Received: 4 March 2022 | Revised: 26 April 2022 | Accepted: 6 May 2022

DOI: 10.1111/jcpe.13649

ORIGINAL ARTICLE

Journal of Clinical Periodontology WILEY

Association between bone turnover markers and periodontitis: A population-based cross-sectional study

Stefan Lars Reckelkamm[1] | Anke Hannemann[2,3] | Thomas Kocher[4] | Matthias Nauck[2,3] | Henry Völzke[5] | Benjamin Ehmke[6] | Martina Rauner[7] | Zoheir Alayash[1] | Sebastian-Edgar Baumeister[1] | Michael Nolde[1] | Birte Holtfreter[4]

[1]Institute of Health Services Research in Dentistry, University of Münster, Münster, Germany

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

[3]DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine Greifswald, Greifswald, Germany

[4]Department of Restorative Dentistry, Periodontology, Endodontology, and Preventive and Pediatric Dentistry, University Medicine Greifswald, Greifswald, Germany

[5]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

[6]Clinic for Periodontology and Conservative Dentistry, University of Münster, Münster, Germany

[7]Department of Medicine III and Center for Healthy Aging, Technical University of Dresden, Dresden, Germany

Correspondence
Stefan Lars Reckelkamm, Institute of Health Services Research in Dentistry, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany.
Email: reckelkamm@uni-muenster.de

Abstract

Aim: To examine the associations between bone turnover markers and periodontitis in two cross-sectional population-based studies.

Materials and Methods: We used data from two independent adult samples ($N = 4993$), collected within the Study of Health in Pomerania project, to analyse cross-sectional associations of N-procollagen type 1 amino-terminal propeptide (P1NP), C-terminal cross-linking telopeptide, osteocalcin, bone-specific alkaline phosphatase (BAP), fibroblast growth factor 23, wingless-type mouse mammary tumour virus integration site family member 5a (WNT5A), and sclerostin values with periodontitis. Confounder-adjusted gamma and fractional response regression models were applied.

Results: Positive associations were found for P1NP with mean pocket probing depth (PPD; $e^{\beta} = 1.008$; 95% confidence interval [CI]: 1.001–1.015), mean clinical attachment loss (mean CAL; $e^{\beta} = 1.027$; 95% CI: 1.011–1.044), and proportion of sites with bleeding on probing (%BOP; $e^{\beta} = 1.055$; 95% CI: 1.005–1.109). Similar associations were seen for BAP with %BOP ($e^{\beta} = 1.121$; 95% CI: 1.042–1.205), proportion of sites with PPD ≥4 mm (%PPD4) ($e^{\beta} = 1.080$; 95% CI: 1.005–1.161), and sclerostin with %BOP ($e^{\beta} = 1.308$; 95% CI: 1.005–1.704). WNT5A was inversely associated with mean PPD ($e^{\beta} = 0.956$; 95% CI: 0.920–0.993) and %PPD4 ($e^{\beta} = 0.794$; 95% CI: 0.642–0.982).

Conclusions: This study revealed scattered associations of P1NP, BAP, WNT5A, and sclerostin with periodontitis, but the results are contradictory in the overall context. Associations reported in previous studies could not be confirmed.

KEYWORDS
bone remodelling, bone turnover marker, periodontitis, serum markers, Study of Health in Pomerania

Michael Nolde and Birte Holtfreter contributed equally to this study.

Clinical Relevance

Scientific rationale for study: Previous studies have not been conclusive regarding the association between bone turnover markers (BTMs) and periodontitis.

Principal findings: We found scattered associations of periodontitis markers with N-procollagen type 1 amino-terminal propeptide, bone-specific alkaline phosphatase, wingless-type mouse mammal tumour virus integration site family member 5a, and sclerostin. However, the most commonly used marker for bone resorption (C-terminal cross-linking telopeptide) did not reveal any association.

Practical implications: Altered serum BTM levels may be associated with progressive deterioration of the periodontium. However, the markers most commonly used appear unsuitable in a cross-sectional context.

1 | INTRODUCTION

Periodontitis is a chronic multifactorial disease characterized by a host-mediated inflammation of the periodontium, which is associated with dysbiotic plaque biofilms. It affects around 50% of the adult population, with 10% suffering from severe periodontitis, and its clinical appearance is marked by a loss of periodontal tissue (Papapanou et al., 2018; Bernabé et al., 2020). Although plaque is necessary, its mere presence is not sufficient for the disease to occur. The susceptibility to periodontitis is related to several risk factors (Meyle & Chapple, 2015), including conditions modulating bone homeostasis such as osteoporosis (Kinane, 2001; Bouchard et al., 2017). Osteoporosis, one of the most common metabolic bone disorders (Shetty et al., 2016), arises from an imbalance between bone-building and bone-degrading processes and is associated with a decrease in the total bone mass (Payne et al., 2011). Bone loss in the context of chronic inflammatory or degenerative conditions is accompanied by alterations in biomarkers in the surrounding tissue and blood because the resorption process releases peptides into the surrounding area, which are normally embedded in the bone matrix (Funck-Brentano et al., 2011; Payne et al., 2011). Markers associated with metabolizing or restructuring of bone are summarized under the term "bone turnover markers" (BTMs). An increase in many of these metabolites is associated with faster cortical and trabecular bone loss in men and women (Marques et al., 2016). Decreased bone stiffness, in turn, is associated with greater periodontal damage (Silveira et al., 2016).

Elevated levels of BTMs in the gingival crevicular fluid and saliva of individuals with periodontitis have already been described (Miricescu et al., 2014; Gursoy et al., 2016; Betsy et al., 2019). Local effects aside, recent findings show that periodontal bacteria-induced systemic interleukin (IL)-6 release can also systemically boost osteoclastogenesis and thus influence bone resorption throughout the body (Hajishengallis & Chavakis, 2021), making a bidirectional relationship between BTMs and periodontitis plausible.

Altered BTM levels could indicate both a general reduction in total bone mass that damages the periodontium and a systemic consequence of periodontitis releasing metabolites and bacteria in the circulation. Few studies have examined serum BTM levels in relation to periodontal status in population-based data. Furthermore, the majority of available studies on the relationship between BTMs and periodontal markers are limited to post-menopausal women, while only few studies have been conducted in men (Payne et al., 2011; Yoshihara et al., 2011; Schulze-Späte et al., 2015).

We investigated cross-sectional associations of N-procollagen type 1 amino-terminal propeptide (P1NP), C-terminal cross-linking telopeptide (CTX), osteocalcin, bone-specific alkaline phosphatase (BAP), fibroblast growth factor 23 (FGF23), wingless-type mouse mammal tumour virus integration site family member 5a (WNT5A), and sclerostin values with periodontitis parameters in two large population-based studies involving adult men and women after adjusting for relevant confounding factors.

2 | MATERIALS AND METHODS

2.1 | Study population

The present study is based on data from two independent studies from the Study of Health in Pomerania (SHIP) project conducted in a region in north-eastern Germany (Völzke et al., 2022). In the first study, a sample of 6265 eligible individuals (20–79 years) was drawn from local population registries, and 4308 participated in the baseline examination between 1997 and 2001 (SHIP-START-0; response of 69%). A second examination cycle (SHIP-START-1) was conducted between 2002 and 2006 and comprised 3300 participants (1711 women). A second independent study (SHIP-TREND-0) was conducted between 2008 and 2012. A stratified random sample of 8826 men and women, aged 20–79 years, was selected from the same catchment area as SHIP-START. In total, 4420 individuals participated (2272 women) in SHIP-TREND-0 (response of 50.1%).

For the present cross-sectional analyses, we pooled data from SHIP-START-1 and SHIP-TREND-0. After exclusions (see Section 2.1.2 and Figure S1 for a detailed description), the analytical samples ranged from 138 to 4993 subjects. All participants gave written informed consent, and both studies followed the recommendations of the Declaration of Helsinki and were approved by the Ethics Committee of the University of Greifswald. The study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of

Observational Studies in Epidemiology) guidelines (Vandenbroucke et al., 2007).

2.1.1 | Periodontal examination

The periodontal assessment included clinical attachment loss (CAL), pocket probing depth (PPD), and bleeding on probing (BOP). The periodontal examination was performed on either the left-side or the right-side quadrants. The examination side was changed from individual to individual (SHIP-START-1) or randomly selected (SHIP-TREND-0). All fully erupted teeth were assessed, excluding the third molars. CAL and PPD were assessed with a periodontal probe (SHIP-START-1: PCP 11, SHIP-TREND-0: PCPUNC 15, Hu-Friedy, Chicago, IL) at the mesio-buccal, disto-buccal, mid-buccal, and mid-lingual aspect on each selected tooth. We applied a mathematical correction for differences between the two probes (Holtfreter et al., 2012). CAL is represented by the distance from the cemento-enamel junction to the bottom and PPD by the distance from the gingival margin to the bottom of the periodontal pocket. Measurements were recorded as whole millimetres. BOP was recorded at four identical sites on the first incisor, the canine, and the first molar in each probed quadrant. If teeth were missing, the next distally located tooth was assessed. The percentage of bleeding sites was determined.

Dental examinations were performed by six and five calibrated and licensed dentists in SHIP-START-1 and SHIP-TREND-0, respectively. In SHIP-START-1, intra-rater correlations of 0.70–0.89 per examiner and an inter-rater correlation of 0.90 for CAL measurements were achieved. For PPD measurements, intra-rater correlations ranged between 0.43 and 0.82 per examiner and pairwise inter-rater correlations ranged between 0.41 and 0.78. In SHIP-TREND-0, intra-rater correlations for CAL measurements ranged between 0.67 and 0.89 and inter-rater correlation was 0.70. For PPD measurements, the examiners yielded intra-rater correlations between 0.68 and 0.88 and an inter-rater correlation of 0.72.

We not only calculated the mean CAL and mean PPD, but also considered the proportion of sites with BOP (%BOP), PPD ≥ 4 mm (%PPD4), PPD ≥ 6 mm (%PPD6), and CAL ≥ 4 mm (%CAL4) (Caton et al., 2018).

2.1.2 | Bone turnover markers

Venous blood samples were taken from the cubital vein in supine position. Serum and plasma samples were stored at −80°C in the Integrated Research Biobank of the University Medicine Greifswald and used in accordance with its regulations (Winter et al., 2020). Serum CTX, P1NP, osteocalcin, and BAP were measured on the IDS-iSYS Multi-Discipline Automated Analyser (Immunodiagnostic Systems Limited, Frankfurt am Main, Germany). CTX and P1NP were determined in all subjects of both studies. Osteocalcin was determined in the entire SHIP-START-1 cohort and the first 1000 subjects of SHIP-TREND-0 who underwent an oral glucose tolerance test (OGTT). BAP was measured exclusively in SHIP-START-1.

FGF23 was determined in EDTA plasma with the HUMAN FGF-23 (C-Term) enzyme-linked immunosorbent assay (ELISA; Immuntopicy, Inc. San Clemente, CA) in the first 1000 participants of SHIP-TREND-1 who underwent an OGTT. WNT5A was measured using a sandwich ELISA kit (Uscn Life Science Inc, Wuhan, China) in a specifically selected subgroup (matched healthy control group to cases of osteo or rheumatoid arthritis). Sclerostin was measured in serum using an immunoassay (Biomedica Medizinprodukte GmbH & Co KG, Wien, Austria) in a matched healthy control group (to patients receiving glucocorticoids for treatment of rheumatoid arthritis or polymyalgia rheumatic).

2.1.3 | Drugs modulating bone metabolism

Medication was categorized using the Anatomical Therapeutic Chemical Classification System (ATC) code. Bisphosphonates (ATC M05BA and M05BB), selective oestrogen receptor modulators (ATC G03XC), parathyroid hormone (ATC H05AA), strontium ranelate (ATC M05BX03), calcium (ATC A12A), vitamin D (ATC A11CC), and corticosteroids (ATC H02AB and H02BX) were defined as drugs that modulate bone metabolism (Silveira et al., 2016). Subjects reporting the intake of at least one of these medications were excluded from the analytical sample.

2.2 | Confounders

We applied the modified disjunctive cause criterion to select covariates, assuming that direct causes of the exposure or outcome, excluding possible instrumental variables, would identify a sufficient set of confounders (VanderWeele et al., 2021). We controlled our multivariable regression models for several covariates that were assumed to induce a change in BTMs or cause periodontitis (Burch et al., 2014; Natto et al., 2018). The confounding variables included age, sex, school education, body mass index (BMI), smoking status, alcohol consumption, and glycated haemoglobin (HbA1c). School education was categorized as >10, 10, and <10 years. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). Smoking was grouped into never, former, or current smoking. Average alcohol consumption was assessed with a beverage-specific quantity–frequency measure and was calculated by multiplying the frequency and amount of alcohol from beer, wine, and spirits on a usual day over the last 30 days, using beverage-specific pure ethanol volume content (Baumeister et al., 2018). HbA1c was determined by high-performance liquid chromatography (Diamat, Bio-Rad Laboratories, Munich, Germany). Regression models further included a binary dummy covariate for each participant's membership in each substudy, thereby accounting for additional inter-study differences including differences in periodontal marker definitions.

2.3 | Statistical analysis

The associations of BTMs with mean CAL and mean PPD were examined using multivariable generalized linear models with gamma distribution family and log link, considering the skewness of the distributions. The gamma regression coefficients were exponentiated (i.e., e^{β}) and interpreted as a percent change of the outcome (Manning et al., 2005). Fractional response logit models were used to analyse the association of BTMs with %BOP, %PPD4, and %CAL4, as these variables were restricted to a unit interval between 0 and 1 (Papke & Wooldridge, 1996). Fractional response models are used when the outcome distribution falls between 0 and 1 and a non-zero probability prevails for the border values. Continuous covariates were modelled using restricted cubic splines with three knots at fixed quantiles (0.1, 0.5 and 0.9) of the distribution. A test of non-linearity was conducted by testing the coefficient of the second spline transformation (Harrell, 2015). After confirming that the linearity assumption was met by testing cubic spline transformations, effect estimates for BTMs were reported as increment per SD for easy comparability between exposures. We investigated multiplicative effect modification by testing interaction terms between BTMs and sex and BTMs and menopausal status (the latter in women only).

We performed a sensitivity analysis to investigate the robustness to sample attrition from SHIP-START-0 to SHIP-START-1 and tested the possibility of the missing-completely-at random assumption underlying our primary models. Because baseline oral health measures were inversely associated with participation in SHIP-START-1, we performed a multivariable logistic model to estimate the probability of participating in the SHIP-START-1 analytical samples. The inverses of these probabilities were used as weights in weighted gamma and fractional response regression models (Seaman & White, 2013). We performed the analysis using R version 4.0.5 (R Foundation for Statistical Computing) using the *stats* (4.0.5), *rms* (6.2-0), and *sandwich* (3.0-1) packages.

3 | RESULTS

Combining both studies resulted in a total of 7720 individuals. The sample characteristics and sizes for each BTM are provided in Table 1. Study participants were excluded from the analytical sample because dental data were missing (due to edentulism, medical contraindication to the examination, or refusal [1341]) or because they reported intake of bone-modulating drugs (1086). The analytical sample for P1NP had a mean (SD) age of 48.8 (14.2) years, included 52% male subjects, and had a prevalence for known diabetes of 8.5%.

Overall, results were inconsistent regarding the effect of BTMs on periodontitis, highlighting only few occasional significant associations (Table 2). We found evidence for positive associations of P1NP with mean CAL, %CAL4, and mean PPD; BAP with %BOP and % PPD4; and sclerostin with %BOP, after adjustment for age, sex, school education, BMI, smoking status, alcohol consumption, and HbA1c. Also, evidence for an inverse association of WNT5A with mean PPD and %PPD4 was found. For example, a 1 SD increment in P1NP was associated with a 0.8% increase in mean PPD ($e^{\beta} = 1.008$; 95% confidence interval [CI]: 1.001–1.015), and an increase of WNT5A by 1 SD was associated with a 4.4% decrease in mean PPD ($e^{\beta} = 0.956$; 95% CI: 0.920–0.993).

In line, investigations of BTMs as outcomes revealed only sporadic significant associations (Table 3). Higher mean PPD was associated with lower levels of WNT5A; higher %PPD4 and %BOP were accompanied by increased BAP; and, additionally, higher %BOP was associated with an increment in P1NP. For example, a 1-mm increment in mean PPD was associated with a 14% lower WNT5A value ($e^{\beta} = 0.859$; 95% CI: 0.753–0.984). A 100% increment in BOP was associated with an increase of P1NP by 5.5% ($e^{\beta} = 1.055$; 95% CI: 1.005–1.109).

Examination of remaining combinations of BTM levels and periodontitis markers did not reveal any further relationships.

We tested whether sex modified the association between BTMs and periodontal parameters, and found *p*-values for interaction to range from .05 to .89. An analysis stratified by sex is provided in Tables S4–S7, revealing a possible gender specificity of the markers BAP and P1NP. Furthermore, we tested for an effect modification of the BTM–periodontitis relationship by menopausal status (in women only) and obtained *p*-values in the range .08–.83.

Additional application of weighted models using inverse probability weighting (not shown here) as sensitivity analysis did not lead to any substantial change in the results. In contrast, using an alternative threshold of %PPD ≥6 mm as a periodontitis outcome revealed an inverse association with CTX ($e^{\beta} = 0.892$; 95% CI: 0.807–0.987) and a positive association with sclerostin ($e^{\beta} = 1.784$; 95% CI: 1.003–3.175).

4 | DISCUSSION

We examined several biomarkers that are used to assess bone turnover and found scattered associations of P1NP, BAP, WNT5A, and sclerostin with markers reflecting periodontal burden. Yet, for CTX, the most commonly used reference marker of bone resorption (Vasikaran et al., 2011), our study was unable to reveal solid associations.

In accordance with our results, a study of 1107 older men (65 years and above) did not find any differences in serum concentrations of CTX and P1NP in relation to periodontal severity (Schulze-Späte et al., 2015). For P1NP, we found evidence of a weak, but clinically negligible association. Another analysis of serum osteocalcin levels and periodontal parameters in 73 post-menopausal women also found no association between the measures (Bullon et al., 2005). Also, a connection between sclerostin and periodontitis, as suggested by our data, could not be verified in a study including 61 post-menopausal women (Pinho et al., 2017).

In contrast to our study, a possible linkage of BTMs and periodontitis was supported by results of a cross-sectional study on 148 elderly subjects aged 77 years (Yoshihara et al., 2011) and by a longitudinal study on 128 post-menopausal women with a history of generalized

TABLE 1 Study sample characteristics

	Eligible cases	P1NP	CTX	Osteocalcin	BAP	FGF23	WNT5A	Sclerostin
N	5075	4993	4960	2864	2053	797	140	138
Mean CAL (mm)	2.38 (1.69)	2.38 (1.70)	2.38 (1.69)	2.31 (1.66)	2.33 (1.73)	2.28 (1.48)	2.93 (1.85)	2.86 (2.03)
Mean PPD (mm)	2.45 (0.68)	2.45 (0.68)	2.45 (0.68)	2.35 (0.66)	2.29 (0.67)	2.52 (0.60)	2.39 (0.66)	2.38 (0.75)
%BOP	0.24 (0.25)	0.24 (0.25)	0.24 (0.25)	0.24 (0.26)	0.24 (0.27)	0.26 (0.25)	0.30 (0.30)	0.27 (0.30)
%PPD4	0.14 (0.19)	0.14 (0.19)	0.14 (0.19)	0.14 (0.19)	0.15 (0.19)	0.13 (0.17)	0.19 (0.20)	0.19 (0.21)
Age (years)	48.8 (14.3)	48.8 (14.2)	48.8 (14.3)	49.1 (13.6)	49.5 (13.7)	48.0 (13.3)	58.6 (12.2)	56.0 (13.6)
Male	52.2%	52.2%	52.4%	50.7%	51.7%	48.6%	36.4%	37.0%
School education								
<10 years	21.4%	21.5%	21.6%	23.6%	29.0%	10.0%	43.6%	43.5%
10 years	54.0%	54.1%	54.1%	54.2%	53.1%	56.7%	37.1%	40.6%
>10 years	24.6%	24.3%	24.3%	22.2%	17.9%	33.2%	19.3%	15.9%
Body mass index (kg/m^2)	27.56 (4.86)	27.56 (4.85)	27.55 (4.85)	27.42 (4.68)	27.54 (4.77)	27.16 (4.43)	27.58 (4.84)	27.82 (4.99)
Smoker status								
Never	38.3%	38.1%	38.1%	41.3%	41.4%	41.2%	53.6%	48.6%
Former	33.7%	33.8%	33.7%	32.3%	30.7%	36.0%	25.0%	24.6%
Current	28.0%	28.1%	28.2%	26.4%	27.9%	22.8%	21.4%	26.8%
Alcohol (g/day)	10.17 (14.68)	10.21 (14.73)	10.23 (14.76)	10.52 (15.10)	11.15 (15.56)	8.95 (14.01)	6.21 (6.24)	6.33 (5.76)
Menopausal women	21.5%	21.5%	21.4%	22.2%	21.7%	23.6%	51.4%	40.6%
Diabetes	8.5%	8.5%	8.4%	6.2%	7.6%	2.8%	10.7%	10.9%
HbA1c (%)	5.27 (0.77)	5.27 (0.77)	5.27 (0.77)	5.25 (0.72)	5.29 (0.77)	5.17 (0.58)	5.46 (0.74)	5.43 (0.81)
SHIP-START-1	40.8%	41.2%	41.3%	71.8%	100%	0%	100%	100%

Note: Data are presented as mean (SD) or percentages.

Abbreviations: BAP, bone-specific alkaline phosphatase; %BOP, proportion of sites bleeding on probing; CAL, clinical attachment loss; CTX, C-terminal cross-linking telopeptide; FGF23, fibroblast growth factor 23; P1NP, N-procollagen type 1 amino-terminal propeptide; PPD, pocket probing depth; %PPD4, proportion of sites with PPD ≥4 mm; WNT5A, wingless-type mouse mammary tumour virus integration site family member 5a.

TABLE 2 Association between bone turnover markers (exposure) and periodontal markers (outcome)

	Mean CAL	Mean PPD	%BOP	%PPD4	%CAL4
P1NP	1.027 [1.011–1.044]	1.008 [1.001–1.015]	1.039 [0.997–1.083]	0.995 [0.951–1.040]	1.069 [1.013–1.128]
CTX	1.011 [0.994–1.029]	1.001 [0.994–1.009]	0.992 [0.951–1.034]	1.023 [0.976–1.073]	0.960 [0.908–1.015]
Osteocalcin	1.008 [0.982–1.036]	1.001 [0.990–1.012]	0.973 [0.911–1.039]	0.935 [0.869–1.006]	0.941 [0.86–1.029]
BAP	1.011 [0.981–1.043]	1.007 [0.995–1.019]	1.121 [1.042–1.205]	1.080 [1.005–1.161]	1.085 [0.990–1.189]
FGF23	1.015 [0.979–1.054]	1.001 [0.987–1.015]	0.986 [0.899–1.081]	0.981 [0.879–1.095]	1.075 [0.950–1.217]
WNT5A	0.969 [0.867–1.087]	0.956 [0.920–0.993]	0.922 [0.726–1.171]	0.794 [0.642–0.982]	0.856 [0.659–1.112]
Sclerostin	1.010 [0.897–1.140]	1.024 [0.978–1.073]	1.308 [1.005–1.704]	1.143 [0.930–1.405]	0.811 [0.563–1.17]

Note: BTM values in SDs. For CAL and PPD, a gamma regression adjusted for age, sex, school education, body mass index, smoking status, alcohol consumption, and glycated haemoglobin was used. The continuous covariates were modelled as splines with three knots. For %BOP, %PPD4, and %CAL4, a fractional logit response model adjusted for age, sex, school education, body mass index, smoking status, alcohol consumption, and glycated haemoglobin was used. Coefficients reported as factor change (e^{β}) (95% CI).

Abbreviations: BAP, bone-specific alkaline phosphatase; %BOP, proportion of sites bleeding on probing; CAL, clinical attachment level; %CAL4, proportion of sites with CAL ≥4 mm; CI, confidence interval; CTX, C-terminal cross-linking telopeptide; FGF23, fibroblast growth factor 23; P1NP, N-procollagen type 1 amino-terminal propeptide; PPD, pocket probing depth; %PPD4, proportion of sites with PPD ≥4 mm; WNT5A, wingless-type mouse mammary tumour virus integration site family member 5a.

moderate to advanced chronic periodontitis (Payne et al., 2011). Yoshihara et al. found inverse associations of the proportion of sites with PPD ≥4 mm, PPD ≥6 mm, and mean CAL with serum osteocalcin levels after adjusting for demographic variables (results that we could not verify even with an additional analysis of %PPD6 as outcome, see Table S8). The study of Payne et al. revealed an association between

TABLE 3 Association between periodontal markers (exposure) and bone turnover markers (outcome)

	P1NP	CTX	Osteocalcin	BAP	FGF23	WNT5A	Sclerostin
Mean CAL (mm)	1.009 [1.000–1.018]	1.004 [0.991–1.017]	0.997 [0.985–1.009]	1.006 [0.994–1.018]	1.008 [0.975–1.042]	0.970 [0.923–1.021]	0.997 [0.949–1.047]
Mean PPD (mm)	1.017 [0.997–1.037]	1.002 [0.975–1.030]	0.993 [0.968–1.019]	1.015 [0.989–1.043]	1.006 [0.936–1.081]	0.859 [0.753–0.984]	1.077 [0.963–1.209]
%PPD4	1.001 [0.935–1.071]	1.084 [0.982–1.197]	0.935 [0.855–1.023]	1.103 [1.009–1.207]	1.036 [0.802–1.345]	0.744 [0.485–1.152]	1.263 [0.844–1.905]
%BOP	1.055 [1.005–1.109]	1.001 [0.932–1.075]	0.991 [0.932–1.055]	1.121 [1.052–1.195]	0.963 [0.817–1.136]	0.938 [0.710–1.246]	1.264 [0.991–1.618]

Note: BTM values in SDs. For the BTMs, a gamma regression adjusted for age, sex, school education, body mass index, smoking status, alcohol, and glycated haemoglobin was used. The continuous covariates were modelled as splines with three knots. Coefficients reported as factor change (e^{β}) (95% CI).

Abbreviations: BAP, bone-specific alkaline phosphatase; %BOP, proportion of bleeding on probing sites; CAL, clinical attachment loss; CI, confidence interval; CTX, C-terminal cross-linking telopeptide; FGF23, fibroblast growth factor 23; P1NP, N-procollagen type 1 amino-terminal propeptide; PPD, pocket probing depth; %PPD4, proportion of sites with PPD ≥4 mm; WNT5A, wingless-type mouse mammary tumour virus integration site family member 5a.

2-year changes in serum osteocalcin and pyridinoline-crosslink fragment of type I collagen and alveolar bone loss.

(Alveolar) Bone underlies dynamic constant remodelling processes while providing mechanical support for various other tissues, including the teeth. A homeostatic imbalance, with prevailing excessive bone resorption, results in degenerative conditions (Rosen, 2000) and a weakening of the bone structure, which is further associated with both increased periodontal damage (Penoni et al., 2017) and altered biomarkers (Biver et al., 2012). It is assumed that reduced bone mineral density—a consequence of prolonged bone loss (Hardy & Cooper, 2009)— reduces the healing qualities of the bone (Wölfl et al., 2014). Here, systemic BTMs can provide an early indication of overall bone loss (Kotlarczyk et al., 2020) and might even predict active periodontitis burden and progression (Payne et al., 2011).

Because periodontitis, which is associated with locally elevated levels of BTMs (Obrant et al., 2005; Szulc, 2018), can alter components of peripheral blood and blood plasma by affecting the bone marrow (Loos, 2006), it allegedly also may affect serum BTM levels. Periodontal infection causes thereby a change in haematopoiesis, which leads to increased proliferation of osteoclast progenitor cells. These progenitor cells can enter sites of active bone resorption via the bloodstream, where they differentiate into mature osteoclasts (Hajishengallis & Chavakis, 2021). It is important to note that an increase in bone formation markers with concomitant net bone loss is not necessarily a contradiction, as it may represent coupled compensatory mechanisms of the body for increased resorption. Increased osteocalcin levels were, for example, observed in participants with osteoporosis due to the coupling of formation and resorption (Giannobile et al., 2003).

However, the reasons for an imbalance of bone remodelling are manifold. Local or systemic diseases, lifestyle habits, and a variety of further (external and internal) factors influence bone metabolism through several pathways. Such (patho)-physiological mechanisms alter BTM serum concentrations to varying degrees (Burch et al., 2014). This leads to high inter- and intra-personal variability of these metabolites, which was also observed in the present study. BAP, for instance, had an interquartile range of 6.4 μg/L with a median of 13.3 μg/L in our dataset. Next to this variability, BTMs are formed by different cells and tissues (e.g., osteoclasts or osteoblasts, see Figure S2) and are degraded at different rates. These conditions presumably mask possible associations between BTMs and periodontitis and may also explain the different results between the individual markers presented here and in previous studies.

In this context, our study—to the best of our knowledge, the largest cross-sectional evaluation of this topic—could not confirm a clear and robust association of BTMs with periodontal severity in general. It is thus in line with previous cross-sectional research questioning the usefulness of these markers for disease prediction and monitoring (Funck-Brentano et al., 2011; Biver et al., 2012; Burch et al., 2014; Eastell & Szulc, 2017). Previous studies that examined similar associations with periodontitis and reported stronger associations mostly targeted a more specific population (e.g., older or female) had smaller sample sizes or analysed fewer BTMs.

Several limitations of our study warrant mention. First, owing to the cross-sectional design, the study could not infer a temporal ordering of exposures and outcomes. Longitudinal measurements could reveal possible hidden correlations, which are masked by the high inter-personal variability of the serum metabolite levels. Moreover, all recorded periodontal markers except CAL—the result of the cumulative periodontal damage over time—reflect the current inflammatory state and are accordingly variable as well (Demmer et al., 2008). Second, periodontal examinations were performed according to a half-mouth protocol, and BOP was recorded only on index teeth (first incisors, canines, and first molars). Although this allows a good classification of periodontitis severity, the absolute area of inflammation (and correspondingly the bone surface affected by resorption) would be more suitable to assess the systemic effects of periodontitis. The approach used may lead to an underestimation of the inflammatory surface (Nesse et al., 2008). Third, in contrast to the markers P1NP, CTX, osteocalcin, and BAP, the markers FGF23, WNT5A, and sclerostin were measured in smaller and selected subgroups. Especially for WNT5A and sclerostin, the representativeness of the study results is thus limited. Fourth, because participation at follow-up (SHIP-START-1) might be affected by attrition, the external validity of the study population may be limited, although a corresponding sensitivity analysis showed no substantial change in estimates. Fifth, blood sampling was performed throughout the day (SHIP-START) or throughout the mornings (SHIP-TREND). This might have negatively impacted the comparability of serum levels, as diurnal fluctuations are known for selected BTMs, in particular CTX. Sixth, there is limited information on other interfering factors such as fasting time, diet, recently contracted fractures, or extracted teeth, all of which modulate the BTM values (Eastell & Szulc, 2017). These fluctuations possibly mask systemic effects.

Altogether, with the scattered associations found for P1NP, BAP, WNT5A, and sclerostin, our study suggests possible future research approaches, whereas it tends to weaken the assumption of associations for CTX and osteocalcin. To strengthen possible results, the variability of BTMs should be addressed by a longitudinal study design. Further research is needed, as bone markers are a potential key to better assess the individual immune response in periodontitis.

AUTHOR CONTRIBUTIONS

Conception, design, and writing: Stefan Lars Reckelkamm, Anke Hannemann, Sebastian-Edgar Baumeister, Michael Nolde, and Birte Holtfreter. *Analysis and interpretation of data*: Stefan Lars Reckelkamm, Anke Hannemann, Thomas Kocher, Matthias Nauck, Benjamin Ehmke, Zoheir Alayash, Sebastian-Edgar Baumeister, Michael Nolde, and Birte Holtfreter. *Acquisition, processing, and restructuring of data*: Stefan Lars Reckelkamm, Anke Hannemann, Thomas Kocher, Matthias Nauck, Henry Völzke, Martina Rauner, Sebastian-Edgar Baumeister, Michael Nolde, and Birte Holtfreter. *Revised and approved the article*: Stefan Lars Reckelkamm, Anke Hannemann, Thomas Kocher, Matthias Nauck, Henry Völzke, Benjamin Ehmke, Martina Rauner, Zoheir Alayash, Sebastian-Edgar Baumeister, Michael Nolde, and Birte Holtfreter.

ACKNOWLEDGEMENTS

The authors thank all examiners, technicians, interviewers, participants, and other contributors to the SHIP data collection.

FUNDING INFORMATION

The authors did not receive any funding for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Medical University of Greifswald. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://fvcm.med.uni-greifswald.de/institute.html with the permission of Medical University of Greifswald.

ETHICS STATEMENT

The SHIP studies had previously obtained relevant ethical approval and participant consent. These studies complied with all relevant ethical regulations, including the Declaration of Helsinki, and ethical approval for data collection and analysis was obtained by each study from local boards.

ORCID

Stefan Lars Reckelkamm https://orcid.org/0000-0002-5273-7288
Zoheir Alayash https://orcid.org/0000-0002-6850-5668
Sebastian-Edgar Baumeister https://orcid.org/0000-0002-9391-6602
Michael Nolde https://orcid.org/0000-0001-6893-7367
Birte Holtfreter https://orcid.org/0000-0002-6541-3127

REFERENCES

Baumeister, S.-E., Finger, J. D., Gläser, S., Dörr, M., Markus, M. R. P., Ewert, R., Felix, S. B., Grabe, H.-J., Bahls, M., Mensink, G. B., Völzke, H., Piontek, K., & Leitzmann, M. F. (2018). Alcohol consumption and cardiorespiratory fitness in five population-based studies. *European Journal of Preventive Cardiology*, *25*(2), 164–172. https://doi.org/10.1177/2047487317738594

Bernabé, E., Marcenes, W., Hernandez, C. R., Bailey, J., Abreu, L. G., Alipour, V., Amini, S., Arabloo, J., Arefi, Z., Arora, A., Ayanore, M. A., Bärnighausen, T. W., Bijani, A., Cho, D. Y., Chu, D. T., Crowe, C. S., Demoz, G. T., Demsie, D. G., Forooshani, Z. S. D., … Kassebaum, N. J. (2020). Global, regional, and national levels and trends in burden of oral conditions from 1990 to 2017: A systematic analysis for the global burden of disease 2017 study. *Journal of Dental Research*, *99*(4), 362–373. https://doi.org/10.1177/0022034520908533

Betsy, J., Ahmed, J. M., Mohasin, A. K., Mohammed, A., & Nabeeh, A. A. (2019). Diagnostic accuracy of salivary biomarkers of bone turnover in identifying patients with periodontitis in a Saudi Arabian population. *Journal of Dental Sciences*, *14*(3), 269–276. https://doi.org/10.1016/j.jds.2019.03.002

Biver, E., Chopin, F., Coiffier, G., Brentano, T. F., Bouvard, B., Garnero, P., & Cortet, B. (2012). Bone turnover markers for osteoporotic status assessment? A systematic review of their diagnosis value at baseline in osteoporosis. *Joint, Bone, Spine*, *79*(1), 20–25. https://doi.org/10.1016/j.jbspin.2011.05.003

Bouchard, P., Carra, M. C., Boillot, A., Mora, F., & Rangé, H. (2017). Risk factors in periodontology: A conceptual framework. *Journal of Clinical Periodontology*, *44*(2), 125–131. https://doi.org/10.1111/jcpe.12650

Bullon, P., Goberna, B., Guerrero, J. M., Segura, J. J., Perez-Cano, R., & Martinez-Sahuquillo, A. (2005). Serum, saliva, and gingival crevicular fluid osteocalcin: Their relation to periodontal status and bone mineral density in postmenopausal women. *Journal of Periodontology*, *76*(4), 513–519. https://doi.org/10.1902/jop.2005.76.4.513

Burch, J., Rice, S., Yang, H., Neilson, A., Stirk, L., Francis, R., Holloway, P., Selby, P., & Craig, D. (2014). Systematic review of the use of bone turnover markers for monitoring the response to osteoporosis treatment: The secondary prevention of fractures, and primary prevention of fractures in high-risk groups. *Health Technology Assessment*, *18*(11), 1–180. https://doi.org/10.3310/hta18110

Caton, J. G., Armitage, G., Berglundh, T., Chapple, I. L. C., Jepsen, S., Kornman, K. S., Mealey, B. L., Papapanou, P. N., Sanz, M., & Tonetti, M. S. (2018). A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification. *Journal of Periodontology*, *89*, S1–S8. https://doi.org/10.1002/JPER.18-0157

Demmer, R. T., Kocher, T., Schwahn, C., Völzke, H., Jacobs, D. R., & Desvarieux, M. (2008). Refining exposure definitions for studies of periodontal disease and systemic disease associations. *Community Dentistry and Oral Epidemiology*, *36*(6), 493–502. https://doi.org/10.1111/j.1600-0528.2008.00435.x

Eastell, R., & Szulc, P. (2017). Use of bone turnover markers in postmenopausal osteoporosis. *The Lancet Diabetes & Endocrinology*, *5*(11), 908–923. https://doi.org/10.1016/S2213-8587(17)30184-5

Funck-Brentano, T., Biver, E., Chopin, F., Bouvard, B., Coiffier, G., Souberbielle, J.-C., Garnero, P., & Roux, C. (2011). Clinical utility of serum bone turnover markers in postmenopausal osteoporosis therapy monitoring: A systematic review. *Seminars in Arthritis and Rheumatism*, *41*(2), 157–169. https://doi.org/10.1016/j.semarthrit.2011.01.005

Giannobile, W. V., Al-Shammari, K. F., & Sarment, D. P. (2003). Matrix molecules and growth factors as indicators of periodontal disease activity. *Periodontology*, *2000*(31), 125–134. https://doi.org/10.1034/j.1600-0757.2003.03108.x

Gursoy, U. K., Liukkonen, J., Jula, A., Huumonen, S., Suominen, A. L., Puukka, P., & Könönen, E. (2016). Associations between salivary bone metabolism markers and periodontal breakdown. *Journal of Periodontology*, *87*(4), 367–375. https://doi.org/10.1902/jop.2015.150399

Hajishengallis, G., & Chavakis, T. (2021). Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nature Reviews. Immunology*, *21*(7), 426–440. https://doi.org/10.1038/s41577-020-00488-6

Hardy, R., & Cooper, M. S. (2009). Bone loss in inflammatory disorders. *The Journal of Endocrinology*, *201*(3), 309–320. https://doi.org/10.1677/JOE-08-0568

Harrell, F. E. (2015). *Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis Springer series in statistics* (2nd ed.). Springer.

Holtfreter, B., Alte, D., Schwahn, C., Desvarieux, M., & Kocher, T. (2012). Effects of different manual periodontal probes on periodontal measurements. *Journal of Clinical Periodontology*, *39*(11), 1032–1041. https://doi.org/10.1111/j.1600-051X.2012.01941.x

Kinane, D. F. (2001). Causation and pathogenesis of periodontal disease. *Periodontology*, *2000*(25), 8–20. https://doi.org/10.1034/j.1600-0757.2001.22250102.x

Kotlarczyk, M. P., Perera, S., Resnick, N. M., Nace, D. A., & Greenspan, S. L. (2020). Early changes in bone turnover predict longer-term changes in bone mineral density but not trabecular bone score in frail older women. *Archives of Osteoporosis*, *15*(1), 79. https://doi.org/10.1007/s11657-020-00749-w

Loos, B. G. (2006). Systemic effects of periodontitis. *Annals of the Royal Australasian College of Dental Surgeons*, *18*, 27–29.

Manning, W. G., Basu, A., & Mullahy, J. (2005). Generalized modeling approaches to risk adjustment of skewed outcomes data. *Journal of Health Economics*, *24*(3), 465–488. https://doi.org/10.1016/j.jhealeco.2004.09.011

Marques, E. A., Gudnason, V., Lang, T., Sigurdsson, G., Sigurdsson, S., Aspelund, T., Siggeirsdottir, K., Launer, L., Eiriksdottir, G., & Harris, T. B. (2016). Association of bone turnover markers with volumetric bone loss, periosteal apposition, and fracture risk in older men and women: The AGES-Reykjavik longitudinal study. *Osteoporosis International*, *27*(12), 3485–3494. https://doi.org/10.1007/s00198-016-3675-7

Meyle, J., & Chapple, I. (2015). Molecular aspects of the pathogenesis of periodontitis. *Periodontology 2000*, *69*(1), 7–17. https://doi.org/10.1111/prd.12104

Miricescu, D., Totan, A., Calenic, B., Mocanu, B., Didilescu, A., Mohora, M., Spinu, T., & Greabu, M. (2014). Salivary biomarkers: Relationship between oxidative stress and alveolar bone loss in chronic periodontitis. *Acta Odontologica Scandinavica*, *72*(1), 42–47. https://doi.org/10.3109/00016357.2013.795659

Natto, Z. S., Abu Ahmad, R. H., Alsharif, L. T., Alrowithi, H. F., Alsini, D. A., Salih, H. A., & Bissada, N. F. (2018). Chronic periodontitis case definitions and confounders in periodontal research: A systematic assessment. *BioMed Research International*, *2018*, 4578782. https://doi.org/10.1155/2018/4578782

Nesse, W., Abbas, F., van der Ploeg, I., Spijkervet, F. K. L., Dijkstra, P. U., & Vissink, A. (2008). Periodontal inflamed surface area: Quantifying inflammatory burden. *Journal of Clinical Periodontology*, *35*(8), 668–673. https://doi.org/10.1111/j.1600-051X.2008.01249.x

Obrant, K. J., Ivaska, K. K., Gerdhem, P., Alatalo, S. L., Pettersson, K., & Väänänen, H. K. (2005). Biochemical markers of bone turnover are influenced by recently sustained fracture. *Bone*, *36*(5), 786–792. https://doi.org/10.1016/j.bone.2005.02.009

Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., Flemmig, T. F., Garcia, R., Giannobile, W. V., Graziani, F., Greenwell, H., Herrera, D., Kao, R. T., Kebschull, M., Kinane, D. F., Kirkwood, K. L., Kocher, T., Kornman, K. S., Kumar, P. S., … Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *Journal of Clinical Periodontology*, *45*(Suppl. 20), S162–S170. https://doi.org/10.1111/jcpe.12946

Papke, L. E., & Wooldridge, J. M. (1996). Econometric methods for fractional response variables with an application to 401(k) plan participation rates. *Journal of Applied Econometrics*, *11*(6), 619–632. https://doi.org/10.1002/(SICI)1099-1255(199611)11:6<619::AID-JAE418>3.0.CO;2-1

Payne, J. B., Stoner, J. A., Lee, H.-M., Nummikoski, P. V., Reinhardt, R. A., & Golub, L. M. (2011). Serum bone biomarkers and oral/systemic bone loss in humans. *Journal of Dental Research*, *90*(6), 747–751. https://doi.org/10.1177/0022034511402993

Penoni, D. C., Fidalgo, T. K. S., Torres, S. R., Varela, V. M., Masterson, D., Leão, A. T. T., & Maia, L. C. (2017). Bone density and clinical periodontal attachment in postmenopausal women: A systematic review and meta-analysis. *Journal of Dental Research*, *96*(3), 261–269. https://doi.org/10.1177/0022034516682017

Pinho, R. C. M., Pimentel, L. B., Bandeira, F. A. F., Dias, R. S. A. M., & Cimões, R. (2017). Levels of serum sclerostin, metabolic parameters, and periodontitis in -postmenopausal women with diabetes. *Special Care in Dentistry*, *37*(6), 282–289. https://doi.org/10.1111/scd.12250

Rosen, C. J. (2000). The epidemiology and pathogenesis of osteoporosis. [Updated 2020 Jun 21]. In: K. R. Feingold, Anawalt B, Boyce A, et al., (Eds.), *Endotext* [Internet]. MDText.com, Inc.

Schulze-Späte, U., Turner, R., Wang, Y., Chao, R., Schulze, P. C., Phipps, K., Orwoll, E., & Dam, T.-T. (2015). Relationship of bone metabolism biomarkers and periodontal disease: The osteoporotic fractures in men

(MrOS) study. *The Journal of Clinical Endocrinology and Metabolism*, *100*(6), 2425–2433. https://doi.org/10.1210/jc.2014-4180

Seaman, S. R., & White, I. R. (2013). Review of inverse probability weighting for dealing with missing data. *Statistical Methods in Medical Research*, *22*(3), 278–295. https://doi.org/10.1177/0962280210395740

Shetty, S., Kapoor, N., Bondu, J. D., Thomas, N., & Paul, T. V. (2016). Bone turnover markers: Emerging tool in the management of osteoporosis. *Indian Journal of Endocrinology and Metabolism*, *20*(6), 846–852. https://doi.org/10.4103/2230-8210.192914

Silveira, J. L., Albers, M., Vargas, D. M., Santa Helena, E. T., Cordova, C. M., Hannemann, A., Wallaschofski, H., Meisel, P., Pink, C., Samietz, S., Schmidt, C. O., Holtfreter, B., Völzke, H., Dörr, M., Kocher, T., & Markus, M. R. (2016). Reduced bone stiffness in women is associated with clinical attachment and tooth loss: The study of health in Pomerania. *Journal of Dental Research*, *95*(13), 1464–1471. https://doi.org/10.1177/0022034516666491

Szulc, P. (2018). Bone turnover: Biology and assessment tools. *Best Practice & Research. Clinical Endocrinology & Metabolism*, *32*(5), 725–738. https://doi.org/10.1016/j.beem.2018.05.003

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gøtzsche, P. C., Mulrow, C. D., Pocock, S. J., Poole, C., Schlesselman, J. J., & Egger, M. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *PLoS Medicine*, *4*(10), e297. https://doi.org/10.1371/journal.pmed.0040297

VanderWeele, T. J., Rothman, K. J., & Lash, T. L. (2021). Confounding and confounders. In *Modern epidemiology* (pp. 263–286). Wolters Kluwer.

Vasikaran, S., Cooper, C., Eastell, R., Griesmacher, A., Morris, H. A., Trenti, T., & Kanis, J. A. (2011). International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. *Clinical Chemistry and Laboratory Medicine*, *49*(8), 1271–1274. https://doi.org/10.1515/CCLM.2011.602

Völzke, H., Schössow, J., Schmidt, C. O., Jürgens, C., Richter, A., Werner, A., Werner, N., Radke, D., Teumer, A., Ittermann, T., Schauer, B., Henck, V., Friedrich, N., Hannemann, A., Winter, T., Nauck, M., Dörr, M., Bahls, M., Felix, S. B., … Kocher, T. (2022). Cohort profile update: The Study of Health in Pomerania (SHIP). *International Journal of Epidemiology*. [online ahead of print]. https://doi.org/10.1093/ije/dyac034

Winter, T., Friedrich, N., Lamp, S., Schäfer, C., Schattschneider, M., Bollmann, S., Brümmer, D., Riemann, K., Petersmann, A., & Nauck, M. (2020). The integrated research biobank of the University Medicine Greifswald. *Open Journal of Bioresources*, *7*(1), 2. https://doi.org/10.5334/ojb.64

Wölfl, C., Schweppenhäuser, D., Gühring, T., Takur, C., Höner, B., Kneser, U., Grützner, P. A., & Kolios, L. (2014). Characteristics of bone turnover in the long bone metaphysis fractured patients with normal or low Bone Mineral Density (BMD). *PLoS One*, *9*(5), e96058. https://doi.org/10.1371/journal.pone.0096058

Yoshihara, A., Hayashi, Y., & Miyazaki, H. (2011). Relationships among bone turnover, renal function and periodontal disease in elderly Japanese. *Journal of Periodontal Research*, *46*(4), 491–496. https://doi.org/10.1111/j.1600-0765.2011.01365.x

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Reckelkamm, S. L., Hannemann, A., Kocher, T., Nauck, M., Völzke, H., Ehmke, B., Rauner, M., Alayash, Z., Baumeister, S.-E., Nolde, M., & Holtfreter, B. (2022). Association between bone turnover markers and periodontitis: A population-based cross-sectional study. *Journal of Clinical Periodontology*, *49*(7), 633–641. https://doi.org/10.1111/jcpe.13649