± 0.78 ^{a, c}	0.15 ± 0.23 ^{b, e}	1.61 ± 0.52 ^{c, d}	1.03 ± 0.81
CAL (mm)	1.66 ± 0.66 ^b	1.82 ± 0.62 ^b	3.11 ± 0.52 ^{c, e}	2.24 ± 0.90
PD (mm)	1.39 ± 0.36 ^b	1.52 ± 0.48 ^b	2.60 ± 0.49 ^{c, e}	1.87 ± 0.72
Prox. PD (mm)	1.46 ± 0.40 ^b	1.61 ± 0.55 ^b	2.90 ± 0.76 ^{c, e}	2.06 ± 0.91
GCF volume (ml)	56.39 ± 26.14 ^{b, c}	22.85 ± 10.66 ^{b, e}	112.58 ± 24.88 ^{c, e}	69.08 ± 42.73

Values are given as mean ± SD

PI plaque index, GI gingival index, CAL clinical attachment level, GCF gingival crevicular fluid

^aSignificantly different from periodontitis ($p < 0.05$)

^bSignificantly different from periodontitis ($p < 0.001$)

^cSignificantly different from healthy ($p < 0.001$)

^dSignificantly different from acromegaly ($p < 0.05$)

^eSignificantly different from acromegaly ($p < 0.001$)

Table 5 GCF variables

	Acromegaly (N = 30)	Healthy (N = 20)	Periodontitis (N = 30)	Total
GH (μIU/mL)	6.95 ± 2.19 ^a	8.16 ± 2.29 ^a	5.03 ± 0.94 ^{c, e}	6.53 ± 2.22
IGF-1 (ng/mL)	4.15 ± 3.55	4.68 ± 3.93	4.40 ± 4.19	4.38 ± 3.85
Prolactin (pg/mL)	306.14 ± 131.68 ^{a, c}	218.61 ± 32.30 ^e	220.69 ± 42.80 ^e	252.21 ± 95.16
PTH (pg/mL)	30.31 ± 9.93	31.35 ± 12.93	30.16 ± 4.87	30.51 ± 9.24
Vit D (pg/mL)	44.08 ± 2.07	44.43 ± 1.44	45.23 ± 1.42	44.60 ± 1.75
B-ALP (IU/L)	79.25 ± 9.36	88.23 ± 14.01	87.22 ± 17.24	84.48 ± 14.32
RANKL (pg/mL)	320.60 ± 166.33	270.72 ± 39.99	288.96 ± 33.41	296.26 ± 106.59
OPG (pg/mL)	0.29 ± 0.03	0.29 ± 0.07	0.29 ± 0.04	0.29 ± 0.05
RANKL/OPG	1.02 ± 0.04	1.05 ± 0.04	1.16 ± 0.20	1.08 ± 0.00
ICTP (ng/mL)	6.18 ± 2.05 ^b	7.33 ± 1.56 ^d	7.00 ± 1.20	6.78 ± 1.70
IL-1β (pg/mL)	33.59 ± 21.80 ^a	21.47 ± 8.79 ^a	69.53 ± 46.53 ^{c, e}	44.04 ± 37.48
IL-4 (pg/mL)	33.39 ± 3.34	31.48 ± 5.40	31.62 ± 5.62	32.25 ± 4.85
IL-6 (pg/mL)	13.60 ± 1.66	12.35 ± 1.65	13.64 ± 2.79	13.30 ± 2.20
IL-10 (pg/mL)	2.92 ± 2.17 ^{a, c}	4.67 ± 1.61 ^e	5.31 ± 1.57 ^e	4.25 ± 2.10

Values are given as mean ± SD

GH growth hormone, IGF insulin-like growth factor, PTH parathormone, B-ALP bone alkaline phosphatase, RANKL receptor activator of NF-κB ligand, OPG osteoprotegerin, ICTP carboxyterminal telopeptide of type I collagen, IL interleukin

^aSignificantly different from periodontitis ($p < 0.001$)

^bSignificantly different from healthy ($p < 0.05$)

^cSignificantly different from healthy ($p < 0.001$)

^dSignificantly different from acromegaly ($p < 0.05$)

^eSignificantly different from acromegaly ($p < 0.001$)

observed in healthy patients (8.16 ± 2.29 μIU/mL) ($p < 0.05$), acromegalics also showed higher amount of GH (6.95 ± 2.19 μIU/mL) compared with periodontitis cases (5.03 ± 0.94 μIU/mL) ($p < 0.001$). Compared with other two groups, prolactin was remarkably high in acromegaly patients ($p < 0.05$). The mean values for IGF were detected as 4.40 ± 4.19 ng/mL, 4.68 ± 3.93 ng/mL and $4.15 \pm$

3.55 ng/mL all of which did not statistically differ among each other ($p > 0.05$). While the measurements of ICTP ($p < 0.05$) and IL-10 ($p < 0.001$) were lower in acromegalic patients, periodontitis group showed increased IL-1 and -10 values ($p < 0.001$). Other variables involving PTH, Vit D, B-ALP, RANKL, OPG, IL-4, and -6 did not show any significant intergroup difference (Table 6).

Table 6 Correlations among GH, IGF-1, and CAL

	GH	IGF-1	CAL
Acromegaly			
GH	1.000	0.208	0.258
IGF-1	0.208	1.000	-0.074
CAL	0.258	-0.074	1.000
Healthy			
GH	1.000	0.074	-0.294
IGF-1	0.074	1.000	-0.514 ^a
CAL	-0.294	-0.514 ^a	1.000
Periodontitis			
GH	1.000	0.060	-0.148
IGF-1	0.060	1.000	0.063
CAL	-0.148	0.063	1.000
Total			
GH	1.000	0.260 ^a	-0.240 ^a
IGF-1	0.260 ^a	1.000	-0.373 ^b
CAL	-0.240 ^a	-0.373 ^b	1.000

GH growth hormone, IGF insulin-like growth factor, CAL clinical attachment level

^aCorrelation is significant at the 0.05 level (two-tailed)

^bCorrelation is significant at the 0.01 level (two-tailed)

Discussion

The existing data in the literature is still inadequate to arrive at a certain conclusion in periodontal status of the acromegaly patients. The slowed periodontal disease progression was strongly asserted by Lima et al. [21] in 2009 in the shade of knowledge with opposite opinion [29] and some subsequent papers supported their findings by cross-sectional evaluations [20, 30] whereas other half of the relevant literature carried on disclosing contrary results [23]. Periodontal status of acromegalic individuals, through clinical variables, was investigated in the present study. Parallel to some existing results, the tendency of less periodontal destruction was detected in acromegaly patients strengthening the first part's opinion.

Information regarding the underlying mechanisms is still not clear at all. Some papers attributed the expectance of less periodontal destruction in acromegalics to the activated GH-receptor interaction on the osteoblasts and activation of bone morphogenic protein-2 and -4 secretion from fibroblasts [20, 38]. Their results were confirmed by experimental [39] and human [21] studies. More frequent osteoporosis and bone loss related with GH deficiency also supports the expectance albeit the effects of excess GH on bone tissue still need clarification [40, 41]. In the present study, similar to healthy controls, acromegaly patients had higher serum GH levels and less severe periodontal destruction presented by lower CAL compared with

periodontitis. Moreover, even though not significant, a negative correlation between CAL and GH was also detected in healthy and periodontitis patients. These results supported the idea of protective role of GH in bone and periodontal attachment loss. Local serum IGF-1 or IGFBP-3 levels are the second possible mechanism regarding the same issue. From those limited number of relevant studies including healthy control groups, Bascil et al. [30] detected greater whereas Harb et al. [23] showed relatively low values of IGF-1 in acromegaly patients exhibiting more advanced periodontal destruction. Even though GCF IGF-1 values of acromegalics were similar with others, the significant negative correlation between IGF-1 and CAL in the present study also supported this argument. The only study evaluating IGFBP-3 as a potential role player in periodontal status of acromegaly presented lower values in healthy control subjects [23]. Our findings that gave similar IGF-1 amounts in GCF for all participants were different from the abovementioned studies probably associated with the number of acromegalics exposed to pituitary surgery and nutrition habits. However, the real cause-effect relationship must be clarified with further trials.

Previous studies that saw acromegalics with periodontitis featured CAL to define the periodontal diagnosis of their patients; independent from the area and CAL on buccal/lingual areas overestimated the periodontal disease [21, 30]. However, factors such as occlusal problems due to the increased jaw and higher force of mastication or hypertrophy of muscles may change position of teeth and can promote gingival recession. That is why PD seems to be as critical as CAL to understand the status. In furtherance, the new classification of the periodontal diseases elicits the conditions of the proximal areas in defining the status of periodontitis [42]. From this point of view, in the present study, even though no difference was detected in its course compared with CAL, manifesting the PD and especially proximal PD results of those patients was important and will be too in the future.

The role of various hormones such as PTH [43], thyroid hormones [44], cortisol [45], ACTH [46], estrogen, and testosterone [47] in periodontal diseases have been indicated previously. From those, cortisol is a stress-related hormone produced from adrenal cortex and its amount is increased by stimulated ACTH release from pituitary gland. Suppression of immune response by the alteration of cortisol and ACTH may increase the periodontal bone loss potential [46]. In the present study, while acromegaly and periodontitis patients had greater ACTH, similar cortisol levels were measured at all study groups. However, all those values were within the normal range. Despite the presence of previous studies showing a positive correlation between cortisol levels and periodontal disease [48, 49], studies that do not confirm this result also exist [50, 51].

Variable results matching with the present ones can be explained with the high number of factors such as age, gender, socioeconomic status, marital status, and life experiences that may affect cortisol/ACTH interactions.

Increased serum GH and IGF-1 levels have been demonstrated to reduce the quality of bone and might be associated with calcium imbalance and hypercalciuria [9, 52]. A recent trial also detected accelerated bone turnover due to measured biochemical and histomorphometric changes among acromegalics. However, opposite results with normal or high bone density in those patients have also been reported by others [53]. RANKL and OPG are among the effector mediators of IGF-I on bone remodeling [54] and thus, before starting the trial, it was predicted that some of the bone and metabolic variables such as Vit D, B-ALP, PTH with RANKL, OPG, ICTP, or some other inorganic compounds might give important clues about the slowed bone and periodontal destruction in acromegaly patients. However, either in venous blood or in GCF, none of these variables except ICTP showed remarkable intergroup difference. Lower ICTP in acromegalics indicates that the mechanisms associated with collagen metabolism might explain the slowed destruction. However, more variables such as matrix metalloproteinases and other collagen-related mediators should be assessed to highlight the possible associated interactions.

On the other hand, in the present study, plaque-associated gingival inflammation in acromegaly and periodontitis patients complicated the clarification process of these mechanisms by playing significant confounding role in the effects of inflammation-related variables. For example, the severe gingival inflammation findings might be related with relatively higher IL-1 β and lower IL-10 also supports these well-known interactions [55]. Absence of significant intergroup difference in IL-4 and -6 may detract the researchers to investigate their effects in acromegaly patients. Independent from all, the role of ICTP inside these mechanisms still keeps its mystery and remains to be further analyzed with studies carrying the chance of adjusting these effects by their high sample sizes.

Presence of comorbidities must be considered as a potentially important factor that plays role in the periodontal status of the acromegaly patients [56]. Acromegaly is linked with impaired lipid and glucose metabolism that associates with glucose intolerance and related diabetes mellitus [9, 57]. The significant effect of high number of diabetic acromegaly cases to the periodontal status of acromegaly patients in some of the previous reports also supported this phenomenon [20, 21, 23]. However, parallel to some others [58, 59] our data gave similar periodontal status for diabetic and nondiabetic individuals. This result might be linked with the limiting effect of acromegaly on periodontal destruction despite the presence of accompanying diabetes

but must be interpreted with caution because of regulated blood glucose course of the present participants showing HbA1c values around 5% [60]. Furthermore, hypertension, another well-known comorbidity in acromegalics with its cholesterol associated variables [61], did not change the intergroup similarity of this data despite its potential confounding effects on periodontal status. As a speculation, these results might be attributed to the overriding effect of GH to the other comorbidities in modulating the periodontal status of acromegaly patients.

The study harbored some limitations. One is the inadequate number of cases and healthy controls depending on the low prevalence of acromegaly in a specific population [21] and the difficulty to find healthy controls with matched age. The high number of acromegaly cases showing plaque-associated inflammation also limited better understanding the pure effect of acromegaly on these variables. That is why; it seems indispensable to design future studies in a multicentered fashion. The presence of several comorbidities in these patients should be considered as another limitation.

Conclusion

Either because of complex hormonal changes or comorbidities such as diabetes and hypertension, acromegaly is a rare disease that its role on periodontal status is quite difficult to understand. However, the limited information exhibiting slowed periodontal destruction in those patients makes this disease worthwhile to explore. On the other hand, it may present a valuable model to understand the protective mechanisms and lower susceptibility in periodontal destruction. Within its limitations, the present study confirmed the relevant ‘slowed periodontal destruction of acromegalic individuals’ information in the literature and found significant clues regarding the more powerful role of inflammation- and collagen metabolism-related mechanisms rather than bone-associated ones. However, the reduced tendency of periodontitis could not be explained by neither increased IGF-1 nor existing diabetes/hypertension. As a consequence, in addition to the need for further confirmation of slowed periodontal destruction, the other mechanisms possibly bonded to GH/IGF-1 relationships and collagen metabolism, to explain the decelerating periodontal bone loss in acromegalics still needs further investigation.

Acknowledgements The authors express their gratitude to Cigdem Gungor from Medeniyet University for the statistical analyses and Cagman Tan for his efforts in biochemical analysis of gingival crevicular fluid samples.

Funding The study was funded by Hacettepe University Scientific Research Committee (grant number: THD-2015-7584).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Hacettepe University Local Ethics Committee, date: Mar 04, 2015; no: GO15/173-08) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. A. Lavrentaki, A. Paluzzi, J.A. Wass, N. Karavitaki, Epidemiology of acromegaly: review of population studies. *Pituitary* **20**(1), 4–9 (2017). <https://doi.org/10.1007/s11102-016-0754-x>
2. Schilbach, K., Strasburger, C. J., Bidlingmaier, M, Biochemical investigations in diagnosis and follow up of acromegaly. *Pituitary* **20**(1), 33–45 (2017). <https://doi.org/10.1007/s11102-017-0792-z>
3. R. Zahr, M. Fleseriu, Updates in diagnosis and treatment of acromegaly. *Eur. Endocrinol.* **14**(2), 57–61 (2018). <https://doi.org/10.17925/EE.2018.14.2.57>
4. A.P. Heaney, S. Melmed, Molecular targets in pituitary tumours. *Nat. Rev. Cancer* **4**(4), 285–295 (2004). <https://doi.org/10.1038/nrc1320>
5. S. Melmed, A. Colao, A. Barkan, M. Molitch, A.B. Grossman, D. Kleinberg, D. Clemmons, P. Chanson, E. Laws, J. Schlechte, M.L. Vance, K. Ho, A. Giustina, Acromegaly Consensus Group, Guidelines for acromegaly management: an update. *J. Clin. Endocrinol. Metab.* **94**(5), 1509–1517 (2009). <https://doi.org/10.1210/jc.2008-2421>
6. L. Vilar, C.F. Vilar, R. Lyra, R. Lyra, L.A. Naves, Acromegaly: clinical features at diagnosis. *Pituitary* **20**(1), 22–32 (2017). <https://doi.org/10.1007/s11102-016-0772-8>
7. M. Dural, G. Kabakci, N. Cinar, T. Erbas, U. Canpolat, K.M. Gurses, L. Tokgozlu, A. Oto, E.B. Kaya, H. Yorgun, L. Sahiner, S. Dagdelen, K. Aytemir, Assessment of cardiac autonomic functions by heart rate recovery, heart rate variability and QT dynamicity parameters in patients with acromegaly. *Pituitary* **17**(2), 163–170 (2014). <https://doi.org/10.1007/s11102-013-0482-4>
8. I.M. Holdaway, R.C. Rajasoorya, G.D. Gamble, Factors influencing mortality in acromegaly. *J. Clin. Endocrinol. Metab.* **89**(2), 667–674 (2004). <https://doi.org/10.1210/jc.2003-031199>
9. A. Colao, D. Ferone, P. Marzullo, G. Lombardi, Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr. Rev.* **25**(1), 102–152 (2004). <https://doi.org/10.1210/er.2002-0022>
10. S. Dogan, A. Atmaca, S. Dagdelen, B. Erbas, T. Erbas, Evaluation of thyroid diseases and differentiated thyroid cancer in acromegalic patients. *Endocrine* **45**(1), 114–121 (2014). <https://doi.org/10.1007/s12020-013-9981-3>
11. E. Ritvonen, E. Loyttyniemi, P. Jaatinen, T. Ebeling, L. Moilanen, P. Nuutila, R. Kauppinen-Makelin, C. Schalin-Jantti, Mortality in acromegaly: a 20-year follow-up study. *Endocr. Relat. Cancer* **23**(6), 469–480 (2016). <https://doi.org/10.1530/ERC-16-0106>
12. A. Cirese, M.C. Amato, R. Pivonello, E. Nazzari, L.F. Grasso, F. Minuto, D. Ferone, A. Colao, C. Giordano, The metabolic profile in active acromegaly is gender-specific. *J. Clin. Endocrinol. Metab.* **98**(1), E51–E59 (2013). <https://doi.org/10.1210/jc.2012-2896>
13. C. Giordano, A. Cirese, M.C. Amato, R. Pivonello, R.S. Auremma, L.F. Grasso, A. Galluzzo, A. Colao, Clinical and metabolic effects of first-line treatment with somatostatin analogues or surgery in acromegaly: a retrospective and comparative study. *Pituitary* **15**(4), 539–551 (2012). <https://doi.org/10.1007/s11102-011-0365-5>
14. J.L. Ebersole, D. Dawson 3rd, P. Emecen-Huja, R. Nagarajan, K. Howard, M.E. Grady, K. Thompson, R. Peyyala, A. Al-Attar, K. Lethbridge, S. Kirakodu, O.A. Gonzalez, The periodontal war: microbes and immunity. *Periodontol.* **2000** **75**(1), 52–115 (2017). <https://doi.org/10.1111/prd.12222>
15. R.J. Genco, W.S. Borgnakke, Risk factors for periodontal disease. *Periodontol.* **2000** **62**(1), 59–94 (2013). <https://doi.org/10.1111/j.1600-0757.2012.00457.x>
16. P.N. Papananou, C. Susin, Periodontitis epidemiology: is periodontitis under-recognized, over-diagnosed, or both? *Periodontol.* **2000** **75**(1), 45–51 (2017). <https://doi.org/10.1111/prd.12200>
17. American academy of periodontology task force report on the update to the 1999 classification of periodontal diseases and conditions. *J. Periodontol.* **86**(7), 835–838 (2015). <https://doi.org/10.1902/jop.2015.157001>
18. I. Kreitschmann-Andermahr, J. Kohlmann, B. Kleist, U. Hirschfelder, R. Buslei, M. Buchfelder, S. Siegel, Oro-dental pathologies in acromegaly. *Endocrine* **60**(2), 323–328 (2018). <https://doi.org/10.1007/s12020-018-1571-y>
19. A. Ben-Shlomo, S. Melmed, Acromegaly. *Endocrinol. Metab. Clin. North Am.* **37**(1), 101–122 (2008). <https://doi.org/10.1016/j.ecl.2007.10.002>
20. H. Serinsoz, M.E. Ertorer, S. Bascil, O. Bakiner, E. Bozkirli, N.B. Tutuncu, Low prevalence of periodontitis in acromegaly: growth hormone may exert a protective effect. *Turk. J. Endocrinol. Metab.* **19**(2), 42–48 (2015). <https://doi.org/10.4274/tjem.2687>
21. D.L. Lima, R.M. Montenegro Jr., A.P. Vieira, M.F. Albano, D.M. Rego, Absence of periodontitis in acromegalic patients. *Clin. Oral. Invest.* **13**(2), 165–169 (2009). <https://doi.org/10.1007/s00784-008-0216-6>
22. P. Chanson, S. Salenave, Acromegaly. *Orphanet J. Rare Dis.* **3**, 17 (2008). <https://doi.org/10.1186/1750-1172-3-17>
23. A.N. Harb, B. Holtfreter, N. Friedrich, H. Wallaschofski, M. Nauck, M. Albers, P. Meisel, R. Biffar, T. Kocher, Association between the insulin-like growth factor axis in serum and periodontitis in the study of health in pomerania: an exploratory study. *J. Clin. Periodontol.* **39**(10), 931–939 (2012). <https://doi.org/10.1111/j.1600-051X.2012.01935.x>
24. A. Juul, Serum levels of insulin-like growth factor I and its binding proteins in health and disease. *Growth Horm. IGF Res.* **13**(4), 113–170 (2003)
25. J.I. Jones, D.R. Clemmons, Insulin-like growth factors and their binding proteins: biological actions. *Endocr. Rev.* **16**(1), 3–34 (1995). <https://doi.org/10.1210/edrv-16-1-3>
26. W. Gotz, D. Kunert, D. Zhang, A. Kawarizadeh, S. Lossdorfer, A. Jager, Insulin-like growth factor system components in the periodontium during tooth root resorption and early repair processes in the rat. *Eur. J. Oral. Sci.* **114**(4), 318–327 (2006). <https://doi.org/10.1111/j.1600-0722.2006.00381.x>
27. A.C. Sant'Ana, M.M. Marques, T.E. Barroso, E. Passanezi, M.L. de Rezende, Effects of TGF-beta1, PDGF-BB, and IGF-1 on the rate of proliferation and adhesion of a periodontal ligament cell lineage in vitro. *J. Periodontol.* **78**(10), 2007–2017 (2007). <https://doi.org/10.1902/jop.2007.070119>

28. H.L. Levin, Some dental aspects of endocrine diseases. *Oral. Surg. Oral. Med. Oral. Pathol.* **19**, 466–477 (1965)
29. K.S. Mine, C. Nakagawa, T. Hiramoto, K. Murata, T. Tagawa, Gingivitis in acromegaly successfully treated with a growth hormone secretion inhibitor. *Endocrinologist* **17**(1), 20–22 (2007). <https://doi.org/10.1097/01.ten.0000257447.32994.da>
30. S. Bascil, H. Serinsoz, N.B. Tutuncu, Acromegaly is protective for periodontal tissue—advanced chronic periodontitis is rare in acromegalics. *Bratisl. Lek. Listy* **115**(9), 588–592 (2014)
31. J. Meyle, I. Chapple, Molecular aspects of the pathogenesis of periodontitis. *Periodontol.* **69**(1), 7–17 (2015). <https://doi.org/10.1111/prd.12104>
32. J. Mook, C. Albrecht, N. Friedrich, H. Volzke, M. Nauck, M. Koltowska-Haggstrom, T. Kohlmann, H. Wallaschofski, Health-related quality of life and IGF-1 in GH-deficient adult patients on GH replacement therapy: analysis of the German KIMS data and the Study of Health in Pomerania. *Eur. J. Endocrinol.* **160**(1), 17–24 (2009). <https://doi.org/10.1530/EJE-08-0738>
33. G.C. Armitage, Development of a classification system for periodontal diseases and conditions. *Ann. Periodontol.* **4**(1), 1–6 (1999). <https://doi.org/10.1902/annals.1999.4.1.1>
34. B. Rai, J. Kaur, S.C. Anand, Possible relationship between periodontitis and dementia in a North Indian old age population: a pilot study. *Gerodontology* **29**(2), e200–e205 (2012). <https://doi.org/10.1111/j.1741-2358.2010.00441.x>
35. J. Silness, H. Loe, Periodontal disease in pregnancy. II. correlation between oral hygiene and periodontal condition. *Acta Odontol. Scand.* **22**, 121–135 (1964)
36. H. Loe, J. Silness, Periodontal Disease in Pregnancy. I. prevalence and severity. *Acta Odontol. Scand.* **21**, 533–551 (1963)
37. D. Yilmaz, F. Caglayan, E. Buber, E. Kononen, Y. Aksoy, U.K. Gursoy, G.N. Guncu, Gingival crevicular fluid levels of human beta-defensin-1 in type 2 diabetes mellitus and periodontitis. *Clin. Oral. Invest.* **22**(5), 2135–2140 (2018). <https://doi.org/10.1007/s00784-018-2469-z>
38. H. Li, P.M. Bartold, C.Z. Zhang, R.W. Clarkson, W.G. Young, M.J. Waters, Growth hormone and insulin-like growth factor I induce bone morphogenetic proteins 2 and 4: a mediator role in bone and tooth formation? *Endocrinology* **139**(9), 3855–3862 (1998). <https://doi.org/10.1210/endo.139.9.6211>
39. H. Li, P.M. Bartold, W.G. Young, Y. Xiao, M.J. Waters, Growth hormone induces bone morphogenetic proteins and bone-related proteins in the developing rat periodontium. *J. Bone Min. Res.* **16**(6), 1068–1076 (2001). <https://doi.org/10.1359/jbmr.2001.16.6.1068>
40. A. Giustina, G. Mazziotti, E. Canalis, Growth hormone, insulin-like growth factors, and the skeleton. *Endocr. Rev.* **29**(5), 535–559 (2008). <https://doi.org/10.1210/er.2007-0036>
41. H.R. Haase, S. Ivanovski, M.J. Waters, P.M. Bartold, Growth hormone regulates osteogenic marker mRNA expression in human periodontal fibroblasts and alveolar bone-derived cells. *J. Periodontol. Res.* **38**(4), 366–374 (2003)
42. J.G. Caton, G. Armitage, T. Berglundh, I.L.C. Chapple, S. Jepsen, K.S. Kornman, B.L. Mealey, P.N. Papapanou, M. Sanz, M.S. Tonetti, A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. *J. Periodontol.* **89**(Suppl 1), 1–8 (2018). <https://doi.org/10.1002/JPER.18-0157>
43. F. Boabaid, J.E. Berry, A.J. Koh, M.J. Somerman, L.K. McCauley, The role of parathyroid hormone-related protein in the regulation of osteoclastogenesis by cementoblasts. *J. Periodontol.* **75**(9), 1247–1254 (2004). <https://doi.org/10.1902/jop.2004.75.9.1247>
44. S. Feitosa Dda, B. Bezerra Bde, G.M. Ambrosano, F.H. Nociti, M. Z. Casati, E.A. Sallum, S. de Toledo, Thyroid hormones may influence cortical bone healing around titanium implants: a histometric study in rats. *J. Periodontol.* **79**(5), 881–887 (2008). <https://doi.org/10.1902/jop.2008.070466>
45. A. Ishisaka, T. Ansai, I. Soh, K. Inenaga, A. Yoshida, C. Shigeyama, S. Awano, T. Hamasaki, K. Sonoki, Y. Takata, T. Takehara, Association of salivary levels of cortisol and dehydroepiandrosterone with periodontitis in older Japanese adults. *J. Periodontol.* **78**(9), 1767–1773 (2007). <https://doi.org/10.1902/jop.2007.070044>
46. G. Rohini, S. Kalaivani, V. Kumar, S.A. Rajasekar, J. Tuckaram, V. Pandey, Estimation and comparison of serum cortisol levels in periodontally diseased patients and periodontally healthy individuals: a clinical-biochemical study. *J. Pharm. Bioallied Sci.* **7**(Suppl 2), S457–S460 (2015). <https://doi.org/10.4103/0975-7406.163501>
47. M. Morishita, M. Miyagi, Y. Iwamoto, Effects of sex hormones on production of interleukin-1 by human peripheral monocytes. *J. Periodontol.* **70**(7), 757–760 (1999). <https://doi.org/10.1902/jop.1999.70.7.757>
48. A.M. da Silva, H.N. Newman, D.A. Oakley, Psychosocial factors in inflammatory periodontal diseases. a review. *J. Clin. Periodontol.* **22**(7), 516–526 (1995)
49. T. Breivik, P.K. Opstad, P. Gjerme, P.S. Thrane, Effects of hypothalamic-pituitary-adrenal axis reactivity on periodontal tissue destruction in rats. *Eur. J. Oral. Sci.* **108**(2), 115–122 (2000)
50. A.M. Monteiro da Silva, D.A. Oakley, H.N. Newman, F.S. Nohl, H.M. Lloyd, Psychosocial factors and adult onset rapidly progressive periodontitis. *J. Clin. Periodontol.* **23**(8), 789–794 (1996)
51. R. Mengel, M. Bacher, L. Flores-De-Jacoby, Interactions between stress, interleukin-1beta, interleukin-6 and cortisol in periodontally diseased patients. *J. Clin. Periodontol.* **29**(11), 1012–1022 (2002)
52. N.B. Tutuncu, T. Erbas, Factors associated with bone metabolism in acromegalic patients: hypogonadism and female gender. *Exp. Clin. Endocrinol. Diabetes* **112**(6), 328–332 (2004). <https://doi.org/10.1055/s-2004-820913>
53. A. Cohen, D.W. Dempster, R. Muller, X.E. Guo, T.L. Nickolas, X.S. Liu, X.H. Zhang, A.J. Wirth, G.H. van Lenthe, T. Kohler, D.J. McMahon, H. Zhou, M.R. Rubin, J.P. Bilezikian, J.M. Lappe, R.R. Recker, E. Shane, Assessment of trabecular and cortical architecture and mechanical competence of bone by high-resolution peripheral computed tomography: comparison with transiliac bone biopsy. *Osteoporos. Int.* **21**(2), 263–273 (2010). <https://doi.org/10.1007/s00198-009-0945-7>
54. F.F. Ozer, S. Dagdelen, T. Erbas, Relation of RANKL and OPG levels with bone resorption in patients with acromegaly and prolactinoma. *Horm. Metab. Res.* **50**(7), 562–567 (2018). <https://doi.org/10.1055/a-0630-1529>
55. H. Hasturk, A. Kantarci, Activation and resolution of periodontal inflammation and its systemic impact. *Periodontol.* **69**(1), 255–273 (2015). <https://doi.org/10.1111/prd.12105>
56. R. Pivonello, R.S. Auriemma, L.F. Grasso, C. Pivonello, C. Simeoli, R. Patalano, M. Galdiero, A. Colao, Complications of acromegaly: cardiovascular, respiratory and metabolic comorbidities. *Pituitary* **20**(1), 46–62 (2017). <https://doi.org/10.1007/s11102-017-0797-7>
57. M. Mercado, B. Gonzalez, G. Vargas, C. Ramirez, A.L. de los Monteros, E. Sosa, P. Jervis, P. Roldan, V. Mendoza, B. Lopez-Felix, G. Guinto, Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. *J. Clin. Endocrinol. Metab.* **99**(12), 4438–4446 (2014). <https://doi.org/10.1210/jc.2014-2670>
58. K.J. Joshipura, F.J. Munoz-Torres, B.A. Dye, B.G. Leroux, M. Ramirez-Vick, C.M. Perez, Longitudinal association between periodontitis and development of diabetes. *Diabetes Res. Clin. Pr.* **141**, 284–293 (2018). <https://doi.org/10.1016/j.diabres.2018.04.028>

59. D.M. Shearer, W.M. Thomson, J.M. Broadbent, J. Mann, R. Poulton, Periodontitis is not associated with metabolic risk during the fourth decade of life. *J. Clin. Periodontol.* **44**(1), 22–30 (2017). <https://doi.org/10.1111/jcpe.12641>
60. T. Kocher, J. König, W.S. Borgnakke, C. Pink, P. Meisel, Periodontal complications of hyperglycemia/diabetes mellitus: epidemiologic complexity and clinical challenge. *Periodontol.* 2000 **78**(1), 59–97 (2018). <https://doi.org/10.1111/prd.12235>
61. M. Bondanelli, M.R. Ambrosio, E.C. degli Uberti, Pathogenesis and prevalence of hypertension in acromegaly. *Pituitary* **4**(4), 239–249 (2001)