

“Low Testosterone Levels in Body Fluids Are Associated With Chronic Periodontitis”: A Reality or a Myth?

American Journal of Men's Health
1–11
© The Author(s) 2016
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1557988316667692
ajmh.sagepub.com



Sergio Varela Kellesarian, DDS¹, Hans Malmstrom, DDS¹,
Tariq Abduljabbar, BDS, MSc, DMSc², Fahim Vohra, BDS, MRD²,
Tammy Varela Kellesarian, DDS, MPH³, Fawad Javed, BDS, PHD¹,
and Georgios E. Romanos, Prof. Dr. med. dent^{4,5}

Abstract

There is a debate over the association between low testosterone levels in body fluids and the occurrence of chronic periodontitis (CP). The aim of the present systematic review was to assess whether low testosterone levels in body fluids reflect CP. In order to identify studies relevant to the focus question: “Is there a relationship between low testosterone levels in body fluids and CP?” an electronic search without time or language restrictions was conducted up to June 2016 in indexed databases using different keywords: periodontitis, chronic periodontitis, periodontal diseases, testosterone, and gonadal steroid hormones. A total of eight studies were included in the present systematic review. The number of study participants ranged from 24 to 1,838 male individuals with ages ranging from 15 to 95 years. Seven studies measured testosterone levels in serum, two studies in saliva, and one study in gingiva. Four studies reported a negative association between serum testosterone levels and CP. Two studies reported a positive association between decreased testosterone levels in serum and CP. Increased levels of salivary testosterone among patients with CP were reported in one study; whereas one study reported no significant difference in the concentration of salivary testosterone between patients with and without CP. One study identified significant increase in the metabolism of testosterone in the gingiva of patients with CP. Within the limits of the evidence available, the relationship between low testosterone levels and CP remains debatable and further longitudinal studies and control trials are needed.

Keywords

testosterone, hormones, periodontitis, periodontal diseases, men's health

Received June 17, 2016. Received revised July 27, 2016. Accepted for publication August 8, 2016

Introduction

Testosterone is an anabolic hormone produced by testicular Leydig cells and regulated by the hypothalamic–pituitary–gonadal axis (McBride, Carson, & Coward, 2016). Testosterone stimulates and modulates the development of muscles, bone, fat metabolism, skin, and adult male reproductive health (Francis, Gladwell, & Holman, 1984). It is well established that testosterone concentration decrease in men with aging (Moran et al., 2015; Sansone, Sansone, Lenzi, & Romanelli, 2016). Low testosterone levels have been associated with cardiovascular conditions, increased insulin resistance, reduced bone mineral density, and increased fracture risk (Khera, 2016; Mellstrom et al., 2006; Shin, Sung, Lee, & Song, 2016). The negative effects

of testosterone deficiency in bone metabolism have been related to increased levels of proinflammatory cytokines, such as interleukin-6, and enhanced osteoclastic activity (Bellido et al., 1995). Testosterone therapy presents

¹University of Rochester, Rochester, NY, USA

²King Saud University, Riyadh, Saudi Arabia

³Barry University, Miami Shores, FL, USA

⁴University of Frankfurt, Frankfurt, Germany

⁵Stony Brook University, Stony Brook, NY, USA

Corresponding Author:

Sergio V. Kellesarian, Department of General Dentistry, Eastman Institute for Oral Health, University of Rochester, 625 Elmwood Avenue, Rochester, NY 14620, USA.
Email: sergio_kellesarian@urmc.rochester.edu



Creative Commons Non Commercial CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (<http://www.creativecommons.org/licenses/by-nc/3.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

positive effects on sexual function, body composition, and bone density in men, increasing the cortical bone size via stimulation of longitudinal and radial growth (Morgentaler, 2016; Vanderschueren et al., 2004). A positive relationship between low serum testosterone levels and oral health has been suggested. Forsblad-d'Elia et al. (2009) reported a positive relationship between low testosterone serum levels and xerostomia associated with Sjogren's syndrome. Wang, Kessler, Kensler, and Dechow (2016) evaluated the long-term effects of orchidectomy and low testosterone on the craniofacial development and maintenance of skeletal and oral health in rhesus macaques, reporting severe temporomandibular joint osteoarthritis, higher alveolar bone loss, and signs of severe periodontitis in the specimens with low testosterone levels.

Chronic periodontitis (CP) is an inflammatory condition of the tooth supporting structures (cementum, gingiva, periodontal ligament, and alveolar bone) that if left untreated progresses to bone destruction and tooth loss (Ram, Parthiban, Sudhakar, Mithradas, & Prabhakar, 2015). The relationship between female sex hormones (estrogens) and periodontal disease in women during puberty, pregnancy, and menopause, or taking oral contraceptives has been widely reported (Jafri, Bhardwaj, Sawai, & Sultan, 2015; Shapiro & Freeman, 2014); however, only a limited number of studies (Daltaban, Saygun, & Bolu, 2006; Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh, Makker, Tripathi, Singh, & Gupta, 2011; Steffens, Wang, et al., 2015; Vittek, Kirsch, Rappaport, Bergman, & Southren, 1984; Vittek, Rappaport, Gordon, Munnangi, & Southren, 1979) have investigated the association between testosterone levels in men and CP. ElAttar, Lin, and Tira (1982) reported testosterone inhibitory properties in vitro in the cyclooxygenase pathway of arachidonic acid metabolism in gingiva. In one study (Steffens, Coimbra, et al., 2015), testosterone reduced the osteoclast formation in a dose-dependent manner, and significantly influenced the production of tumor necrosis- α in rats. Famili, Cauley, and Greenspan (2007) identified that men with prostate cancer undergoing androgen deprivation therapy were more likely to have periodontal disease (80.5%) than men without androgen deprivation therapy (3.7%). Singh et al. (2011) reported higher testosterone levels among men without tooth loss compared with subjects with tooth loss. However, conflicting results have also been reported. Orwoll et al. (2009) reported no significant difference in periodontal parameters, CP progression and tooth loss, independently of serum testosterone levels. Similar results were reported by Vittek et al. (1979) and Kuraner et al. (1991). Since the role of testosterone levels with reference to CP remains debatable, the aim of the present systematic review was to assess whether low testosterone levels in body fluids reflect CP in men.

Method

Focus Question

This systematic review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). A specific question was constructed according to the Participants, Interventions, Control, and Outcomes principle. The focus question was "Is there a relationship between low testosterone levels in body fluids and CP?"

Literature Search Protocol

The international database of Prospectively Registered Systematic Reviews in Health and Social Care and the Cochrane Register of Systematic Reviews were searched in June 2016, and presented no existing or current review protocols assessing the relationship between CP and testosterone levels in men. An electronic search without time or language restrictions was conducted up to June 2016 using PubMed (National Library of Medicine), Google Scholar, Scopus, EMBASE, MEDLINE (Ovid), and Web of Knowledge databases, to identify studies relevant to the focus question. The following Medical Subject Headings (MeSH) were used: (a) periodontitis, (b) chronic periodontitis, (c) periodontal diseases, (d) testosterone, (e) gonadal steroid hormones, and the combinations a, b or c and d; and a, b or c and e. Other relevant non-Medical Subject Headings words were used in the search process to identify articles discussing periodontal parameters and/or gonadal steroid hormones. These included "bleeding on probing," "clinical attachment loss," "marginal bone loss," "tooth loss," "probing depth," and "sex hormones."

Titles and abstracts of studies identified using the above-described protocol were screened by two authors (SVK and GER) and checked for agreement. Full texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand-searched to identify studies that could have remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors (SVK and GER). Cohen kappa coefficients were used to determine the level of agreement between the two reviewers (kappa score = 0.90; Roberts, 2008). Figure 1 illustrates the literature search strategies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Eligibility Criteria

The eligibility criteria were as follows: (a) original studies, (b) clinical studies, (c) case series, and (d) studies assessing the relationship between periodontal status and testosterone

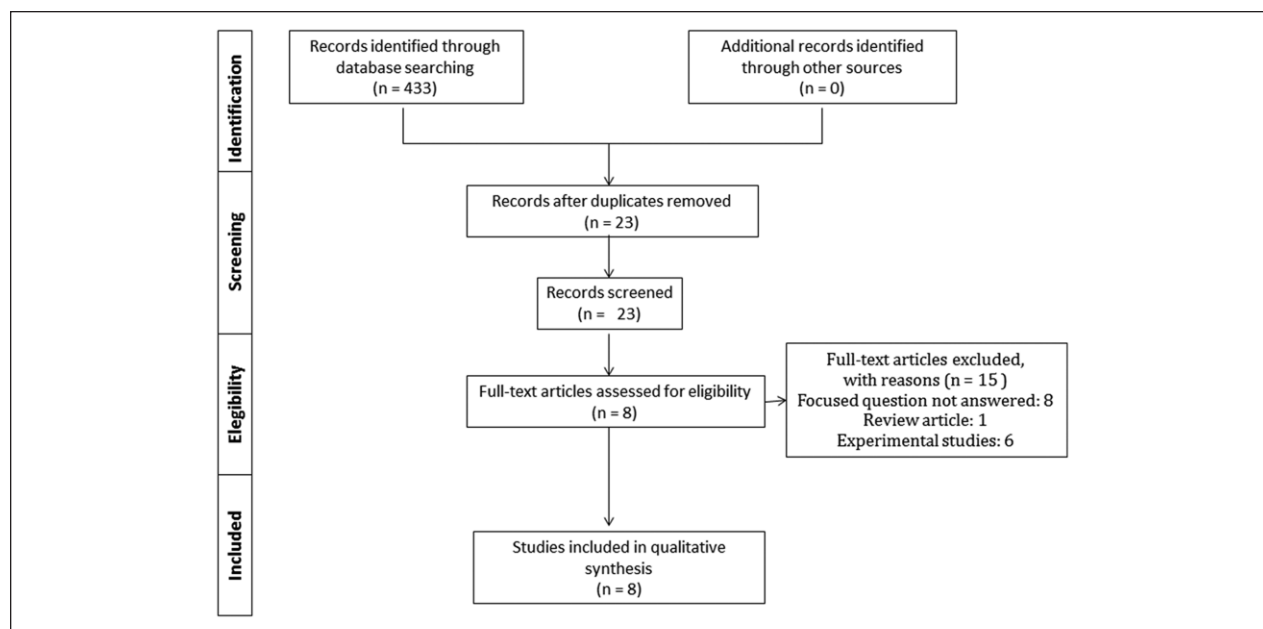


Figure 1. Article selection flow chart for the systematic review according to PRISMA guidelines.

Note. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

levels in men. Letters to the editor, case reports, commentaries, historic reviews, and experimental studies were excluded.

Quality Assessment

The studies that were included underwent a quality assessment with the Critical Appraisal Skills Program (CASP) Cohort Study Checklist (Zeng et al., 2015), in an attempt to increase the strength of the present systematic review. The CASP tool uses a systematic approach based on 12 specific criteria which are as follows: study issue is clearly focused (effect of testosterone levels in periodontal status); cohort is recruited in an acceptable way; exposure (testosterone levels in serum, gingiva, and/or saliva) is accurately measured; outcome (periodontal status) is accurately measured; confounding factors are addressed; follow-up is long and complete; results are clear; results are precise; results are credible; results can be applied to the local population; results fit with available evidence; and there are important clinical implications. Each criterion had a response of “Yes,” “No,” or “Cannot tell.” Each study had a possible maximum score of 12. CASP scores were used to grade the methodological quality of each study assessed in the present systematic review.

Results

Study Selection and Characteristics

Four hundred and thirty-three potential articles were initially identified. After reviewing the abstracts, 410

publications which did not fulfill the eligibility criteria were excluded. In the second step, 15 more articles were excluded because they did not answer the focus question, were experimental studies, reviews, or studies conducted in children (younger than 12 years old) and/or women (see the appendix). A total of eight studies (Daltaban et al., 2006; Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979; Vittek et al., 1984) were included in the present systematic review and processed for data extraction (Figure 1).

All studies (Daltaban et al., 2006; Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979; Vittek et al., 1984) had a cross-sectional design and were performed on men under health care or university settings. These primary studies were conducted in the following countries: Germany, India, Turkey, and the United States. The number of study participants ranged from 24 to 1,838 male individuals with ages ranging from 15 years to 95 years, and a mean age ranging from 20.50 ± 0.67 years to 76.4 years. In six studies (Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979), the participants were systemically healthy individuals. Daltaban et al. (2006) assessed periodontal status in patients with hypergonadotropic hypogonadism (HH), and Vittek et al. (1984) studied testosterone levels associated to periodontal status in patients with diabetes mellitus (DM).

Periodontal Status and Testosterone Level Measurement

In all studies (Daltaban et al., 2006; Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979; Vittek et al., 1984), intraoral examination was conducted to assess the patient's periodontal status. Probing depth (PD) and clinical attachment loss (CAL) were reported in six studies (Daltaban et al., 2006; Kuraner et al., 1991; Orwoll et al., 2009; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1984) and five studies (Daltaban et al., 2006; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015), respectively. Kuraner et al. (1991) and Vittek et al. (1979) determined periodontal tissue health using Russell's periodontal index (based on gingival inflammation and loss of periodontal attachment, used mainly for epidemiological purposes). Teeth mobility was reported in three studies (Kuraner et al., 1991; Singh et al., 2011; Vittek et al., 1984) and number of lost teeth was assessed in two studies (Orwoll et al., 2009; Samietz et al., 2016). Other periodontal parameters reported include oral hygiene index of Greene and Vermillion (Vittek et al., 1979), plaque index (Daltaban et al., 2006), gingival index (GI; Daltaban et al., 2006; Vittek et al., 1984), and bleeding on probing (BOP; Daltaban et al., 2006). In four studies (Daltaban et al., 2006; Kuraner et al., 1991; Vittek et al., 1979; Vittek et al., 1984) radiographs were used to assess alveolar bone loss and to diagnose CP. Vittek et al. (1984) performed histological examination of paraffin sections of gingiva to diagnose periodontitis.

Testosterone levels in serum were measured in seven studies (Daltaban et al., 2006; Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979), out of which radioimmunoassay was used in three studies (Kuraner et al., 1991; Orwoll et al., 2009; Vittek et al., 1979), and enzyme immunoassay in three studies (Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015). Daltaban et al. (2006) did not report the method used to analyze testosterone levels in serum. Vittek et al. (1984) measured testosterone levels in saliva using radioimmunoassay, and Kuraner et al. (1991) collected parotid saliva using a Carlson-Crittenden device and did not report the method to assess testosterone levels. Vittek et al. (1984) obtained gingival tissue samples to assess in vitro the metabolism of testosterone in healthy and diseased gingiva. This significant heterogeneity among all the studies did not allow pooling of results and statistical analysis.

Confounding Factors

In two studies (Kuraner et al., 1991; Vittek et al., 1979) confounding variables were not assessed. Daltaban et al. (2006) assessed systemic disorders such as inflammatory, immune and hormonal conditions (other than HH), and exposure to antibiotics or periodontal therapy within the preceding 6 months. Likewise, Vittek et al. (1984) excluded patients with systemic disorders; however, studied diabetic patients (type 1 and type 2 DM) requiring diet, insulin, or oral antihyperglycemic agents. Four studies (Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015) assessed diverse confounders including race, education level, alcohol, drugs and tobacco exposure, systemic diseases, DM, and/or obesity (body mass index, physical activity, and/or waist circumference; Table 1).

Main Outcomes

Serum Testosterone Levels. Four studies (Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Vittek et al., 1979) reported a negative association between serum testosterone levels and periodontal inflammatory parameters. Orwoll et al. (2009) reported no significant difference in periodontal parameters (CAL, PD, and BOP), CP progression (odds ratio [OR] = 0.97, 95% confidence interval [CI: 0.83, 1.14]), tooth loss (OR = 1.01, 95% CI [0.87, 1.18]), and total testosterone levels in a cohort of 1,210 men followed for 3 years. Similarly, Samietz et al. (2016) reported no consistent association of total testosterone levels and CAL, CP progression, and tooth loss (OR = 0.93, 95% CI [0.80, 1.08]) in a cohort of 1,838 men followed for 5 years.

Two studies (Singh et al., 2011; Steffens, Wang, et al., 2015) reported a positive association between decreased testosterone levels in serum and deteriorated periodontal parameters. Steffens, Wang, et al. (2015) reported that low total testosterone levels were associated with increased CP prevalence (OR = 2.1, 95% CI [1.00, 4.5]) and severity (OR = 2.1, 95% CI [1.00, 4.3]); and that lower levels of free and albumin-bound testosterone were associated with prevalence (OR = 3.9, 95% CI [1, 15]) and severity (OR = 3.4, 95% CI [1.2, 9.8]) of CP. Likewise, Singh et al. (2011) reported higher testosterone levels (4.41 ± 2.57) in subjects without tooth loss compared with subjects with tooth loss (2.79 ± 1.15).

Daltaban et al. (2006) reported that patients with HH (characterized by men with low levels of testosterone) and CP presented significantly higher GI and BOP compared with patients without HH with CP, suggesting a negative correlation between GI and free testosterone levels ($r = -.794$), and that testosterone may have an inhibitory effect on gingival inflammation. However, no

Table 1. General Characteristics of the Studies Included.

Authors (region of study)	Study groups	Age in years (range)	Periodontal status diagnosis method	Testosterone measurement method	Confounding variables assessed
Daltaban et al. (2006; Turkey)	48 Male	19-21	Clinical examination (PI, GI, BOP, PD, CAL)	Serum (NA)	Systemic conditions
	Group 1: 12 HH + CP	Group 1: 20.83 ± 0.93	Radiographs (FMX)		Periodontal therapy
	Group 2: 12 HH + HP	Group 2: 20.50 ± 0.67			
	Group 3: 12 SH + CP	Group 3: 20.58 ± 0.90			
	Group 4: 12 SH + HP	Group 4: 20.91 ± 0.93			
Kuraner et al. (1991; Turkey)	24 Male	Group 1: 30-40	Clinical examination (RPI, PD, mobility, MBL)	Serum: RIA	None
	Group 1: 14 CP	Group 2: 28-36		Parotid saliva: Carlson–Crittenden device	
Orwoll et al. (2009; USA)	Group 2: 10 HP		Radiographs		
	First exam: 1,210 Men	First exam: 74.6 (66-95)	Clinical examination (tooth loss, CAL, PD)	Serum: RIA	Race
	Second exam: 1,019 Men	Second exam: 76.4	Education level		Smoking BMI
Samietz et al. (2016; Germany)	Group 1: 1,838 men for number of teeth	Group 1: 50 (36-63)	Clinical examination (tooth loss, CAL)	Serum: Competitive chemiluminescent enzyme immunoassay	Diabetes mellitus Smoking
	Group 2: 1,548 men for CAL	Group 2: 46 (34-59)			Diabetes mellitus Physical activity Waist circumference Socioeconomic status Educational level Systemic conditions
Singh et al. (2011; India)	203 SH + CP	45-65	Clinical examination (CAL, PD, mobility)	Serum: Enzyme immunoassay	Smoking Alcohol
	Group 1: Completely dentate and partially dentate				
	Group 2: Tooth loss <3 and >3				Medications
	Group 3: Tooth loss <5 and >5				
Steffens, Wang, et al. (2015; USA)	755 Men	45 ± 0.5	Clinical examination (CAL, PD)	Serum: Competitive chemiluminescent enzyme immunoassay	Systemic conditions
					Race

(continued)

Table 1. (continued)

Authors (region of study)	Study groups	Age in years (range)	Periodontal status diagnosis method	Testosterone measurement method	Confounding variables assessed
Vittek et al. (1979; USA)	10 Males	Group 1: 15-32 (31 ± 12)	Clinical examination (RPI, OHI)	Serum: RIA	Diabetes mellitus Smoking Educational level BMI Alcohol NA
	Group 1: RPI <0.5	Group 2: 18-29 (20 ± 6)	Radiographs	Gingiva: Histological evaluation	
	Group 2: RPI 0.5-1.5	Group 3: 18-19 (20 ± 3)			
Vittek et al. (1984; USA)	40 Males	Group 1: 43 ± 13	Clinical examination (GI, PD, mobility)	Saliva: RIA	Systemic conditions
	Group 1: 8 SH + HP	Group 2: 45 ± 15	Radiographs (MBL)		
	Group 2: 11 SH + CP	Group 3: 49 ± 13	Histological evaluation		
	Group 3: 8 DM + HP	Group 4: 50 ± 14			
	Group 4: 13 DM + CP				

Note. HH = hypergonadotropic hypogonadism; CP = chronic periodontitis; HP = healthy periodontum; SH = systemically healthy; PI = plaque index; GI = gingival index; BOP = bleeding on probing; PD = probing depth; CAL = clinical attachment loss; FMX = complete intra oral series; RIA = radioimmunoassay; BMI = body mass index; RPI = Russell's periodontal index; OHI = oral hygiene index; DM = diabetes mellitus; MBL = marginal bone loss; NA = not applicable.

significant difference in PD, CAL, and testosterone levels was reported.

Saliva and Gingival Testosterone Levels. Kuraner et al. (1991) reported increased levels of testosterone in parotid saliva among patients with CP compared with patients with healthy periodontum. Vittek et al. (1984) reported no significant difference in the concentration of salivary testosterone between patients with and without CP. However, in the study by Vittek et al. (1984), higher levels of salivary testosterone were detected in patients with DM and CP. Vittek et al. (1979) reported a significant increase in the overall metabolism of testosterone in the gingival tissue of patients with CP compared with healthy controls (Table 2).

Quality Assessment of Included Studies

Quality scores of the studies (Daltaban et al., 2006; Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979; Vittek et al., 1984) ranged from 9 to

12. Quality assessment identified that in general, recruitment of the patients, exposure (measurement of testosterone levels), and outcome (periodontal status) were adequately performed in these studies. As only studies in human subjects were included, the results could be considered to be applicable to the local population. A common shortcoming among the studies was the omission of confounding variables assessment. This contributed to the difficulty in determining whether the results were in accordance with the available evidence. Quality assessment of the articles included in the systematic review is summarized in Table 3.

Discussion

A limited number of studies have suggested a relationship between common oral diseases such as CP and male reproductive health conditions, including erectile dysfunction, low testosterone levels, and male infertility (Daltaban et al., 2006; Kellesarian, Kellesarian, et al., 2016; Kellesarian, Yunker, et al., 2016; Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh

Table 2. Primary Outcomes of the Studies Included.

Authors	Relationship between male testosterone levels and periodontal disease	
	Saliva and/or gingiva	Serum
Daltaban et al. (2006)	NA	Positive ^a (GI, BOP) Negative (CAL, PD)
Kuraner et al. (1991)	Positive ^b (saliva)	Negative
Orwoll et al. (2009)	NA	Negative
Samietz et al. (2016)	NA	Negative
Singh et al. (2011)	NA	Positive ^a
Steffens, Wang, et al. (2015)	NA	Positive ^a
Vittekk et al. (1979)	Positive ^b (gingiva)	Negative
Vittekk et al. (1984)	Negative (saliva)	NA

Note. GI = gingival index; BOP = bleeding on probing; PD = probing depth; CAL = clinical attachment loss; NA = not applicable.

^aLower testosterone levels. ^bHigher testosterone levels.

Table 3. CASP Quality Assessment of the Reviewed Articles.

Authors	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total quality score (0-12)
Daltaban et al. (2006)	Yes	Yes	Cannot tell	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Kuraner et al. (1991)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	10
Orwoll et al. (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12
Samietz et al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12
Singh et al. (2011)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	11
Steffens, Wang, et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12
Vittekk et al. (1979)	Yes	Cannot tell	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Vittekk et al. (1984)	Yes	Yes	Yes	Yes	Cannot tell	No	Yes	Yes	Yes	Yes	Yes	Yes	10

Note. Item 1 = study issue is clearly focused; Item 2 = cohort is recruited in an acceptable way; Item 3 = exposure is accurately measured; Item 4 = outcome is accurately measured; Item 5 = confounding factors are addressed; Item 6 = follow-up is long and complete; Item 7 = results are clear; Item 8 = results are precise; Item 9 = results are credible; Item 10 = results can be applied to the local population; Item 11 = results fit with available evidence; Item 12 = there are important clinical implications.

et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979; Vittek et al., 1984). To the best of our knowledge from indexed literature, this is the first study systematically reviewing the effect of testosterone levels in men's periodontal status. The purpose of this study was to highlight the use of testosterone levels as an analytical tool in the assessment of CP. Results from approximately 65% of the studies (Daltaban et al., 2006; Kuraner et al., 1991; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979) included reported a positive correlation between testosterone levels (saliva, gingiva, and/or serum) and CP. A possible explanation for these findings

is related to an increased growth of periodontopathogenic bacteria and altered vasculogenesis stimulated by hormones (Steffens, Wang, et al., 2015). It has been also proposed that testosterone could affect the gingival stromal cell response to inflammatory challenges by downregulation of proinflammatory cytokines production (Gornstein, Lapp, Bustos-Valdes, & Zamorano, 1999). Other proposed mechanisms include exacerbated response in the periodontal tissue by immune-endocrine interactions and a hormonal modulation of specific cell lines (fibroblast and epithelial cells; Steffens, Wang, et al., 2015). However, it is pertinent to mention that a variety

of factors may have biased the results of the included studies, and these findings need to be interpreted with caution. First, notwithstanding immunoassays are considered a valid method to measure testosterone levels, the lack of standardization in steroid hormones assays is well documented in the literature and considered an important limitation and deficiency in many epidemiological studies (Ankarberg-Lindgren & Norjavaara, 2015). The accuracy of immunoassays' measurements has been criticized when low testosterone concentrations are present, and high-quality steroid hormone assays with very good sensitivity, specificity, and reproducibility are required to validate the data of epidemiologic studies (Stanczyk, Lee, & Santen, 2007). Moreover, liquid chromatography–mass spectrometry is considered the gold standard and the only reliable method to measure sex steroids, including testosterone (Buttler et al., 2015; Trost & Mulhall, 2016). On a vigilant evaluation of the studies included in the present systematic review, it was identified that approximately 88% of the studies (Kuraner et al., 1991; Orwoll et al., 2009; Samietz et al., 2016; Singh et al., 2011; Steffens, Wang, et al., 2015; Vittek et al., 1979; Vittek et al., 1984) used different immunoassays to determine testosterone levels in serum and Daltaban et al. (2006) did not report the method used to assess testosterone levels. It is feasible that this lack of standardization in the methods to measure testosterone levels in serum may explain the conflicting results among the studies included. Well-designed prospective studies including liquid chromatography–mass spectrometry to assess testosterone levels are needed to draw definitive conclusions.

Second, several factors might influence testosterone levels, including aging, genetics, and comorbidities such as glycemic levels and obesity (Trost & Mulhall, 2016). Furthermore, the aforementioned factors have been similarly associated with increased prevalence and severity of periodontitis (Hajishengallis, 2014; Javed, Bashir Ahmed, & Romanos, 2014; Javed et al., 2016; Kellesarian, Kellesarian, et al., 2016; Xuan et al., 2016). It is noteworthy that the age between the included studies varied significantly. Daltaban et al. (2006) studied men with HH with age ranged between 19 and 21 years. Kuraner et al. (1991) assessed testosterone levels in patients aged between 28 and 40 years, and Orwoll et al. (2009) studied men between 66 and 95 years. Furthermore, it is noteworthy that 50% among the studies included (Daltaban et al., 2006; Kuraner et al., 1991; Vittek et al., 1979; Vittek et al., 1984) did not adjust the results for smoking, and approximately 63% of the studies (Daltaban et al., 2006; Kuraner et al., 1991; Singh et al., 2011; Vittek et al., 1979; Vittek et al., 1984) remained unadjusted for obesity. It is speculated that low testosterone levels are simply a risk indicator for CP, originated from common exposures, such as chronic hyperglycemia, aging, obesity, and/or smoking. It is pertinent to mention that all

the studies included were conducted for a relatively short period of time in only four countries, where the majority of the studies participants were of Caucasian origin. It is hard to generalize these findings to the whole population. Additional prospective studies including stringent confounder assessment, larger samples, for a longer period of time, and including different ethnicities are needed.

In two studies (Kuraner et al., 1991; Vittek et al., 1984), testosterone levels were measured in whole saliva; however, the results were conflicting. Kuraner et al. (1991) reported a positive association between CP and higher salivary testosterone levels, whereas Vittek et al. (1984) reported a negative association. The role of whole saliva as a diagnostic tool has gain popularity in the past decade due to its noninvasive accessibility (Javaid, Ahmed, Durand, & Tran, 2016). The effectiveness of saliva as a reliable diagnostic fluid to measure testosterone levels remains debatable. For example, Hayes et al. (2015) reported poor levels of agreement between saliva and serum measurements of testosterone among aging men, whereas Lippi et al. (2016) reported a significant correlation between free testosterone in serum and saliva, whereas no significant correlation was reported between total testosterone in serum and saliva. Therefore, the authors of the present systematic review suggest extreme caution when interpreting the conclusions of the studies included in the present systematic review.

It is imperative for general physicians and oral health care providers to be aware of the fact that oral inflammatory conditions (such as CP) can influence the systemic health, including men's reproductive health. Likewise, systemic conditions (such as erectile dysfunction) may influence oral health status (Kellesarian, Kellesarian, et al., 2016). It is therefore recommended that evaluations of patients' medical histories should be considered as an integral component of comprehensive dental examinations. Moreover, patients exhibiting low testosterone levels in body fluids should be referred to oral health care providers for dental examinations and treatment. Such regimens may also help improve the overall quality of life of patients.

Conclusion

Within the limits of the evidence available, the relationship between low testosterone levels and CP remains debatable and further longitudinal studies and control trials are needed.

Appendix

List of Excluded Articles

Coletta, R. D., Reynolds, M. A., Martelli-Junior, H., Graner, E., Almeida, O. P., & Sauk, J. J. (2002). Testosterone

- stimulates proliferation and inhibits interleukin-6 production of normal and hereditary gingival fibromatosis fibroblasts. *Oral Microbiology and Immunology*, 17, 186-192. (Experimental study)
- Ishisaka, A., Ansai, T., Soh, I., Inenaga, K., Awano, S., Yoshida, A., . . . Takehara, T. (2008). Association of cortisol and dehydroepiandrosterone sulphate levels in serum with periodontal status in older Japanese adults. *Journal of Clinical Periodontology*, 35, 853-861. doi:10.1111/j.1600-051X.2008.01309.x (Focus question not answered)
- Ishisaka, A., Ansai, T., Soh, I., Inenaga, K., Yoshida, A., Shigeyama, C., . . . Takehara, T. (2007). Association of salivary levels of cortisol and dehydroepiandrosterone with periodontitis in older Japanese adults. *Journal of Periodontology*, 78, 1767-1773. (Focus question not answered)
- Jönsson, D., Aggarwal, P., Nilsson, B. O., & Demmer, R. T. (2013). Beneficial effects of hormone replacement therapy on periodontitis are vitamin D associated. *Journal of Periodontology*, 84, 1048-1057. (Focus question not answered)
- Morishita, M., Aoyama, H., Tokumoto, K., & Iwamoto, Y. (1988). The concentration of salivary steroid hormones and the prevalence of gingivitis at puberty. *Advances in Dental Research*, 2, 397-400. (Focus question not answered)
- Morishita, M., Miyagi, M., & Iwamoto, Y. (1999). Effects of sex hormones on production of interleukin-1 by human peripheral monocytes. *Journal of Periodontology*, 70, 757-760. (Experimental study)
- Nakagawa, S., Fujii, H., Machida, Y., & Okuda, K. (1994). A longitudinal study from prepuberty to puberty of gingivitis: Correlation between the occurrence of *Prevotella intermedia* and sex hormones. *Journal of Clinical Periodontology*, 21, 658-665. (Focus question not answered)
- Ozelik, O., Haytac, M. C., & Seydaoglu, G. (2006). The effects of anabolic androgenic steroid abuse on gingival tissues. *Journal of Periodontology*, 77, 1104-1109. (Focus question not answered)
- Parazzoli, L., & Vernole, B. (1965). Effect of proteinanabolizer therapy on the serum and salivary protein electrophoresis of healthy periodontal disease patients. *Rivista Italiana di Stomatologia*, 20, 528-537. (Focus question not answered)
- Shiau, H. J., Aichelmann-Reidy, M. E., & Reynolds, M. A. (2014). Influence of sex steroids on inflammation and bone metabolism. *Periodontology 2000*, 64, 81-94. doi:10.1111/prd.12033 (Review)
- Sooriyamoorthy, M., & Gower, D. B. (1989). Phenytoin stimulation of testosterone metabolism in inflamed human gingival fibroblasts. *Biochemical Society Transactions*, 17, 1020-1021. (Experimental study)
- Steffens, J. P., Coimbra, L. S., Ramalho-Lucas, P. D., Rossa, C. Jr., & Spolidorio, L. C. (2012). The effect of supra- and subphysiologic testosterone levels on ligature-induced bone loss in rats—A radiographic and histologic pilot study. *Journal of Periodontology*, 83, 1432-1439. doi:10.1902/jop.2012.110658 (Experimental study)
- Steffens, J. P., Coimbra, L. S., Rossa, C., Jr., Kantarci, A., Van Dyke, T. E., & Spolidorio, L. C. (2015). Androgen receptors and experimental bone loss—An *in vivo* and *in vitro* study. *Bone*, 81, 683-690. doi:10.1016/j.bone.2015.10.001 (Experimental study)
- Steffens, J. P., Herrera, B. S., Coimbra, L. S., Stephens, D. N., Rossa, C. Jr., Spolidorio, L. C., . . . Van Dyke, T. E. (2014). Testosterone regulates bone response to inflammation. *Hormone and Metabolic Research*, 46, 193-200. doi:10.1055/s-0034-1367031 (Experimental study)
- Xu, Z., Peng, X., & Ma, H. (1995). [Relationship between kidney insufficiency and some endocrine hormones in periodontitis patients]. *Zhonghua Kou Qiang Yi Xue Za Zhi*, 30, 301-303. (Focus question not answered)

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors extend their sincere appreciations to Deanship of Scientific Research at King Saud University for its funding of this prolific research group (PRG-1437-38).

References

- Ankarberg-Lindgren, C., & Norjavaara, E. (2015). Sensitive RIA measures testosterone concentrations in prepubertal and pubertal children comparable to tandem mass spectrometry. *Scandinavian Journal of Clinical & Laboratory Investigation*, 75, 341-344. doi:10.3109/00365513.2014.942694
- Bellido, T., Jilka, R. L., Boyce, B. F., Girasole, G., Broxmeyer, H., Dalrymple, S. A., . . . Manolagas, S. C. (1995). Regulation of interleukin-6, osteoclastogenesis, and bone mass by androgens. The role of the androgen receptor. *Journal of Clinical Investigation*, 95, 2886-2895. doi:10.1172/jci117995
- Buttler, R. M., Martens, F., Fanelli, F., Pham, H. T., Kushnir, M. M., Janssen, M. J., . . . Heijboer, A. C. (2015). Comparison of 7 published LC-MS/MS methods for the simultaneous measurement of testosterone, androstenedione, and dehydroepiandrosterone in serum. *Clinical Chemistry*, 61, 1475-1483. doi:10.1373/clinchem.2015.242859
- Daltaban, O., Saygun, I., & Bolu, E. (2006). Periodontal status in men with hypergonadotropic hypogonadism: Effects of testosterone deficiency. *Journal of Periodontology*, 77, 1179-1183. doi:10.1902/jop.2006.050286
- ElAttar, T. M., Lin, H. S., & Tira, D. E. (1982). Testosterone inhibits prostaglandin formation by human gingival connective tissue: Relationship to 14C-arachidonic acid metabolism. *Prostaglandins, Leukotrienes and Medicine*, 9, 25-34.
- Famili, P., Cauley, J. A., & Greenspan, S. L. (2007). The effect of androgen deprivation therapy on periodontal disease in men with prostate cancer. *Journal of Urology*, 177, 921-924. doi:10.1016/j.juro.2006.10.067
- Forsblad-d'Elia, H., Carlsten, H., Labrie, F., Kontinen, Y.T., & Ohlsson, C. (2009). Low serum levels of sex steroids

- are associated with disease characteristics in primary Sjogren's syndrome; supplementation with dehydroepiandrosterone restores the concentrations. *Journal of Clinical Endocrinology & Metabolism*, *94*, 2044-2051.
- Francis, P. T., Gladwell, R. T., & Holman, R. B. (1984). The effect of testosterone on the release of endogenous catecholamines from the hypothalamus of the cockerel in vitro. *Psychoneuroendocrinology*, *9*, 69-76.
- Gornstein, R. A., Lapp, C. A., Bustos-Valdes, S. M., & Zamorano, P. (1999). Androgens modulate interleukin-6 production by gingival fibroblasts in vitro. *Journal of Periodontology*, *70*, 604-609. doi:10.1902/jop.1999.70.6.604
- Hajishengallis, G. (2014). Aging and its impact on innate immunity and inflammation: Implications for periodontitis. *Journal of Oral Biosciences*, *56*(1), 30-37. doi:10.1016/j.job.2013.09.001
- Hayes, L. D., Sculthorpe, N., Herbert, P., Baker, J. S., Hullin, D. A., Kilduff, L. P., & Grace, F. M. (2015). Poor levels of agreement between serum and saliva testosterone measurement following exercise training in aging men. *Aging Male*, *18*, 67-70. doi:10.3109/13685538.2015.1018158
- Jafri, Z., Bhardwaj, A., Sawai, M., & Sultan, N. (2015). Influence of female sex hormones on periodontium: A case series. *Journal of Natural Science, Biology and Medicine*, *6*(Suppl. 1), S146-S149. doi:10.4103/0976-9668.166124
- Javaid, M. A., Ahmed, A. S., Durand, R., & Tran, S. D. (2016). Saliva as a diagnostic tool for oral and systemic diseases. *Journal of Oral Biology and Craniofacial Research*, *6*, 66-75. doi:10.1016/j.jobcr.2015.08.006
- Javed, F., Bashir Ahmed, H., & Romanos, G. E. (2014). Association between environmental tobacco smoke and periodontal disease: A systematic review. *Environmental Research*, *133*, 117-122. doi:10.1016/j.envres.2014.05.008
- Javed, F., Kellesarian, S. V., Al-Kheraif, A. A., Ranna, V., Qadri, T., Yunker, M., . . . Romanos, G. E. (2016). Effect of Nd:YAG laser-assisted non-surgical periodontal therapy on clinical periodontal and serum biomarkers in patients with and without coronary artery disease: A short-term pilot study. *Lasers in Surgery and Medicine*. Advance online publication. doi:10.1002/lsm.22483
- Kellesarian, S. V., Kellesarian, T. V., Ros Malignaggi, V., Al-Askar, M., Ghanem, A., Malmstrom, H., & Javed, F. (2016). Association between periodontal disease and erectile dysfunction: A systematic review. *American Journal of Men's Health*. Advance online publication. doi:10.1177/1557988316639050
- Kellesarian, S. V., Yunker, M., Malmstrom, H., Almas, K., Romanos, G. E., & Javed, F. (2016). Male infertility and dental health status: A systematic review. *American Journal of Men's Health*. Advance online publication. doi:10.1177/1557988316655529
- Khera, M. (2016). Male hormones and men's quality of life. *Current Opinion in Urology*, *26*, 152-157. doi:10.1097/mou.0000000000000256
- Kuraner, T., Beksac, M. S., Kayakirilmaz, K., Caglayan, F., Onderoglu, L. S., & Ozgunes, H. (1991). Serum and parotid saliva testosterone, calcium, magnesium, and zinc levels in males, with and without periodontitis. *Biological Trace Element Research*, *31*, 43-49.
- Lippi, G., Dipalo, M., Buonocore, R., Gnocchi, C., Aloe, R., & Delsignore, R. (2016). Analytical evaluation of free testosterone and cortisol immunoassays in saliva as a reliable alternative to serum in sports medicine. *Journal of Clinical Laboratory Analysis*. Advance online publication. doi:10.1002/jcla.21929
- McBride, J. A., Carson, C. C., III, & Coward, R. M. (2016). Testosterone deficiency in the aging male. *Therapeutic Advances in Urology*, *8*, 47-60. doi:10.1177/1756287215612961
- Mellstrom, D., Johnell, O., Ljunggren, O., Eriksson, A. L., Lorentzon, M., Mallmin, H., . . . Ohlsson, C. (2006). Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. *Journal of Bone and Mineral Research*, *21*, 529-535. doi:10.1359/jbmr.060110
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred Reporting Items for Systematic reviews and Meta-Analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. doi:10.1371/journal.pmed.1000097
- Moran, J. M., Martin, R. R., Pedrera-Canal, M., Alonso-Terron, J., Rodriguez-Velasco, F. J., & Pedrera-Zamorano, J. D. (2015). Low testosterone levels are associated with poor peripheral bone mineral density and quantitative bone ultrasound at phalanges and calcaneus in healthy elderly men. *Biological Research for Nursing*, *17*, 169-174. doi:10.1177/1099800414532710
- Morgentaler, A. (2016). Controversies and advances with testosterone therapy: A 40-year perspective. *Urology*, *89*, 27-32. doi:10.1016/j.urology.2015.11.034
- Orwoll, E. S., Chan, B. K., Lambert, L. C., Marshall, L. M., Lewis, C., & Phipps, K. R. (2009). Sex steroids, periodontal health, and tooth loss in older men. *Journal of Dental Research*, *88*, 704-708. doi:10.1177/0022034509341013
- Ram, V. S., Parthiban Sudhakar, U., Mithradas, N., & Prabhakar, R. (2015). Bonebiomarkers in periodontal disease: A review article. *Journal of Clinical and Diagnostic Research*, *9*(1), Ze07-Ze10. doi:10.7860/jcdr/2015/11268.5438
- Roberts, C. (2008). Modelling patterns of agreement for nominal scales. *Statistics in Medicine*, *27*, 810-830. doi:10.1002/sim.2945
- Samietz, S., Holtfreter, B., Friedrich, N., Mundt, T., Hoffmann, W., Volzke, H., . . . Biffar, R. (2016). Prospective association of sex steroid concentrations with periodontal progression and incident tooth loss. *Journal of Clinical Periodontology*, *43*, 10-18. doi:10.1111/jcpe.12493
- Sansone, A., Sansone, M., Lenzi, A., & Romanelli, F. (2016). Testosterone replacement therapy: The emperor's new clothes. *Rejuvenation Research*. Advance online publication. doi:10.1089/rej.2016.1818
- Shapiro, L. F., & Freeman, K. (2014). The relationship between estrogen, estrogen receptors and periodontal disease in adult women: A review of the literature. *New York State Dental Journal*, *80*(3), 30-34.
- Shin, J., Sung, J., Lee, K., & Song, Y. M. (2016). Genetic influence on the association between bone mineral density and testosterone in Korean men. *Osteoporosis International*, *27*, 643-651. doi:10.1007/s00198-015-3298-4

- Singh, B. P., Makker, A., Tripathi, A., Singh, M. M., & Gupta, V. (2011). Association of testosterone and bone mineral density with tooth loss in men with chronic periodontitis. *Journal of Oral Science*, *53*, 333-339.
- Stanczyk, F. Z., Lee, J. S., & Santen, R. J. (2007). Standardization of steroid hormone assays: Why, how, and when? *Cancer Epidemiology, Biomarkers & Prevention*, *16*, 1713-1719. doi:10.1158/1055-9965.epi-06-0765
- Steffens, J. P., Coimbra, L. S., Rossa, C., Jr., Kantarci, A., Van Dyke, T. E., & Spolidorio, L. C. (2015). Androgen receptors and experimental bone loss—An *in vivo* and *in vitro* study. *Bone*, *81*, 683-690. doi:10.1016/j.bone.2015.10.001
- Steffens, J. P., Wang, X., Starr, J. R., Spolidorio, L. C., Van Dyke, T. E., & Kantarci, A. (2015). Associations between sex hormone levels and periodontitis in men: Results from NHANES III. *Journal of Periodontology*, *86*, 1116-1125. doi:10.1902/jop.2015.140530
- Trost, L. W., & Mulhall, J. P. (2016). Challenges in testosterone measurement, data interpretation, and methodological appraisal of interventional trials. *Journal of Sexual Medicine*, *13*, 1029-1046. doi:10.1016/j.jsxm.2016.04.068
- Vanderschueren, D., Vandenput, L., Boonen, S., Lindberg, M. K., Bouillon, R., & Ohlsson, C. (2004). Androgens and bone. *Endocrine Reviews*, *25*, 389-425. doi:10.1210/er.2003-0003
- Vittek, J., Kirsch, S., Rappaport, S. C., Bergman, M., & Southren, A. L. (1984). Salivary concentrations of steroid hormones in males and in cycling and postmenopausal females with and without periodontitis. *Journal of Periodontal Research*, *19*, 545-555.
- Vittek, J., Rappaport, S. C., Gordon, G. G., Munnangi, P. R., & Southren, A. L. (1979). Concentration of circulating hormones and metabolism of androgens by human gingiva. *Journal of Periodontology*, *50*, 254-264. doi:10.1902/jop.1979.50.5.254
- Wang, Q., Kessler, M. J., Kensler, T. B., & Dechow, P. C. (2016). The mandibles of castrated male rhesus macaques (*Macaca mulatta*): The effects of orchidectomy on bone and teeth. *American Journal of Physical Anthropology*, *159*, 31-51. doi:10.1002/ajpa.22833
- Xuan, D., Han, Q., Tu, Q., Zhang, L., Yu, L., Murry, D., . . . Chen, J. (2016). Epigenetic modulation in periodontitis: Interaction of adiponectin and JMJD3-IRF4 axis in macrophages. *Journal of Cellular Physiology*, *231*, 1090-1096. doi:10.1002/jcp.25201
- Zeng, X., Zhang, Y., Kwong, J. S., Zhang, C., Li, S., Sun, F., . . . Du, L. (2015). The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. *Journal of Evidence-Based Medicine*, *8*, 2-10. doi:10.1111/jebm.12141