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Prolonged multimodal fasting modulates periodontal inflammation in female patients with metabolic syndrome: A prospective cohort study

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Abstract

Aim: To determine the potential anti-inflammatory effect of a multimodal periodic fasting programme on surrogate parameters of periodontal inflammation in hospitalized patients diagnosed for metabolic syndrome (MetS).

Material and methods: A total of 47 patients were recruited and hospitalized in an integrative ward for an intensified two-week multimodal fasting, diet and lifestyle programme. Patients were periodontally examined at baseline (t1), after the 2-week fasting protocol (t2) and, subsequently, 4 months after fasting (t3). The following parameters were determined: periodontal screening index (PSI), bleeding on probing (BOP), gingival crevicular fluid volume (GCF), plaque index (PI), C-reactive protein (CRP), blood pressure (BP), waist circumference (WC), fasting glucose (FGLU), triglycerides (TRG), high-density lipoprotein (HDL) and HbA1c.

Results: A total of 28 female and 8 male patients fulfilled the defined criteria for MetS and were analysed separately by gender. At t2, BOP and GCF were reduced when compared to t1 (median: t2 = 39; t1 = 33.1%; $p < .001$ and t2 = 73.9; t1 = 59.3 Periotron units $p = .02$, respectively). BOP reduction correlated to FGLU ($R = .37$, $p = .049$) and weight reduction ($R = .4$, $p = .04$).

Conclusion: This study showed for the first time that clinically supervised periodic fasting in female patients with MetS may facilitate the reduction of periodontal inflammation.

KEYWORDS
bleeding on probing, C-reactive protein, fasting, gingival crevicular fluid, metabolic syndrome, periodontal inflammation

1 | INTRODUCTION

The metabolic syndrome (MetS) is defined as a compilation of various diseases and conditions leading to a generalized metabolic dysregulation that is associated with, for example, hypertension, hyperlipidemia, obesity and insulin resistance (Grundy et al., 2004; Saklayen, 2018). This condition facilitates chronic inflammatory reactions and is associated with an increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (Grundy et al., 2005). Several definitions have been proposed, for example, by the World Health Organization (WHO, 1998), the Adult Treatment Panel (ATP3, 2001), the International Diabetes Federation (IDF, 2005), the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI, 2005) (Grundy et al., 2005). Depending on the definition, the global prevalence of MetS is highly variable among countries and regions, and ranges between 24.3% and 45.5% (Saklayen, 2018). From 2003 to 2012, the overall prevalence of MetS was 35.6% and 30.3% in women and men, respectively, in the US population (Aguilar et al., 2015). It is estimated that one in five adults in Germany suffers from a MetS (Moebus et al., 2008).

Patients with MetS exhibit elevated serum levels of pro-inflammatory mediators, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP), and, therewith, present an underlying pro-inflammatory status that cannot be independently treated (Bullo et al., 2003; Grundy et al., 2005; Ridker et al., 2003, 2004). Regarding the underlying pro-inflammatory status, similar mediators, such as IL-6, TNF-α and CRP, are also elevated in patients with severe periodontitis (Loos, 2005; Loos et al., 2000). It has been shown that CRP level correlated with the severity of periodontitis, and it can be reduced when periodontitis has been successfully treated (D'Aiuto et al., 2004, 2006, 2010; Tonetti et al., 2007; Moura Foz et al., 2010; Polak & Shapira, 2018).

A number of cross-sectional studies showed an association between MetS and periodontitis (Genco et al., 2005; Saito et al., 2005; D'Aiuto et al., 2008; Khader et al., 2008; Li et al., 2009; Watanabe & Cho, 2014; Keller et al., 2015). A bidirectional relationship between MetS, obesity and periodontitis has been suggested, and various mechanisms have been proposed (Jepsen et al., 2020). Periodontitis is an independent risk factor for cardiovascular disease, and both diseases exhibit shared genetic risk factors (Dietrich et al., 2008; Schaefer et al., 2009, 2015; Aarabi et al., 2017; Sanz et al., 2020). Diabetes mellitus (DM) and periodontitis show a bidirectional relationship (Preshaw et al., 2012). Patients with DM are at higher risk to develop periodontitis along with a faster progression rate and greater disease severity. This risk is even greater in patients with uncontrolled diabetes (Sanz et al., 2018). In addition, in patients with and without DM severe periodontitis negatively influences the blood sugar control (Graziani et al., 2018).

Fasting has been shown to exhibit positive effects on inflammatory processes throughout the human body by neuroendocrine activation, reduced signalling of insulin and mTor, enhanced cellular repair mechanisms and reduction of mitochondrial oxidative stress (Michalsen & Li, 2013). Therefore, it has been proposed that fasting may positively influence prevention and treatment of chronic inflammatory diseases (Michalsen & Li, 2013). In the context of MetS, first clinical studies demonstrated that prolonged (periodic) fasting may exert positive effects in patients with T2DM, obesity, hyperlipidaemia and arterial hypertension (Goldhamer et al., 2001; Papagiannopoulos et al., 2013; Stange et al., 2013; Li et al., 2013, 2017). So far, the potential influence of fasting on the periodontal inflammatory status is yet unknown.

Thus, the aim of the present study was to investigate the influence of a clinically controlled periodic fasting protocol on periodontal inflammation in patients diagnosed with MetS. We hypothesized that fasting does influence periodontal inflammation in patients with MetS. Immediate fasting effects were validated using bleeding on probing (BOP) as the primary outcome variable and change in Periotron® units (PU) as secondary outcome variable.

Clinical Relevance

Scientific rationale for study: The metabolic syndrome (MetS), characterized by the presence of obesity, hypertension, dyslipidaemia and dysglycaemia, significantly increases the risk of type 2 diabetes and cardiovascular disease for the affected patients. Therapeutic interventions may include fasting programmes that can help to reduce their systemic inflammatory status. An association between MetS and periodontitis is well established. However, at present it is not known whether fasting can also influence the status of periodontal inflammation.

Principal findings: This study indicated for the first time that a controlled fasting period may reduce periodontal inflammation (bleeding on probing) in MetS patients.

Clinical implications: The results suggest that controlled fasting in patients with metabolic syndrome has beneficial effects on periodontal inflammation and might thus be of therapeutic value for patients affected by both MetS and periodontitis.

2 | MATERIAL AND METHODS

2.1 | Study design

This study was designed as a prospective clinical trial in a cohort of patients with metabolic syndrome (MetS) and approved by the institutional ethical review board of the Charité—Universitätsmedizin Berlin (EA4/054/15). Each patient agreed to participate had signed an informed consent prior to fasting and dental examination. The study protocol is outlined in Figure 1.

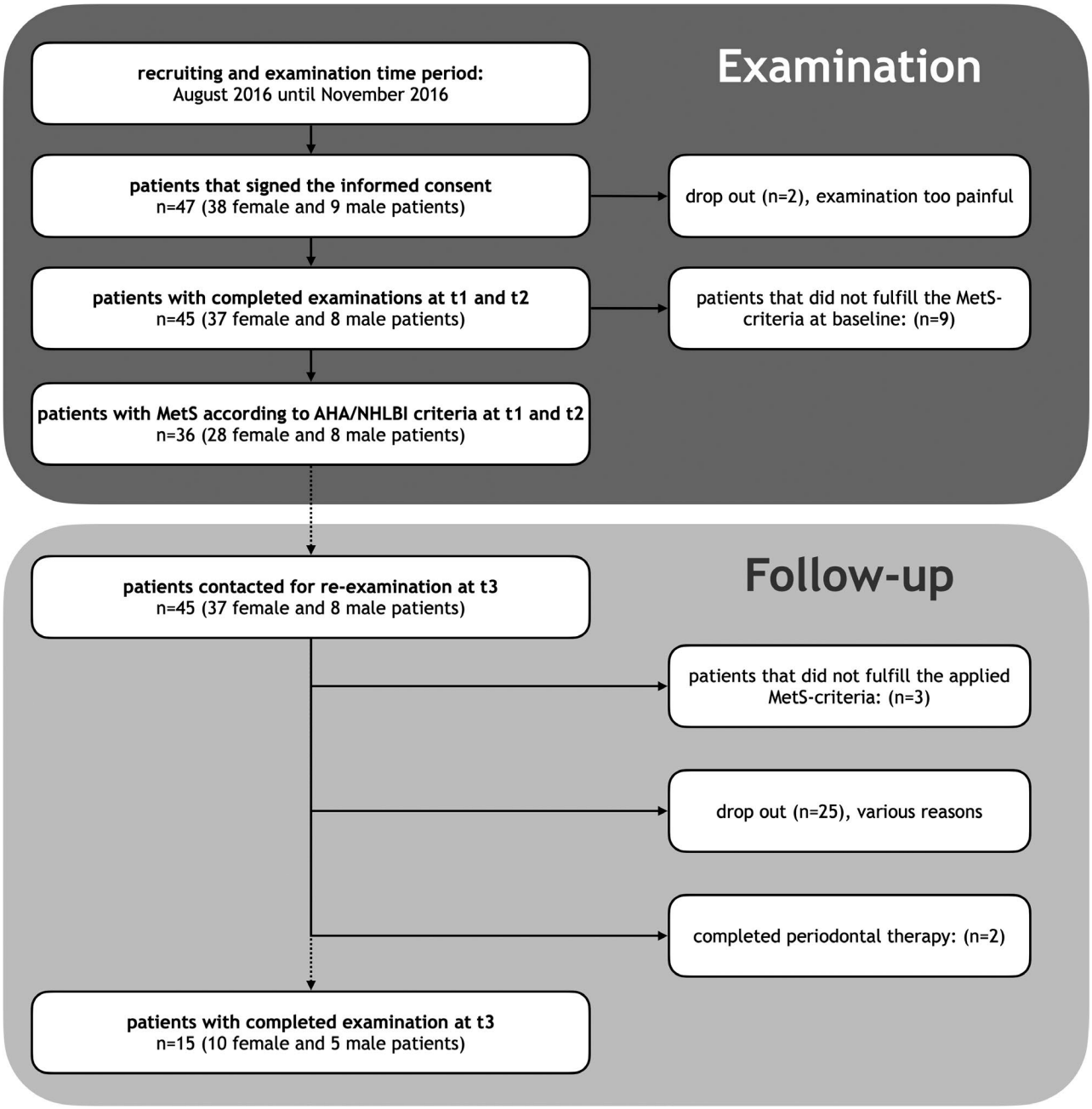

FIGURE 1 Flow chart of the number of included patients at t1 and t2 (examination phase), and t3 (follow-up) after correction for excluded patients and dropouts

2.2 | Study population

All patients were recruited in the Department of Clinic for General Medicine, Integrative Medicine, Institute for Social Medicine, Epidemiology, and Health Economics (Charité—Universitätsmedizin Berlin, Immanuel Hospital Berlin, Berlin, Germany) between August and November 2016 after being clinically diagnosed with MetS. The included patients were hospitalized for fasting intervention.

The inclusion criteria were as follows: age 18–80 years; diagnosis for MetS; planned therapeutic fasting therapy; non-smoker for at least two years; and signed informed consent.

The exclusion criteria were as follows: general medical conditions that do not allow fasting therapy; patients with the history of endocarditis; intake of antibiotics (minimum 4 months before); alcohol abuse; drug abuse; psychological disorders; eating disorder; dementia; pregnancy; and breast feeding.

The enrolled patients were examined for periodontal and metabolic parameters at baseline. When applying MetS criteria described by AHA/NHLBI (Grundy et al., 2005), the initial MetS diagnosis by clinicians needed re-evaluation in some cases. Due to gender-specific variations in fasting, immune response and fat distribution, data for females and males were separately analysed (Goschke et al., 1976; Ross et al., 1994; Giefing-Kroll et al., 2015).

2.3 | Fasting intervention

Patients diagnosed with MetS were hospitalized for a two-week multimodal Buchinger fasting programme. This therapeutic approach included a course of medically controlled fasting following the criteria proposed by Buchinger (Buchinger, 1979; Li et al., 2013). During fasting, patients prepared received specific nutrients, and the maximum daily calories were limited to 300–500 kcal/1256–2092 kJ. Fasting was continued for a minimum of 4 and a maximum of 10 days depending on the patient's general health and well-being. Further information is given in the electronic supplementary file.

Patient-reported outcomes (PROMs) related to fasting, such as headache, dizziness, fatigue, appetite or euphoria, were determined by medical interviewing and rated by the patients.

2.4 | Clinical examination

Each of the included patients received dental examination at three time points (t1 = baseline; t2 = immediately following fasting for measurement of primary outcome variables; and t3 = at four-month follow-up). The examination included the bleeding on probing (BOP) at 6 sites per tooth (Ainamo & Bay, 1975) (full-mouth bleeding scores (FMBS)) and periodontal screening index (PSI) (Meyle & Jepsen, 2000), plaque index (PI) (O'Leary et al., 1972) and measurement of the gingival crevicular fluid (GCF) in Periotron units (PU) collected from both interproximal areas of two upper premolars (Periotron© 8000; Oraflow Inc, Long Island, New York, USA). GCF samples were collected under dry conditions (using cotton rolls) from the mesial and distal aspect of both upper first premolars using PerioPaper® (Oralflow Inc) for 30 s. Subsequently, PUs were determined and mean values were calculated. Between measurements, the Periotron® instrument was cleaned using 70% ethanol, dried and calibrated using a dry PerioPaper® strip. Then, BOP was determined using a pressure calibrated periodontal probe (0.25 N; Kerr; Hawe Click-Probe© 3/6/9/12, 3/Art. No. 1390, Kerr GmbH, Biberach, Deutschland). Measurements were performed by a calibrated examiner (CP). Each patient was asked not to perform oral hygiene procedures 2 h prior to the dental examination.

Additionally, medical history, measurements of blood pressure (BP) and waist circumference (WC), and blood samples were taken at t1 and t2. Each patient was re-contacted for follow-up measurements at t3. The following blood parameters were determined: C-reactive protein (CRP), high-density lipoprotein (HDL), fasting glucose (FGLU), triglycerides (TRG) and HbA1c (t1). Body weight (BW) and the body mass index (BMI) were determined using the BF508 balance (Omron, Medical Technology, Hoofddorp, the Netherlands).

Patients did not receive oral hygiene instructions (OHI) or information regarding their dental and periodontal status at t1 and t2. It was crucial that oral hygiene procedures and behaviours did not change during the fasting period, and therewith to minimize a potential "Hawthorne effect" (bias). Following t2, patients received oral hygiene instructions, and their dental and periodontal status was explained. Periodontal therapy was recommended if appropriate.

Further information is given in the electronic supplementary file.

2.5 | Statistical analyses

The statistical analyses were performed using R (R Version 3.4.0 (2017-04-21), RStudio Inc. Version 1.0.143, The R Foundation for Statistical Computing, Wien, Austria). Prior to statistical evaluation, values in per cent (BOP, plaque) were arcSinus-transformed using Microsoft© Excel (Microsoft© Excel for Mac, Version 16.12 (180410), Microsoft Corporation, Redmond, USA). This was an explorative study analysing various parameters and research questions. Statistical tests were not adjusted for multiplicity. Therefore, given p-values should be descriptively interpreted. Wilcoxon's signed-rank test was used to compare the different time points (t1 vs. t2, as primary outcome). In order to evaluate changes in outcome parameters, a ratio was calculated dividing t1 and t2 (primary) as well as t1 and t3 values (follow-up). These ratios and parameters from all time points were used for Spearman's correlation analyses (R). A subgroup of the remaining patients at t3 was analysed using Wilcoxon's signed-rank test comparing t1 and t3. In case of missing data, no replacement was performed. In all tables, median and 25% (Q1)/75%(Q3) quartiles are given.

3 | RESULTS

3.1 | Population and drop-out analyses

A total of 47 patients (38 females, 9 males) had signed the informed consent for participation. Two patients (1 female, 1 male) dropped out as they felt uncomfortable with periodontal probing. Nine females did not fulfil the MetS criteria as proposed by AHA/NHLBI and were, therefore, excluded (Figure 1). A total of 36 patients (28 female and 8 male) with confirmed MetS were included and evaluated for metabolic and periodontal parameters before and after fasting. Twenty-three women depicted a BMI over 30, 26 were diagnosed with hypertension and 15 with T2DM. From those, 5 were under antidiabetic medication. Patients exhibited elevated glucose levels, elevated triglycerides levels and low HDL levels accordingly to the criteria. For the analysed population, demographic information as well as periodontal and MetS-related parameters are depicted in Table 1 and supplementary Table S2.

Each of the included patients was contacted for follow-up examination (t3). Five patients could not be contacted as they moved, 7 patients declined because of the far distance, 5 patients reported impaired general health preventing them from travelling, and 8 patients were not interested in any type of follow-up. Two patients needed to be excluded as they were systematically treated for periodontitis, and 3 women did not fulfil the initially applied criteria for MetS. At t3, 15 patients (10 female, 5 male) could be examined (Figure 1).

TABLE 1 Baseline values (t1) for female patients

	Females			
t1	***n* (%)**	**Median**	**Q1**	**Q3**
Age (years)	28 (100)	63	55.75	67.5
BW (kg)	28 (100)	89.8	78.58	114.28
WC (cm)	28 (100)	111	103.75	125.5
BMI	28 (100)	34.95	31.10	42.13
BMI ≥25	5 (18)			
BMI ≥30	23 (82)			
Non-smokers				
Lifelong	20 (71.4)			
>2 years	8 (28.6)			
BP (mmHg)				
Systolic	28 (100)	135	130	140
Diastolic		80	80	90
FGLU (mg/dl)	28 100	96.4	87.85	142.3
HbA1c (%)	28 (100)	5.9	5.28	6.33
TRG (mg/dl)	27 (96.4)	163.6	122.06	195.56
HDL level (mg/dl)	25 (89.3)	50.3	42.50	58
CRP (mg/l)	28 (100)	3.8	1.78	7.98
Number of teeth	28 (100)	22.5	17.50	26
PI (%)	28 (100)	69.2	54.09	82.97
PSI				
Code 3	6 (21)			
Code 4	22 (79)			
BOP (%)	28 (100)	39.01	32.02	51.41
GCF (Periotron units)	28 (100)	73.88	60.69	88.5

Abbreviations: BMI, body mass index; BOP, bleeding on probing; BP, blood pressure; BW, body weight; CRP, C-reactive protein; FGLU, fasting glucose; GCF, gingival crevicular fluid; HbA1c, percentage of glycated haemoglobin, HDL, high-density lipoprotein; PI, plaque index; PSI, periodontal screening index; TRG, triglycerides; WC, waist circumference.

TABLE 2 Differences between baseline (t1) and t2

	Females				
t1–t2	***n***	**(%)**	**Median**	**Q1**	**Q3**
Hospitalization (days)	28	(100)	14	13	15
Fasting period (days)	28	(100)	8	7	9
Juice fasting	20	(71.4)			
Gruel fasting	8	(28.6)			
	t1			**t2**	
	n	**(%)**		***n***	**(%)**
Hypertension (>130/85 mmHg)	26	(92.9)		7	(25)
Hypertension medication	24	(85.7)		20	(71.4)
BP medication reduced				13	(46.4)
Diabetes mellitus (anamnese)	15	(53.6)			
FGLU (>100 mg/dl)	13	(46.4)		3	(10.7)
Diabetes medication	5	(17.5)		1	(3.6)
TRG ≥150 mg/dl	17	(60.7)		4	(14.3)
Lipid medication	4	(14.3)		3	(10.7)
HDL level <50 mg/dl	10	(35.7)		16	(57.1)
MetS diagnose	28	(100)		15	(53.6)

Abbreviations: BP, blood pressure; FGLU, fasting glucose; HDL, high-density lipoprotein; MetS, metabolic syndrome; TRG, triglycerides.

In the following, data derived from female patients are presented, and descriptive data for men are shown in electronic supplementary files.

3.2 | Medical interventions, examinations and outcome

All females were hospitalized for the duration of 14 days. The median strict fasting period lasted 8 days (Q1 = 7- Q3 = 9) (Table 2). During that time, patients received nutritional advice and moderate physical therapy. Additionally, 25 females were psychologically supervised. After the first days of fasting, 4 females discontinued intake of antidiabetic and antihypertensive medication, while blood sugar was routinely controlled on a daily basis. During the fasting period, 13 female patients reduced the dosage and 4 stopped the intake of medication for BP control. For 1 patient, the statin medication could be discontinued. Twelve female patients received additional phytotherapeutics. Further, 17 women were substituted with vitamin D, and 4 women received high-dose i.v. vitamin C (250 ml 0.9% NaCl, 7.5 g ascorbic acid) three times every other day.

Following the fasting period (t2), patients showed a reduction in all metabolic parameters. (BW, BMI, WC, BP, FGLU, TRG and HDL, $p < .002$), whereas CRP level did not change over time (4.2–4.9 mg/L, $p = .178$). After fasting, the number of patients diagnosed with MetS dropped from 28 to 15. Detailed information is given in Tables 2 and 3, and supplementary Table S1.

At t3, 3 out of 10 patients were still under the same blood sugar control medication as corrected while fasting. Patients still exhibited a reduced BW and BMI, while BP, WC and HbA1c did not change compared with baseline (Table 4, supplementary Table S1).

At t1, CRP showed correlations with WC (Spearman's $R = .45$, $p = .015$), FGLU ($R = .42$, $p = .029$), HbA1c ($R = .48$, $p = .009$) and TRG ($R = .54$, $p = .008$; Table 5).

For male patients, data are displayed in supplementary Tables 3–5.

TABLE 3 Comparison of findings at t1 versus t2 in female patients

		t1			t2			
Females	***n***	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	***p*-value**
BW (kg)	28	89.8	78.58	114.28	86.9	75.1	108.7	<.001
BMI	28	34.9	31.1	42.13	33.6	29.53	40.13	<.001
WC (cm)	28	111	103.75	125.5	107	99.75	121	<.001
BP (mmHg)								<.001
Systolic	28	135	130	140	120	117.5	126.25	<.001
Diastolic	28	80	80	90	75	70	80	
FGLU (mg/dl)	26	99.1	90.1	142.3	76.6	68.95	86.50	<.001
TRG (mg/dl)	22	173.7	136.07	198.41	135.2	114.41	147.22	<.001
HDL (md/dl)	19	50.3	44.45	59.95	46.4	38.7	50.3	.002
CRP (mg/l)	26	4.2	2	8.13	4.9	2.83	8.15	.178
BOP (%)	28	39	32.02	51.41	33.1	22.2	43.98	<.001
GCF (PU)	28	73.9	60.69	88.5	59.3	40.38	76.31	.021
PI (%)	28	69.2	54.09	82.97	69.3	43.38	80.34	.446

Note: Statistical analyses were performed using the Wilcoxon signed-rank test.

Abbreviations: BMI, body mass index; BOP, bleeding on probing; BP, blood pressure; BW, body weight; CRP, C-reactive protein; FGLU, fasting glucose; GCF, gingival crevicular fluid; HDL, high-density lipoprotein; PI, plaque index; TRG, triglycerides; WC, waist circumference.

3.3 | Periodontal examinations and outcome

At baseline, PSI evaluation showed a code 3 in at least 2 sextants in 6 female patients and at least 1 sextant of code 4 in 22 females. In the group of female patients, BOP correlated with WC (R = .42, p = .025), and GCF correlated with the patient's age (R = .43, p = .023) at t1 (Table 5). The detailed comparison of t1 and t2 is depicted in Table 3. At t2, PI remained unchanged, BOP (39%–33.1%, p < .001) and GCF (73.9–59.3 PU, p = .021) were reduced when compared to t1. The relative reduction of BOP (Q-BOP) correlated with fasting time (R = .36, p = .062), baseline glucose (R = .37; p = .049) and weight reduction (R = .4, p = .04). A suggested correlation had been observed in HbA1c levels (R = .3, p = .131) (Table 5).

At t3, the number of teeth and PI remained unchanged. From 10 female patients, 6 presented maximal PSI code 3 and 4 patients a code 4. BOP and GCF were still reduced at t3 (37.2%–21.9%, p = .009 and 73.9 PU – 43.6 PU, p = .009, respectively). The relative reduction of BOP correlated with the relative reduction of WC (R = .71, p = .0027), dental visits or HbA1c reduction did not show an effect. A summary of all time points (t1, t2, t3) comparing data from t1 and t3 is given in Table 4 and supplement Table S1.

For male patients, data are displayed in the supplementary Tables 3–5.

3.4 | PROMs and adverse events

Generally, fasting was well tolerated and accepted. Symptoms that often go along with fasting were rated as irrelevant by all patients. One female patient with severe periodontal destruction (stage III, grade B periodontitis) experienced a periodontal abscess two days after study entry. Another female patient suffering from angina pectoris-like complaints was extensively medically examined, including electrocardiogram and precise blood sample analyses, but without results that pointed towards coronary heart disease.

4 | DISCUSSION

Periodontitis is a complex non-communicable chronic inflammatory disease affecting a significant percentage of the worldwide population, and it is considered as the 6th most common human disease (Kassebaum et al., 2014; Tonetti et al., 2017). Associations between periodontitis and systemic diseases, such as DM and cardiovascular diseases, are well known (Sanz et al., 2018, 2020). Patients presenting symptoms referring to the MetS also suffer from periodontitis more frequently (D'Aiuto et al., 2008; Li et al., 2009; Morita et al., 2010; Watanabe & Cho, 2014; Jepsen et al., 2020). Underlying the bidirectional relationship therapeutic interventions for either DM or periodontitis facilitate improvement of parameters for both diseases (D'Aiuto et al., 2018; Sanz et al., 2018). To date, it is unknown whether periodic fasting as a form of severe caloric restriction and a promising therapeutic intervention also affects periodontal inflammation in patients with MetS. In this context, calorie restriction was found to be effective to facilitate T2DM disease remission (Lean et al., 2018). Thus, we aimed to periodontally examine patients with MetS prior to fasting, immediately after fasting and at a follow-up time point 4 months later. Patients did not receive OHI or periodontal intervention before or while fasting. It was crucial to determine whether there is a sole effect of fasting on periodontal inflammation. In general, an anti-inflammatory and metabolic effect has been described for patients when fasting (Michalsen & Li, 2013). As patients were

TABLE 4 Comparison of findings at t1 and t3 in female patients

	t1			t2			t3			t1 vs t3
Females	***n***	**Median**	**Q1**	**Q3**	***n***	**Median**	**Q1**	**Q3**	***n***	**Median**	**Q1**	**Q3**	***p*-value**
BW (kg)	10	89.7	81.92	96.88		86.3	77.78	93.62		86.7	77.4	97.25	.027
BMI	10	33.8	33.48	38.92		32.6	31.7	37.52		33	31.4	38.38	.027
WC (cm)	10	108	104.5	121.2		104.5	101.2	116.8		105	103.2	118	.052
BP (mmHg)											129	147.5	.646
Systolic	10	135	130	140		120	120	128		146	78.5	94.5	.082
Diastolic	10	80	80	87.5		77.5	70	80		85.5			
HbA1c (%)	10	5.3	5.1	5.6						5.6	5.43	5.85	.056
TRG (mg/dl)	9	162.8	130.4	193.4		124.3	107.19	140.88		227	164	270	.055
HDL (md/dl)	8	54.1	50.3	70.58		46.4	38.7	53.15		59.5	48.5	71.5	1.000
CRP (mg/l)	10	2.5	1.08	6.7		2.8	1.5	6.9		1.7	1	4.35	.183
BOP (%)	10	37.2	30.61	47.28		30.2	21.84	44.95		21.9	20.93	34.65	.009
GCF (PU)	10	73.9	68.81	84.81		65.4	43.31	79.69		43.6	36.75	58	.009
PI (%)	10	78.7	57.78	87.29		61.8	42.29	80.76		57.9	52.28	84.79	.108
Number of teeth	10	26	20	28		26	20	28		26	20	28	
PSI (*n*)													
Code 3	1				1				6				.025
Code 4	9				9				4				.025

Note: Statistical analyses were performed using the Wilcoxon signed-rank test.

Abbreviations: BMI, body mass index; BOP, bleeding on probing; BP, blood pressure; BW, body weight; CRP, C-reactive protein; FGLU, fasting glucose; GCF, gingival crevicular fluid; HDL, high-density lipoprotein; PI, plaque index; PSI, periodontal screening index; TRG, triglycerides; WC, waist circumference.

hospitalized for a multimodal fasting and lifestyle programme, it was critical to choose reproducible parameters that can be determined at bedside, and therefore, BOP was considered as primary and GCF as secondary outcome parameters, and the periodontal screening index was chosen to screen for periodontal diseases. Similarly, it was crucial to precise and define for MetS. Variations in the prevalence of Mets have been described when applying different definitions as proposed by the IDF and compared to NCEP-ATP III. Thus, the AHA/NHBLI definition was chosen because values for the prevalence of MetS were rather intermediate (Guize et al., 2008). The high number of excluded patients—after applying the criteria—shows the difficulty using them in daily practice.

In this study, PSI code 3 or code 4 was detected in all included patients indicating moderate to severe periodontal inflammation in each examined female patient with MetS. Immediately after the fasting period, a reduction of BOP and GCF was observed, while the oral hygiene procedures and behaviours remained unchanged (measured by PI evaluation). In addition, parameters relevant in the context of MetS, such as BW, BP, FGLU, TRG and HDL, were reduced upon fasting. Together with the reduction of BW, the WC was also reduced. WC partly reflects the amount of visceral fat that plays a crucial role in patients with MetS (Chan et al., 2003). Within the visceral fat, a number of different cytokines and adipokines are synthesized that affect the CRP production in the liver (Bullo et al., 2003). An increase in WC and BMI is associated with systemic inflammation (Gonzalez et al., 2006; Unno et al., 2012). In relation to periodontitis, analyses from the 3rd National Health and Nutrition Examination (NHANES) revealed an association between increased BMI as well as hip-waist-ratio and periodontal attachment loss, increased pocket probing depth and gingival bleeding (Wood et al., 2003). These findings were also reflected elsewhere (Chaffee & Weston, 2010; Haffajee & Socransky, 2009). In the present study, BOP and WC showed an association which is in concert with earlier reports (D'Aiuto et al., 2008; Munoz-Torres et al., 2014). In contrast, the parameters BOP and BMI were not associated in this study, which may, however, be an age-related effect in the presented cohort (Al-Zahrani et al., 2003). Furthermore, it is conceivable that changes in nutrition will eventually alter the immune response and/or homeostasis (Steckhan et al., 2016; Chapple et al., 2017; Dommisch et al., 2018). Thus, it may be assumed that the systemic effects of periodic fasting also lead to changes in the periodontal inflammatory response, which could be demonstrated in the present study. In our cohort, the PI remained unchanged throughout the study period. Without intervention to remove/reduce the amount of biofilm, BOP levels should remain unchanged accordingly (Morrison et al., 1980; Tonetti et al., 2015). However, not only BOP but also GCF levels were reduced following the fasting period. The correlation between the level of gingival inflammation as well as plaque accumulation and the volume of GCF has been extensively proven by experimental gingivitis studies (Loe et al., 1965; Dommisch et al., 2015, 2019).

TABLE 5 Correlation analyses at t1, the comparison of t1 and t2, and the comparison of t1 and t3

t1	Spearman's	*R*	*p*-value
BOP	WC	.42	.025
	BW	.37	.055
	BMI	.35	.071
	PI	.36	.061
GCF	CRP	.12	.545
	TRG	.33	.137
	HDL	.13	.600
	Age	.43	.023
CRP	BMI	.35	.067
	BW	.30	.126
	WC	.45	.015
	FGLU	.42	.029
	HbA1c	.48	.009
	TRG	.54	.008
t1 vs t2		***R***	***p*-value**
Q-BOP	Fasting period	.36	.062
	HbA1c at t1	.30	.131
	FGLU at t1	.37	.049
	Q-FGLU	.38	.054
	Q-BW	.40	.04
	Q-WC	−.24	.23
	Vitamin C	.15	.44
t1 vs t3		***R***	***p*-value**
Q-BOP	Q-HbA1c	.30	.403
	Q-WC	.71	.027
	Dental treatment	.19	.599

Note: Statistical analyses were performed using Spearman's correlation (R).
Abbreviations: BMI, body mass index; BOP, bleeding on probing; BP, blood pressure; BW, body weight; CRP, C-reactive protein; FGLU, fasting glucose; GCF, gingival crevicular fluid; HDL, high-density lipoprotein; PI, plaque index; Q, quotient as the ratio of t1/t2 and t1/t3, respectively; TRG, triglycerides; WC, waist circumference.
See supplementary Table S1.

There are several potential mechanisms by which MetS increases the risk of periodontal inflammation (Jepsen et al., 2020) as it has been shown in the investigated cohort. In obese patients, adipose tissues exhibit an increased production of pro-inflammatory adipokines (Krysiak et al., 2012; Adamczak & Wiecek, 2013), which contribute to increased protease secretion and bone resorption relevant to the periodontium (Garlet, 2010; Taylor, 2010). In this context, the impact of bariatric surgery and its effect on periodontal inflammation have been discussed (Maria de Souza et al., 2018).

Several limitations of our study have to be considered. MetS is reflected by a variable combination of different diseases and conditions, and therefore, the presented cohort is by definition highly heterogeneous (Grundy et al., 2004; Saklayen, 2018). To increase comparability, the criteria proposed by AHA/NHLBI were considered (Grundy et al., 2005), and patients who did not fulfil these criteria were excluded from further analyses. During the fasting period, all patients were hospitalized which was an important advantage of this cohort study because compliance with the intervention can be well controlled. At the same time, however, hospitalization introduced a limitation to the sample size of our population, and MetS inclusion criteria allowed analysis of female patients only. During clinical examination and measurements, blood sample analysis exhibited some inconsistency due to individual analytical and medical needs. Therefore, there were several missing values in the follow-up blood sample analysis. Furthermore, from the initial cohort, only 15 patients could be included in the follow-up analysis (t3). This additional examination time point was intended to identify potential long-term effects of the 4- to 10-day fasting period. However, only a low number of patients could be recruited for re-examination, which hindered identification of significant changes in primary or secondary variables. Thus, results need to be interpreted with caution and rated as trends. Also, this investigation was designed as a prospective cohort study without a control group. This aspect should be considered in future studies with a higher number of patients. Besides fasting, patients also received some additional therapies according to the concept of the applied integrative fasting concept. Thus, the observed effects might be due not only to the pure fasting intervention.

In conclusion, this study showed, for the first time, a beneficial effect of a defined clinically controlled periodic fasting programme on periodontal inflammation in female patients with MetS. Periodontal inflammation as determined by BOP and GCF measurements was correlated to parameters relevant for patients with MetS. Clinically controlled fasting led not only to the expected reduction of BW, BMI, WC BP, FGLU, TRG and HDL but also to a reduction of BOP and GCF levels, while the PI remained unaffected throughout the study. Within the limitations of this study, it may be proposed that fasting should be considered as an adjunctive intervention to conventional periodontal treatment regimens in obese patients. There may also be potential for fasting as an additional tool during primary and secondary prevention of periodontal inflammation. Future randomized trials in patients with both MetS and periodontal disease are warranted.

CONFLICT OF INTEREST AND SOURCE OF FUNDING STATEMENT

The authors declare that they have no conflict of interest.

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AUTHOR CONTRIBUTIONS

C. L. Pappe contributed to study conception, clinical periodontal examination, statistical evaluation and data interpretation, and critical reading of the manuscript; N. Steckhan contributed to clinical medical examination, fasting intervention, data interpretation, critical reading of the manuscript; D. Hoedke contributed to statistical evaluation and data interpretation, and critical reading of the manuscript; S. Jepsen contributed to data interpretation and critical reading of the manuscript; G. Rauch contributed to statistical analyses, data interpretation and critical reading of the manuscript; T. Keller contributed to statistical analyses, data interpretation, and critical reading of the manuscript; A. Michalsen contributed to study design and conception, coordination of the fasting protocol, funding, data interpretation and critical reading of the manuscript; and H. Dommisch* contributed to study design and conception, coordination of clinical examinations, funding, data interpretation, and writing of the manuscript.

DATA AVAILABILITY STATEMENT

Data are available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

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

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