Received: 27 November 2019 | Revised: 21 February 2020 | Accepted: 24 March 2020

DOI: 10.1111/jcpe.13288

Journal of Clinical Periodontology WILEY

Effect of periodontal therapy on adipokine biomarkers in overweight

Johannes Matern[1] | Raphael Koch[2] | Astrid Petersmann[3] | Thomas Kocher[4] | Peter Eickholz[5] | Katrin Lorenz[6] | Ti-Sun Kim[7] | Jörg Meyle[8] | Doğan Kaner[9,10] | Ulrich Schlagenhauf[11] | Martina Gravemeier[1] | Inga Harks[1] | Benjamin Ehmke[1]

[1]Department of Periodontology and Operative Dentistry, University Hospital Münster, Münster, Germany

[2]Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany

[3]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany

[4]Unit of Periodontology, University Medicine Greifswald, Greifswald, Germany

[5]Department of Periodontology, Johann Wolfgang Goethe-University Frankfurt, Frankfurt, Germany

[6]Department of Periodontology, TU Dresden, Dresden, Germany

[7]Section of Periodontology, Department of Conservative Dentistry, University Hospital Heidelberg, Heidelberg, Germany

[8]Department of Periodontology, University of Giessen, Giessen, Germany

[9]Departments of Periodontology and Synoptic Dentistry, Charite-Universitatsmedizin Berlin, Berlin, Germany

[10]Department of Periodontology, Dental School, Faculty of Health, University of Witten/Herdecke, Witten, Germany

[11]Department of Periodontology, University Hospital Würzburg, Würzburg, Germany

Correspondence
Johannes Matern, Department of Periodontology and Operative Dentistry, University Hospital Münster, Albert-Schweitzer-Campus 1, Gebäude W30, 48149 Münster, Germany.
Email: johannes.matern@ukmuenster.de

Funding information
The study was exclusively supported by a grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG: EH 365 1-1), the ARPA Research Foundation, and from the authors' institutions. No writing assistance other than copy editing was provided.

Abstract

Aim: The aim of this study was to evaluate the effect of non-surgical periodontal therapy on circulating levels of the systemic inflammation-associated biomarkers orosomucoid (ORM), high-sensitivity C-reactive protein (hsCRP), chemerin, and retinol-binding protein 4 (RBP4) in overweight or normal-weight patients with periodontitis at 27.5 months after therapy.

Materials and methods: This exploratory subanalysis includes patients from the ABPARO-trial (ClinicalTrials.gov NCT00707369). The per-protocol collective provided untreated periodontitis patients with high (≥28 kg/m^2) or moderate (21–24 kg/m^2) BMI. Out of the per-protocol collective, 80 patients were randomly selected and stratified for BMI group, sex, and treatment group (antibiotics/placebo), resulting in 40 overweight and normal-weight patients. Patients received non-surgical periodontal therapy and maintenance at 3-month intervals. Plasma samples from baseline and 27.5 months following initial treatment were used to measure the concentrations of ORM, hsCRP, chemerin, and RBP4.

Matern and Koch contributed equally to the manuscript.

Harks and Ehmke contributed equally to the manuscript.

Results: At the 27.5-month examination, ORM and hsCRP decreased noticeably in the overweight group (ORM: $p = .001$, hsCRP: $p = .004$) and normal-weight patients (ORM: $p = .007$, hsCRP: $p < .001$). Chemerin decreased in the overweight group ($p = .048$), and RBP4 concentrations remained stable.

Conclusion: Non-surgical periodontal therapy reduced systemically elevated inflammation-associated biomarkers in periodontitis patients. These improvements were more pronounced in overweight patients than in normal-weight patients.

KEYWORDS

chemerin, orosomucoid, overweight, periodontitis, retinol-binding protein 4

1 | INTRODUCTION

Periodontitis is a chronic inflammatory disease that develops as a consequence of an inadequate immune response to a dysbiotic oral microbiome (Meyle & Chapple, 2015). The impact of being overweight on the course of periodontitis has become an objective of a fast-growing number of studies and was recently reviewed in a meta-review (Suvan, Finer, & D'Aiuto, 2018). Results consistently demonstrate that the development and progression of periodontitis are increased in overweight individuals compared with normal-weight individuals.

Overweight is commonly assessed by calculating the body mass index (BMI), which is defined as the body mass in kilograms divided by the squared body height in meters. For adults, normal-weight, overweight, and obesity are defined as BMI 18.5 to <25 kg/m^2, BMI 25 to <30 kg/m^2, and BMI ≥ 30 kg/m^2, respectively. Albeit it does not take into account the stature, sex, and fat-to-muscle ratio of a person, the BMI is a sufficient parameter to indicate the percentage of body fat and risk of overweight-associated comorbidities or increased mortality (Bray et al., 2008; Gallagher et al., 1996; Kopelman, 2007; WHO, 2018).

In overweight subjects, adipose tissue produces an excess of pro-inflammatory adipokine biomarkers, which correlates with an increased systemic inflammatory state. High levels of those pro-inflammatory adipokines are assumed to promote the development of overweight-associated co-morbidities and chronic inflammatory diseases (Maury & Brichard, 2010). A rat model showed that periodontitis induces low-grade systemic inflammation, and the highest levels of inflammatory biomarkers were found in the co-occurrence of both periodontitis and obesity (Endo et al., 2010). The underlying molecular mechanisms between periodontitis and systemic inflammation are not yet fully understood. It is assumed that locally released cytokines or bacterial material such as lipopolysaccharides enter the bloodstream and reach the liver where an acute-phase response is initiated. The subsequently released circulating acute-phase proteins then increase the systemic inflammatory state.

Systemic inflammation can be monitored by measuring inflammation-associated biomarkers such as orosomucoid (ORM), high sensitivity C-reactive protein (hsCRP), chemerin, and retinol-binding protein 4 (RBP4). ORM, also known as alpha-1 acid glycoprotein, is a plasma protein that is primarily produced in the liver, but extra-hepatic expression was also found in adipose tissue (Alfadda et al., 2012). The plasma levels of ORM correlate with BMI (Benedek, Blouin, & McNamara, 1984). A cross-sectional study comprising morbidly obese patients reported that circulating ORM levels were associated with the severity of periodontitis (Rangé et al., 2013). The acute-phase protein ORM can be used as a diagnostic and prognostic marker during clinical therapy (Fournier, Medjoubi, & Porquet, 2000). However, it is unknown whether plasma ORM levels are influenced by periodontal treatment in general. The acute-phase protein CRP is commonly used to monitor systemic inflammation. There is evidence that the plasma concentration of CRP is elevated by BMI as well as by periodontitis (Meisel, Eremenko, Holtfreter, Völzke, & Kocher, 2019). Nonetheless, data on the long-term development of the plasma concentration of CRP following periodontitis therapy for overweight or normal-weight patients are limited. Chemerin is an adipokine that is primarily produced in white adipose tissue. A review article stated that elevated chemerin levels indicated inflammatory

Clinical Relevance

Scientific rationale for the study: Overweight has been consistently identified as a risk factor for periodontitis. The outcome of periodontal therapy regarding systemic inflammation-associated biomarkers is inconsistent, and the inferior treatment response in overweight subjects is still discussed.

Principal findings: Following non-surgical periodontal therapy, overweight and normal-weight patients develop similar clinical improvements and reductions of systemic inflammation-associated biomarkers.

Practical implications: Non-surgical periodontal therapy reduces systemic inflammation-associated biomarkers in overweight and normal-weight patients and might therefore contribute to improved general health.

diseases and suggested measuring circulating chemerin as a diagnostic tool and biomarker for inflammatory diseases (Rourke, Dranse, & Sinal, 2013). Non-surgical periodontal therapy in obese and non-obese patients resulted in decreased chemerin levels locally in the gingival crevicular fluid at 6 weeks following treatment (Balli, Ongoz, Bozkurt, Gulsoy, & Sertoglu, 2016). However, there are no longitudinal studies that analysed the effect of periodontal treatment and maintenance therapy on circulating levels of chemerin. RBP4 belongs to the lipocalin family and is a specific carrier for retinol. RBP4 is mainly produced by the liver and adipose tissue and was found to be associated with insulin resistance by interfering with the insulin receptor (Gerrits et al., 2012). Recently, a cross-sectional study reported gingival crevicular fluid RBP4 to be correlated with obesity and periodontitis (Kanoriya, Pradeep, Mallika, Singhal, & Garg, 2017). An interventional study reported decreased serum RBP4 at 12 weeks after periodontal treatment and serum RBP4 levels to be associated with periodontitis when comparing periodontally healthy patients and individuals with periodontitis (Martinez-Herrera et al., 2018).

Therefore, adipokine biomarkers may be helpful in a personalized dentistry approach as an additional diagnostic tool to monitor the patients' periodontal status or the course of periodontal therapy.

However, evidence of the impact of overweight on periodontal treatment outcome regarding systemic inflammation is inconsistent (Suvan et al., 2018). Thus, prospective long-term studies are needed to clarify if the systemic inflammatory burden, represented by increased levels of inflammation-associated biomarkers, can be positively influenced by periodontal treatment and if overweight worsens the clinical outcome.

The aim of this study was to evaluate the effect of non-surgical periodontal therapy on circulating levels of systemic inflammation-associated biomarkers ORM, hsCRP, chemerin, and RBP4 in overweight or normal-weight patients with periodontitis at 27.5 months after therapy.

2 | MATERIALS AND METHOD

2.1 | Study design

This is an exploratory subanalysis comprising patients from the per-protocol collective of the prospective, randomized, double-blinded, parallel-group, and multi-centre ABPARO trial (ClinicalTrials.gov NCT00707369) with eight participating study centres. This research was conducted to evaluate the effect of systematic non-surgical periodontal therapy on circulating levels of ORM, chemerin, and RBP4 in overweight or normal-weight patients with periodontitis at 27.5 months after therapy.

The per-protocol collective provided two therapy groups, 175 patients assigned to receive a placebo, and 170 patients assigned to receive amoxicillin 500 mg plus metronidazole 400 mg three times per day for 7 days adjunctive to the mechanical therapy. A total of 80 patients were randomly and stratified selected from the per-protocol collective, so that in each of the eight combinations of BMI group (normal/overweight), sex (male/female), and therapy group (placebo/antibiotics), the same number of patients (n = 10) was present. The subsampling was intended to create two subgroups with substantially different BMI. An accumulation of participants slightly under or over 25 kg/m^2, as threshold between normal-weight and overweight, should be avoided.

The stratified selection was carried out using the procedure *surveyselect* in SAS software, version 9.4 of the SAS System for Windows (SAS Institute). Consequently, this resulted in two BMI subgroups (high: ≥28 kg/m^2, moderate: 21–24 kg/m^2) stratified for therapy and sex, each consisting of 40 patients suffering from moderate to severe chronic periodontitis.

The study's specifications and main clinical results were already described (Eickholz et al., 2016, 2019; Hagenfeld et al., 2018; Harks et al., 2014, 2015). In short, clinical periodontal parameters were measured at six sites of each tooth [pocket probing depth (PPD), bleeding on probing (Lang, Adler, Joss, & Nyman, 1990)), or four sites [plaque index (O'Leary, Drake, & Naylor, 1972)], respectively. Measurements were carried out by masked examiners not involved in periodontal therapy, as described formerly (Harks et al., 2015). Within 6 weeks after baseline measurements and oral hygiene instructions, all patients received mechanical therapy in one to two sessions on two consecutive days. The mechanical therapy comprised supra- and subgingival mechanical debridement, which was performed using sonic/ultrasonic scalers, hand instruments (curettes), and air powder devices under local anaesthesia.

Directly after completion of mechanical therapy, patients received an empiric adjunctive antimicrobial therapy (amoxicillin $3H_2O$ 574 mg [Amoxicillin-ratiopharm® 500 mg, Ratiopharm); metronidazole 400 mg (Flagyl® 400; Sanofi-Aventis]) or placebo therapy comprising two placebo drugs, depending on therapy group allocation, each to be taken three times a day for 7 days.

The re-evaluation was timed at 2 months after initial therapy. Subsequently, patients received supportive periodontal treatment, which included full-mouth supragingival debridement and oral hygiene instructions, at 3-month intervals. Sites with PPD ≥ 4 mm obtained subgingival re-debridement. All treatments were performed by blinded qualified dentists or dental hygienists.

2.2 | Collection of plasma samples

Venous blood samples (EDTA: 1 × 6 ml) were taken at baseline after screening examination and 27.5 months after initial treatment. The samples were shipped immediately for further processing to the medical laboratory of the University Medicine Greifswald.

2.3 | Laboratory biomarker analyses

Plasma samples were stored at −80°C prior to measurements. The Dimension Vista 1500 (Siemens Healthcare Diagnostics) was used

to quantify plasma concentrations of ORM, cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.

The enzyme-linked immunosorbent assay (ELISA) method was used to measure plasma concentrations of chemerin and RBP4 using the following assays: Chemerin ELISA kit (Mediagnost) and Quantikine ELISA Human RBP4 (R&D Systems). High-sensitivity CRP was determined by particle-enhanced immuno-nephelometry with a test sensitivity of 0.2 mg/L (hsCRP kit; Dade Behring). All assays were used according to the instructions of the manufacturer.

All measurements were carried out by blinded laboratory assistants.

2.4 | Statistical analysis

Standard univariate statistical analyses were applied. Categorical variables are reported as absolute and relative frequencies. Fisher's exact tests were used to compare categorical variables between the BMI groups. Continuous variables are displayed as median and inter-quartile-range (25% quantile/75% quantile, IQR) and were compared between the two BMI or treatment groups using two-sided Mann–Whitney *U* tests. Intra-group changes between values from baseline and 27.5 months were evaluated using two-sided Wilcoxon signed-rank tests.

Statistical analyses were performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute). Inferential statistics, like *p*-values and confidence intervals, were intended to be exploratory, not confirmatory. Therefore, neither global nor local significance levels were determined, and no adjustment for multiplicity was applied. Consequently, explorative two-sided *p*-values ≤ .05 were denominated as statistically noticeable instead of significant.

3 | RESULTS

3.1 | Patient demography and clinical characteristics

In this exploratory subanalysis, 80 patients were randomly and stratified selected from 345 per-protocol patients.

The BMI of the overweight group (BMI-O) was 30.0 kg/m^2 (IQR: 28.9/32.3 kg/m^2) and of the normal-weight group (BMI-N) 22.9 kg/m^2 (IQR: 21.8/23.3 kg/m^2). The BMI-N group contained a slightly increased proportion of smokers compared with the BMI-O group (BMI-N: *n* = 13 [32.5%], BMI-O: *n* = 5 [12.5%], *p* = .059; Table 1). At baseline, there were no noticeable differences in clinical parameters between both BMI groups, except for the number of teeth (BMI-N: 27 [IQR: 23.5/28], BMI-O: 24 [21.5/26], *p* = .008; Table 2).

At 27.5 months after baseline, both groups showed comparable clinical improvements in the reduction of sites with gingival bleeding and sites with PPD ≥ 3.5 mm, as well as an increase in sites with PPD < 3.5 mm. Compared with baseline, there were no relevant changes in the number of teeth and sites with detectable plaque in both groups (Table 2).

TABLE 1 Baseline patient characteristics according to group allocation

	Overweight (*n* = 40)	Normal weight (*n* = 40)	*p*-value
Body mass index (kg/m^2)	30.0 (28.9/32.3)	22.9 (21.8/23.3)	<.001^M
Age (year)	54.0 (46.0/61.5)	51.0 (42.5/59.5)	.435^M
Sex			
Female–no. (%)	20 (50)	20 (50)	1.000^F
Male–no. (%)	20 (50)	20 (50)	
Treatment			
Adjunctive placebo–no. (%)	20 (50)	20 (50)	1.000^F
Adjunctive antibiotics–no. (%)	20 (50)	20 (50)	
Smoking status–no. (%)	5 (12.5%)	13 (32.5%)	.059^F
Cholesterol (mM)	5.6 (4.6/6.8)	5.6 (4.9/6.3)	.973^M
HDL cholesterol (mM)	1.4 (1.1/1.7)	1.8 (1.5/2.1)	<.001^M
LDL cholesterol (mM)	3.5 (2.8/4.2)	3.4 (2.7/3.8)	.429^M
Triglycerides (mM)	2.1 (1.5/3.3)	1.3 (0.9/1.6)	<.001^M

Note: Patient parameters: Continuous variables are displayed as median and inter-quartile range (25% quantile/75% quantile, IQR), and categorical variables are shown as absolute and relative frequencies. *p*-values are from two-sided Mann–Whitney *U* tests (M) for continuous variables or Fisher's exact tests (F) for categorical variables.

3.2 | Biomarkers

From a total of 160 included plasma samples, three samples from two patients (overweight group [*n* = 1], normal-weight group [*n* = 1]) were excluded due to insufficient material. At baseline, overweight patients showed notably higher plasma concentrations of ORM compared with normal-weight patients (*p* < .001). At the 27.5-month examination, plasma concentrations of ORM were lower in both groups, and reductions of ORM between baseline and 27.5 months after therapy were more pronounced in the overweight group (*p* = .001) than in the normal-weight group (*p* = .007) but not noticeably different between both groups (*p* = .242). Reduced plasma concentrations of ORM from the overweight group were still higher than the initial values from the normal-weight group (Figure 1).

At baseline, plasma concentrations of hsCRP were not noticeably different between both BMI-groups (*p* = .176). At the 27.5-month examination, both BMI-groups showed statistically noticeable decreased hsCRP levels compared with baseline (BMI-O: *p* < .001, BMI-N: *p* = .004). The magnitude of the reduction was comparable in both groups (*p* = .964). However, the absolute hsCRP concentration

TABLE 2 Clinical characteristics at baseline and 27.5 months after therapy

	Visit	Overweight (n = 40)	Normal weight (n = 40)	p-value
Number of teeth	Baseline	24.0 (21.5/26.0)	27.0 (23.5/28.0)	.008
	27.5 months	24.0 (20.0/26.0)	26.0 (23.0/28.0)	.014
	Δ	0.0 (−1.0/0.0)*	0.0 (−1.0/0.0)*	.958
Mean attachment level per patient (mm)	Baseline	4.3 (3.5/4.7)	3.9 (3.5/4.6)	.874
	27.5 months	3.5 (3.0/4.4)	3.6 (3.0/4.3)	.822
	Δ	−0.7 (−0.9/−0.2)*	−0.5 (−1.0/−0.1)*	.476
Mean pocket probing depth per patient (mm)	Baseline	3.4 (3.1/4.0)	3.4 (3.0/3.8)	.476
	27.5 months	2.4 (1.9/3.0)	2.4 (2.0/2.9)	.927
	Δ	−1.0 (−1.6/−0.7)*	−0.8 (−1.5/−0.5)*	.309
Proportion of sites per patient with pocket probing depth				
% <3.5 mm	Baseline	60.3 (46.1/69.2)	60.6 (46.0/72.5)	.687
	27.5 months	85.6 (71.2/95.6)	84.6 (71.4/91.1)	.527
	Δ	24.8 (15.0/34.3)*	21.2 (9.8/33.3)*	.419
3.5 mm ≤ % <6.5 mm	Baseline	34.0 (25.9/41.4)	32.7 (23.6/42.3)	.777
	27.5 months	13.3 (4.1/23.0)	14.0 (7.8/26.4)	.464
	Δ	−19.2 (−27.1/−9.1)*	−16.0 (−25.5/−4.9)*	.295
% ≥6.5 mm	Baseline	6.6 (1.9/10.8)	4.3 (1.9/8.7)	.455
	27.5 months	0.7 (0.0/3.1)	0.6 (0.0/2.6)	.762
	Δ	−4.2 (−9.5/−1.0)*	−4.0 (−7.1/−0.6)*	.652
Proportion of sites per patient with gingival bleeding (%)	Baseline	35.3 (25.6/45.9)	35.9 (17.5/44.9)	.521
	27.5 months	14.7 (3.5/22.9)	11.5 (5.8/18.1)	.939
	Δ	−24.4 (−34.1/−11.2)*	−22.0 (−35.7/−3.5)*	.503
Proportion of sites per patient with detectable plaque (%)	Baseline	31.0 (21.8/57.5)	27.8 (15.5/54.9)	.264
	27.5 months	32.6 (20.5/52.7)	28.6 (18.8/49.4)	.458
	Δ	3.5 (−18.8/14.9)	1.3 (−17.8/21.7)	.737

Note: Clinical parameters: Variables are shown as median and inter-quartile-range (25% quantile/75% quantile, IQR). The Greek letter Δ indicates the intra-group changes from baseline to 27.5 months. p-values are from two-sided Mann–Whitney U tests that were performed to compare the variables between the overweight and normal-weight groups. Two-sided Wilcoxon signed-rank tests were used to analyse the changes within the same weight group between baseline and 27.5 months. Statistically noticeable intra-group changes (p < .05) are marked by the symbol *.

at 27.5 months was slightly but noticeably higher in the overweight group (p = .048; Table 3).

Initial plasma concentrations of chemerin were distinctly higher in the overweight group compared with the normal-weight group (p = .001). At 27.5 months after therapy, we observed decreased plasma concentrations of chemerin in the overweight group (p = .048), whereas the normal-weight group's values remained constant (Table 3). Nevertheless, the changes between the two groups were not noticeably different (p = .215).

For plasma concentrations of RBP4, no statistically noticeable differences between the groups were observed at baseline and after therapy. Also, no noticeable intra-group changes were observed (Table 3).

At baseline, overweight patients showed statistically noticeable higher plasma concentrations of triglycerides (p < .001) and lower plasma concentrations of HDL cholesterol (p < .001) compared with normal-weight groups. For plasma concentrations of cholesterol and LDL cholesterol, we could not observe major differences between the groups (Table 1).

Therapy subgroups receiving adjunctive antibiotics or adjunctive placebo showed no clinically relevant differences in plasma concentrations of biomarkers, and there were no statistically noticeable differences in changes in plasma concentrations of biomarkers (Table S3).

3.3 | Validity of measurements

The imprecision of the used assays was monitored by low and high internal quality controls. The imprecision of our measurements was

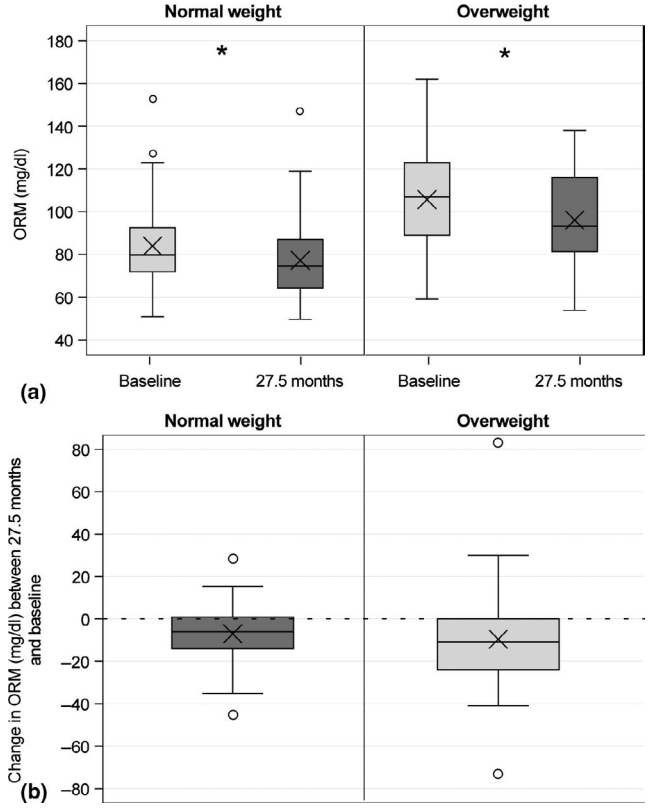

FIGURE 1 Plasma concentration of ORM at baseline and 27.5 months after therapy. The box plots show (a) the plasma concentrations of ORM at baseline and 27.5 months after therapy and (b) the intra-group changes (27.5 months - baseline). The two-sided Mann–Whitney U test was performed to compare the values at each time point and the changes between the BMI groups. Two-sided Wilcoxon signed-rank tests were applied to evaluate the intra-BMI group changes between baseline and 27.5 months after therapy. Statistically noticeable intra-group changes ($p < .05$) are marked with the symbol *. An X denotes the mean

within the manufacturer's specifications except for chemerin, where we obtained slightly higher coefficients of variation (Tables S1 and S2).

4 | DISCUSSION

This study analysed the effect of non-surgical periodontal therapy after 27.5 months on plasma levels of the biomarkers ORM, hsCRP, chemerin, and RBP4 in periodontitis patients who were or were not overweight. To the best of our knowledge, this is the first study that tracks the long-term development of plasma concentrations of ORM, chemerin, and RBP4 after periodontal therapy. Both overweight and normal-weight patients were successfully treated with respect to clinical periodontal parameters.

We found that baseline plasma concentrations of ORM were higher in overweight compared with normal-weight patients. These findings can be considered to be expected, according to the available literature. Serum ORM concentrations were reported to be significantly increased by BMI (Benedek et al., 1984; Ferrari et al., 2014). Both a higher volume of adipose tissue as well as an increased inflammatory state in overweight patients can explain increased ORM levels because adipose tissue has been identified as an additional location of ORM expression (Alfadda et al., 2012). ORM plasma concentrations decreased in both overweight and normal-weight groups after periodontal therapy. One relatively small interventional study observed decreased ORM levels at 3 and 6 months after non-surgical periodontal treatment in one subgroup (Pinho, Oliveira, Novaes, & Voltarelli, 2009). This, as well as the results of the present investigation, may indicate that the applied periodontal therapies lead to a lower inflammatory state in both groups.

The observed decrease of systemic hsCRP levels at the 27.5-month examination conforms to previous interventional studies with few months of follow-up (Akram et al., 2016; Marcaccini et al., 2009). Initial levels of hsCRP were approximately halved during our observation period in both BMI groups. This may underscore the beneficial impact of periodontal therapy on systemic health. Nevertheless, some investigations have been interpreted to suggest that obesity may nullify the positive systemic anti-inflammatory effect of periodontal therapy, due to an overwhelming impact of increased pro-inflammatory serum markers released by excess adipose tissue. It was interpreted that treating periodontal disease among people with obesity might have no effect on lowering serum marker levels, e.g. hsCRP, unless the patient also lost weight at the same time (Offenbacher et al., 2009; Slade et al., 2003). However, in the Offenbacher study, participants had to have earlier severe cardiovascular events as an inclusion criterion. This may indicate that these patients were less systemically healthy compared with the present study's participants. Additionally, in the present study, a more stringent maintenance therapy consisting of supra- and subgingival debridement in 3 months intervals was performed over 27.5 months. In summary, in the present study, the application of long-term intense periodontal maintenance therapy resulted in a measurable reduction of inflammatory serum markers in obese and normal-weighted patients. Analogous to that a subsample of pre-diabetes patients from the ABPARO-collective showed that periodontal therapy improves haemoglobin A1c and hsCRP values in patients with pre-diabetes to a clinically relevant extent and thereby prevents a proportion of those individuals from developing diabetes (Kocher et al., 2019). The joint EFP/ORCA workshop's consensus report of the “Interaction of lifestyle, behaviour or systemic diseases with oral health, dental caries, and periodontal diseases” already recommended including oral health in preventive medical programs (Chapple et al., 2017). Our results support this suggestion with data about the long-term effect of periodontal therapy on plasma biomarkers. However, clear evidence on how periodontal therapy affects the development and progression of the wide variety of inflammation-associated disease and general health is limited.

As expected, the plasma concentrations of chemerin were noticeably higher in overweight patients compared with normal-weight patients despite similar clinical findings. Our results are in line with previous publications that show BMI-related chemerin levels

TABLE 3 Plasma concentrations of ORM, hsCRP, chemerin, and RBP4 at baseline and 27.5 months after therapy

	Visit	Overweight (n = 39)	Normal weight (n = 39)	p-value
ORM (mg/dl)	Baseline	107.0 (89.0/123.0)	79.7 (71.9/92.6)	<.001
	27.5 months	93.2 (81.3/116.0)	74.6 (64.3/87.0)	<.001
	Δ	−10.8 (−24.0/0.0)*	−6.1 (−14.0/0.9)*	.242
hsCRP (mg/L)	Baseline	1.5 (0.9/3.5)	1.4 (0.7/2.4)	.176
	27.5 months	0.8 (0.6/1.8)	0.7 (0.4/1.1)	.046
	Δ	−0.5 (−1.7/−0.1)*	−0.6 (−1.4/−0.0)*	.964
Chemerin (ng/ml)	Baseline	113.6 (86.3/125.0)	87.9 (73.0/103.3)	.001
	27.5 months	98.5 (88.3/122.0)	87.7 (78.1/105.6)	.040
	Δ	−6.2 (−23.8/11.8)*	−1.5 (−11.4/11.7)	.215
RBP4 (μg/ml)	Baseline	31.5 (27.2/37.1)	32.7 (28.8/39.2)	.548
	27.5 months	33.9 (29.7/40.5)	33.6 (28.9/40.4)	1.000
	Δ	0.6 (−3.8/6.0)	0.3 (−3.9/6.5)	.981

Note: Plasma concentrations are shown as median and inter-quartile-range (25% quantile/75% quantile, IQR). The Greek letter Δ indicates the intra-group changes from baseline to 27.5 months. p-values are from two-sided Mann–Whitney U tests that were performed to compare the variables between the overweight and normal-weight groups. Two-sided Wilcoxon signed-rank tests were used to analyse the changes within the same weight group between baseline and 27.5 months. Statistically noticeable intra-group changes (p < .05) are marked by the symbol *.

systemically as well as locally (Balli et al., 2016; Jentsch et al., 2017; Maghsoudi, Kelishadi, & Hosseinzadeh-Attar, 2016; Sledzinski et al., 2013). The plasma concentrations of chemerin in the overweight group decreased slightly but statistically noticeably, whereas this biomarker showed mostly unchanged levels in the normal-weight group. Compared with the interventional study that found decreased chemerin concentrations in the GCF 6 weeks following non-surgical periodontal treatment in both obese and normal-weight patients, we detected decreased plasma concentrations of chemerin after 27.5 months only in our overweight group where relatively high initial values were present (Balli et al., 2016). Although interpreted with caution, this may indicate an overall anti-inflammatory effect of the non-surgical periodontal therapy, which is obviously measurable in groups with high inflammatory activity, e.g. periodontitis patients who are overweight.

Plasma concentrations of RBP4 did not differ between groups, and no statistically noticeable changes after periodontal therapy could be observed. However, a recent interventional case–control study reported decreasing serum concentrations of RBP4 at 12 weeks after non-surgical periodontal treatment in lean and obese patients (Martinez-Herrera et al., 2018). However, we could not confirm these results for our 27.5-months observation and treatment period.

It is important to note that the therapy groups receiving adjunctive antibiotics did not realize any additional benefits in terms of reduction of systemic inflammation-associated biomarkers compared with the therapy groups that received adjunctive placebo.

As expected, the overweight group showed remarkably higher plasma concentrations of triglycerides and lower HDL cholesterol compared with the normal-weight group. For the overweight group, this indicates a status of dyslipidemia, meaning that the elevated BMI in these patients is due to increased proportions of body fat. Furthermore, the dyslipidemia was also present in people who were overweight at the end of the investigation (Table S3). This constant lipid profile indicates that these patients obviously did not alter nutrition or body constitution over the course of the investigation.

At baseline, patients who were overweight showed similar clinical parameters compared with normal-weight patients except for the number of teeth. These results are in line with a relatively large cross-sectional study that found BMI inversely related to the number of natural teeth (Zhu & Hollis, 2015). Within our period of observation, both groups developed similar clinical improvements as result of systematic non-surgical periodontal therapy. The available evidence on the effect of obesity on response to periodontal therapy was reported to be inconsistent by the recent meta-review (Suvan et al., 2018). It is noteworthy that most of the original underlying studies were limited to between 2 and 9 months of observation and focused on PPD as an outcome parameter in relatively heterogeneous or small-sized samples.

Potential limitations of this study are due to the fact that its findings stem from a secondary, exploratory analysis of data from a randomized clinical trial which addressed a different research question. In particular, the restricted sample size of n = 40 per group and the relatively large sampling interval of 27.5 months should be considered. Thus, we cannot infer short-term developments. Prospective clinical trials that include sampling more often over the course of the study are needed to reveal the continuity of short-term and long-term effects. On the other hand, due to the lifelong character of periodontitis and the therefore lifelong need for therapy, biomarkers for periodontitis should be identified and evaluated in long-term studies.

This study adds long-term results of plasma levels of inflammation-associated biomarkers following non-surgical periodontal therapy in overweight and normal-weight patients to the available evidence. Our data indicate that periodontal therapy reduces elevated circulating inflammatory biomarkers and, thereby, the overall inflammatory burden in patients.

Periodontitis is a chronic disease, and only in rare cases is it combined with noticeable symptoms such as pain. Unfortunately, it takes often years or decades until patients become aware of the detrimental effects of periodontitis. Other chronic diseases that are associated with periodontitis are likewise imperceptible at the beginning. Monitoring inflammation-associated biomarkers could potentially help to identify patients with a high risk for comorbidities and quantify the impact of periodontal therapy on general health.

5 | CONCLUSION

This exploratory subanalysis of the prospective, randomized, double-blinded, parallel-group, and multi-centre ABPARO trial indicates that non-surgical periodontal therapy reduces ORM and hsCRP in both normal-weight and overweight patients and chemerin in patients who are overweight. Irrespective of BMI, patients with periodontitis benefit from periodontal therapy and develop similar clinical improvements. Positive long-term effects, for example decreased plasma levels of ORM and chemerin, seem to be more pronounced in patients who are overweight compared with normal-weight patients.

Non-surgical periodontal therapy may reduce the systemic inflammatory burden and might thereby retard the onset of potential inflammation-associated morbidities in overweight and normal-weight individuals. Ultimately, continuous periodontal treatment may support a health-oriented lifestyle and might contribute to improved general health.

ACKNOWLEDGEMENTS

We thank the members of the Center for Clinical Trials, Medical Faculty Münster, Germany, for supporting the trial: Sonja Baier, Trude Butterfaß-Bahloul, Jürgen Grebe, Kerstin Hovestadt, Heidi Oellers, Anita Ripkens-Reinhard, and Gudrun Würthwein. Last but not least, we are greatly indebted to the collaborators and staff members representing the ABPARO Group for their successful work on this project, as follows. Study Center, University Hospital Münster: Christina Elberg, Heike Frieling-Braithwaite, Anna-Maria Marx, Marie Christin Ohlmeier, Martin Sachs, and Thomas Weniger. University Hospital Berlin: Peter Purucker, Marta Czownicka, Kathleen Kraatz, Nicole Pischon, and Bernd-Michael Kleber. University Hospital Dresden: Gerlinde Bruhn, Ihssan Khallili, and Katrin Lorenz. Center for Dentistry and Oral Medicine Frankfurt: Bettina Dannewitz, Katrin Nickles, Lasse Röllke, Susanne Scharf, and Martin Wohlfeil. University Hospital Giessen: Heidi Fastnacht, Jose Roberto Gonzales, and Tomas Cabrera-Chica. University Medicine Greifswald: Jutta Dauss and Jutta Fanghänel. University Hospital Heidelberg: Raluca Cosgarea, Amelie Meyer-Bäumer, Nihad El Sayed, Sven Zehaczek, and Nils Zimmermann. University Hospital Würzburg: Markus Bechtold, Yvonne Jockel-Schneider, and Simone Veihelmann. Institute of Biostatistics and Clinical Research, Medical Faculty Muenster: Andreas Faldum, Joachim Gerß, and Achim Heinecke. Clinical Pharmacy, University Hospital Dresden: Ina-Maria Klut and Madeleine Schubert. Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Greifswald: Matthias Nauck, Astrid Petersmann, and Helma Preez. Data Monitoring and Safety Board: Guido Knapp, Gregor Petersilka, and Anne Sonntag.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in this study.

ORCID

Johannes Matern https://orcid.org/0000-0003-0679-5759
Peter Eickholz https://orcid.org/0000-0002-1655-8055
Jörg Meyle https://orcid.org/0000-0003-0495-6926
Benjamin Ehmke https://orcid.org/0000-0002-2418-6765

REFERENCES

Akram, Z., Safii, S. H., Vaithilingam, R. D., Baharuddin, N. A., Javed, F., & Vohra, F. (2016). Efficacy of non-surgical periodontal therapy in the management of chronic periodontitis among obese and non-obese patients: A systematic review and meta-analysis. *Clinical Oral Investigations*, *20*(5), 903–914.

Alfadda, A. A., Fatma, S., Chishti, M. A., Al-Naami, M. Y., Elawad, R., Mendoza, C. D. O., … Lee, Y. S. (2012). Orosomucoid serum concentrations and fat depot-specific mRNA and protein expression in humans. *Molecules and Cells*, *33*(1), 35–41.

Balli, U., Ongoz, D. F., Bozkurt, D. S., Gulsoy, Z., & Sertoglu, E. (2016). Chemerin and interleukin-6 levels in obese individuals following periodontal treatment. *Oral Diseases*, *22*(7), 673–680.

Benedek, I. H., Blouin, R., & McNamara, P. J. (1984). Serum protein binding and the role of increased alpha 1-acid glycoprotein in moderately obese male subjects. *British Journal of Clinical Pharmacology*, *18*(6), 941–946.

Bray, G. A., Jablonski, K. A., Fujimoto, W. Y., Barrett-Connor, E., Haffner, S., Hanson, R. L., … Pi-Sunyer, F. X. (2008). Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. *American Journal of Clinical Nutrition*, *87*(5), 1212–1218.

Chapple, I. L. C., Bouchard, P., Cagetti, M. G., Campus, G., Carra, M.-C., Cocco, F., … Schulte, A. G. (2017). Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: Consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. *Journal of Clinical Periodontology*, *44*(18 Suppl), 39S–51S.

Eickholz, P., Koch, R., Kocher, T., Hoffmann, T., Kim, T.-S., Meyle, J., … Ehmke, B. (2019). Clinical benefits of systemic amoxicillin/metronidazole may depend on periodontitis severity and patients' age: An exploratory sub-analysis of the ABPARO trial. *Journal of Clinical Periodontology*, *46*(4), 491–501.

Eickholz, P., Nickles, K., Koch, R., Harks, I., Hoffmann, T., Kim, T.-S., … Ehmke, B. (2016). Is furcation involvement affected by adjunctive systemic amoxicillin plus metronidazole? A clinical trials exploratory subanalysis. *Journal of Clinical Periodontology*, *43*(10), 839–848.

Endo, Y., Tomofuji, T., Ekuni, D., Irie, K., Azuma, T., Tamaki, N., … Morita, M. (2010). Experimental periodontitis induces gene expression of

proinflammatory cytokines in liver and white adipose tissues in obesity. *Journal of Periodontology*, *81*(4), 520–526.
Ferrari, M., Cuenca-García, M., Valtueña, J., Moreno, L. A., Censi, L., González-Gross, M., … Leclercq, C. (2014). Inflammation profile in overweight/obese adolescents in Europe: An analysis in relation to iron status. *European Journal of Clinical Nutrition*, *69*(2), 247–255.
Fournier, T., Medjoubi, N., & Porquet, D. (2000). Alpha-1-acid glycoprotein. *Biochimica Et Biophysica Acta (BBA) - Protein Structure and Molecular Enzymology*, *1482*(1–2), 157–171.
Gallagher, D., Visser, M., Sepúlveda, D., Pierson, R. N., Harris, T., & Heymsfield, S. B. (1996). How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *American Journal of Epidemiology*, *143*(3), 228–239.
Gerrits, A. J., Gitz, E., Koekman, C. A., Visseren, F. L., van Haeften, T. W., & Akkerman, J. W. N. (2012). Induction of insulin resistance by the adipokines resistin, leptin, plasminogen activator inhibitor-1 and retinol binding protein 4 in human megakaryocytes. *Haematologica*, *97*(8), 1149–1157.
Hagenfeld, D., Koch, R., Jünemann, S., Prior, K., Harks, I., Eickholz, P., … Harmsen, D. (2018). Do we treat our patients or rather periodontal microbes with adjunctive antibiotics in periodontal therapy? A 16S rDNA microbial community analysis. *PLoS ONE*, *13*(4), e0195534. https://doi.org/10.1371/journal.pone.0195534
Harks, I., Harmsen, D., Gravemeier, M., Prior, K., Koch, R., Doering, S., … Ehmke, B. (2014). A concept for clinical research triggered by suggestions from systematic reviews about adjunctive antibiotics. *Applied Clinical Research, Clinical Trials and Regulatory Affairs*, *1*(1), 43–50. https://doi.org/10.2174/2213476X01666140327211914
Harks, I., Koch, R., Eickholz, P., Hoffmann, T., Kim, T.-S., Kocher, T., … Ehmke, B. (2015). Is progression of periodontitis relevantly influenced by systemic antibiotics? A clinical randomized trial. *Journal of Clinical Periodontology*, *42*(9), 832–842.
Jentsch, H. F. R., Arnold, N., Richter, V., Deschner, J., Kantyka, T., & Eick, S. (2017). Salivary, gingival crevicular fluid and serum levels of ghrelin and chemerin in patients with periodontitis and overweight. *Journal of Periodontal Research*, *52*(6), 1050–1057.
Kanoriya, D., Pradeep, A. R., Mallika, A., Singhal, S., & Garg, V. (2017). Correlation of crevicular fluid and serum levels of retinol-binding protein 4 and leptin in chronic periodontitis and obesity. *Clinical Oral Investigations*, *21*(7), 2319–2325.
Kocher, T., Holtfreter, B., Petersmann, A., Eickholz, P., Hoffmann, T., Kaner, D., … Koch, R. (2019). Effect of periodontal treatment on HbA1c among patients with prediabetes. *Journal of Dental Research*, *98*(2), 171–179.
Kopelman, P. (2007). Health risks associated with overweight and obesity. *Obesity Reviews*, *8*(1 Suppl), 13S–17S.
Lang, N. P., Adler, R., Joss, A., & Nyman, S. (1990). Absence of bleeding on probing. An indicator of periodontal stability. *Journal of Clinical Periodontology*, *17*(10), 714–721.
Maghsoudi, Z., Kelishadi, R., & Hosseinzadeh-Attar, M. J. (2016). The comparison of chemerin, adiponectin and lipid profile indices in obese and non-obese adolescents. *Diabetology and Metabolic Syndrome*, *10*(2 Suppl), 43S–46S.
Marcaccini, A. M., Meschiari, C. A., Sorgi, C. A., Saraiva, M. C. P., de Souza, A. M., Faccioli, L. H., … Gerlach, R. F. (2009). Circulating interleukin-6 and high-sensitivity C-reactive protein decrease after periodontal therapy in otherwise healthy subjects. *Journal of Periodontology*, *80*(4), 594–602.
Martinez-Herrera, M., Silvestre, F. J., Silvestre-Rangil, J., López-Domènech, S., Bañuls, C., & Rocha, M. (2018). Levels of serum retinol-binding protein 4 before and after non-surgical periodontal treatment in lean and obese subjects: An interventional study. *Journal of Clinical Periodontology*, *45*(3), 336–344.
Maury, E., & Brichard, S. M. (2010). Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Molecular and Cellular Endocrinology*, *314*(1), 1–16.
Meisel, P., Eremenko, M., Holtfreter, B., Völzke, H., & Kocher, T. (2019). The sex paradox in the interplay between periodontitis, obesity, and serum C-reactive protein: Data from a general population. *Journal of Periodontology*, *90*(12), 1365–1373. https://doi.org/10.1002/JPER.18-0733
Meyle, J., & Chapple, I. (2015). Molecular aspects of the pathogenesis of periodontitis. *Periodontology 2000*, *69*(1), 7–17.
Offenbacher, S., Beck, J. D., Moss, K., Mendoza, L., Paquette, D. W., Barrow, D. A., … Genco, R. J. (2009). Results from the Periodontitis and Vascular Events (PAVE) Study: A pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. *Journal of Periodontology*, *80*(2), 190–201.
O'Leary, T. J., Drake, R. B., & Naylor, J. E. (1972). The plaque control record. *Journal of Periodontology*, *43*(1), 38.
Pinho, M. N., Oliveira, R. D., Novaes, A. B.Jr, & Voltarelli, J. C. (2009). Relationship between periodontitis and rheumatoid arthritis and the effect of non-surgical periodontal treatment. *Brazilian Dental Journal*, *20*(5), 355–364.
Rangé, H., Poitou, C., Boillot, A., Ciangura, C., Katsahian, S., Lacorte, J.-M., … Chaussain, C. (2013). Orosomucoid, a new biomarker in the association between obesity and periodontitis. *PLoS ONE*, *8*(3), e57645. https://doi.org/10.1371/journal.pone.0057645
Rourke, J. L., Dranse, H. J., & Sinal, C. J. (2013). Towards an integrative approach to understanding the role of chemerin in human health and disease. *Obesity Reviews*, *14*(3), 245–262.
Slade, G. D., Ghezzi, E. M., Heiss, G., Beck, J. D., Riche, E., & Offenbacher, S. (2003). Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities study. *Archives of Internal Medicine*, *163*(10), 1172–1179.
Sledzinski, T., Korczynska, J., Hallmann, A., Kaska, L., Proczko-Markuszewska, M., Stefaniak, T., … Swierczynski, J. (2013). The increase of serum chemerin concentration is mainly associated with the increase of body mass index in obese, non-diabetic subjects. *Journal of Endocrinological Investigation*, *36*(6), 428–434.
Suvan, J. E., Finer, N., & D'Aiuto, F. (2018). Periodontal complications with obesity. *Periodontology 2000*, *78*(1), 98–128.
WHO (2018). *Fact sheet obesity and overweight*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
Zhu, Y., & Hollis, J. H. (2015). Associations between the number of natural teeth and metabolic syndrome in adults. *Journal of Clinical Periodontology*, *42*(2), 113–120.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Matern J, Koch R, Petersmann A, et al. Effect of periodontal therapy on adipokine biomarkers in overweight. *J Clin Periodontol*. 2020;47:842–850. https://doi.org/10.1111/jcpe.13288