

## Review Article

# Relationship between Chronic Periodontitis and Erectile Dysfunction: A Narrative Review

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Received 9 January 2016; Revised 13 February 2016; Accepted 23 February 2016

Academic Editor: Atsushi Saito

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**Objective.** To conduct a descriptive literature review on research studies investigating the association between chronic periodontitis (CP) and erectile dysfunction (ED). **Methods.** Cohort studies, case-control studies, cross-sectional studies, randomized control trials, and animal studies up to July 2015 that studied the relationship between CP and ED were reviewed and reported. Data sources included PubMed, EMBASE, Cochrane Library, and Clinicaltrials.gov. The themes “periodontal disease” and “erectile dysfunction” and the role of periodontal therapy were identified and discussed throughout the narrative review. **Results.** After reviewing the literature, it was found that an association between CP and vasculogenic ED likely exists. Inflammation resulting from CP promotes endothelial dysfunction by increasing the systemic levels of inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Periodontal therapy attempts to decrease the release of TNF- $\alpha$  and could act to restore endothelial function, particularly in the penile vasculature. **Conclusion.** Although the literature reported a positive association between CP and ED, the studies were few and possess several methodological limitations. Large-scale cohort studies and confounder analysis are recommended. Dentists and physicians should collaborate to manage patients with either CP or ED because of their potential association not only with each other but also with other serious systemic comorbidities.

## 1. Introduction

Chronic periodontitis (CP) is defined as the inflammation of the gingiva extending to the adjacent attachment apparatus [1]. CP is characterized by destruction of both the periodontal ligaments and the supporting alveolar bone [1], which if left untreated can result in the loss of dentition [2]. CP patients report significantly poorer Oral Health Related Quality of Life (OHRQoL) [3] when compared to periodontally healthy controls, indicating that CP patients suffer from significant functional, social, and psychological debilitation as a consequence of their disease [3–5]. Globally, around 5–15% of patients with 34–45 years of age suffer from severe periodontitis [6]. According to combined data from the 2009–2010 and 2011–2012 cycles of NHANES, periodontitis affects

45.9% of USA's population, with severe periodontitis affecting 8.9% of the population. As with ED, age is a significant risk factor for CP. 64% of adults with >65 years of age have either moderate or severe periodontitis [7].

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance [8]. Health Related Quality of Life (HRQoL) is significantly diminished in individuals suffering from ED [9–11], suggesting that ED not only impacts physical health but also leads to profound emotional and mental health impairments. ED may result from a variety of causes ranging from organic (e.g., vascular, neurogenic, hormonal, anatomic, and drug-induced) to psychological causes [12]. The majority of men who develop ED have underlying vascular changes [13] often stemming from complications of

atherosclerosis [14]. A chronic consequence of atherosclerosis is occlusive systemic vascular disease [14, 15] which can precipitate vasculogenic ED through impaired relaxation of smooth muscle, occlusion of the cavernosal arteries, or a combination of both [15–17].

152 million men worldwide experienced some form of ED in 1995, and experts predict that in 2025 the worldwide prevalence of ED could reach 322 million [18]. Three population surveys have attempted to estimate the prevalence of ED in USA: the Massachusetts Male Aging Study (MMAS) [19], the National Health and Social Life Survey (NHSLS) [11], and the National Health and Nutrition Examination Survey (NHANES) [20].

The MMAS was a longitudinal study of 1709 Massachusetts men between the ages of 40 and 70 years conducted from 1987 to 1989 [19]. This study found an ED prevalence rate of 52% and noted that both the prevalence and severity of ED increased with age. At follow-up, a crude incidence rate of 25.9 cases per 1,000 person-years (95% CI: 22.5 to 29.9) was reported [21]. The incidence of ED increased with each decade of age and was higher for men with self-reported comorbidities at baseline such as diabetes (50.7 cases per 1,000 man-years), treated heart disease (58.3), or treated hypertension (42.5). The NHSLS was a survey in USA which evaluated general sexual function in both men and women. After evaluating 1410 men, researchers found that with increasing age the prevalence of ED increased and the levels of sexual desire decreased. Moreover, ED was more likely to occur among men in poorer physical and emotional health [11]. A cross-sectional analysis of data from the 2001–2002 NHANES found that the overall prevalence of ED in US men with  $\geq 20$  years of age is 18.4% [20]. In concordance with the findings of similar surveys [11, 19], the prevalence of ED increased with age and with a history of cardiovascular disease or other cardiovascular risk factors [20].

**Rationale.** In addition to its negative impact on OHRQoL, CP is known to be associated with several systemic diseases [22]. This concept of Periodontal Medicine has resulted in multiple studies reporting that individuals with periodontitis have a significantly increased risk of comorbid coronary heart disease, cerebrovascular disease, diabetes mellitus, and chronic obstructive pulmonary disease [22–24]. Recently, there has been a burgeoning interest in the association between CP and ED because both diseases share similar risk factors [24]. To date, there exists no comprehensive review of the literature for this topic. Individually, both CP and ED are serious public health concerns and any association between the two portends worse HRQoL and OHRQoL for affected individuals. It is important to critically review the level of evidence for this association not only to inform the practicing clinician but also to direct future research questions with the hope of improving upon the methodological weaknesses of past studies.

**Goal Statement.** The goal is to conduct a descriptive literature review of studies reporting on the relationship between chronic periodontitis (CP) and erectile dysfunction (ED).

## 2. Methods

**2.1. Data Source.** A search was performed for all existing and “in press” publications up to July 2015 in PubMed, EMBASE, Cochrane Library, and Clinicaltrials.gov. The following search terms were used: (“erectile dysfunction” OR “penile erection” OR “sexual dysfunction”) AND (“periodontal disease” OR “gum disease”). No limits were applied to this search strategy to ensure a thorough search. No language restrictions were made, and citations of relevant studies were checked.

**2.2. Eligibility Criteria.** Cohort studies, case-control studies, cross-sectional studies, randomized control trials, and animal studies evaluating the risk of ED events in relation to CP were considered eligible for inclusion if the following criteria were met: (1) full text could be obtained; (2) clear diagnostic criteria for CP and ED were reported; and (3) the adjusted and/or unadjusted hazard ratios (HR), odds ratios (ORs), or relative risks (RR) and associated 95% confidence intervals (CI) with  $p$  values or the numbers of events (incidence or prevalence) that can be used to calculate them were reported. If  $>1$  study covered the same population, only the report containing the most comprehensive information on that population was included.

**2.3. Search Process.** Two investigators (Jaffer A. Shariff and Kevin C. Lee) independently performed article searches and reviewed the resulting titles and abstracts. Duplicate articles and those not meeting the eligibility criteria were removed. Full texts of all potentially eligible studies were obtained and verified for eligibility. Discrepancies between the two investigators were resolved by the arbitration of a third investigator (Aparna Ingleshwar).

## 3. Results

The literature search yielded 33 unique articles, and after careful review, 9 articles [15, 25–32] meeting the eligibility criteria were selected for inclusion (Figure 1). Of the 9 studies, 1 study [32] examined the pathophysiological association between CP and ED in rats, another study [15] examined the effect of periodontal therapy on ED severity, and the remaining 7 studies [25–31] examined the clinical association between CP and ED in humans.

**3.1. Pathophysiological Association between CP and ED.** Zuo et al. conducted the only experimental study to demonstrate the direct biologic relationship between CP and ED [32]. In their study, periodontitis was induced in five twelve-week-old male rats that were randomly chosen from a group of ten rats. The control group consisted of the remaining five rats. Both the control rats and the periodontitis rats were fed a powder diet for eight weeks. After eight weeks comparisons were made between the two groups on the following 4 measurements: the ratio of maximum intracavernosal pressure/mean arterial pressure ( $ICP_{max}/MAP$ )  $\times 100$ , the expression of endothelial nitric oxide synthase (eNOS)

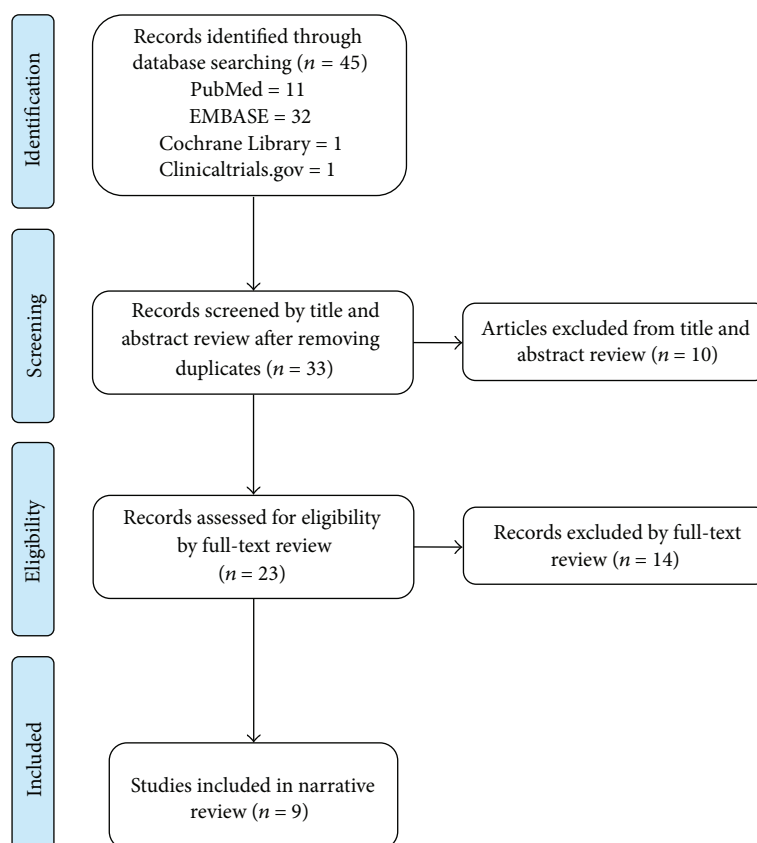


FIGURE 1: Flow chart of the results of the literature search.

in penile tissue, the levels of serum C-reactive protein (CRP) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and the ultrastructural changes of the cavernous tissue. It was reported that the ratio of  $(ICP_{max}/MAP) \times 100$  in the periodontitis rats was significantly less than that of controls ( $19.54 \pm 6.16$  versus  $30.45 \pm 3.12$  and  $30.91 \pm 5.61$  versus  $50.52 \pm 9.52$ , resp.;  $p < 0.05$ ). In the periodontitis rats, serum CRP and TNF- $\alpha$  levels were significantly higher, and cavernous tissue's eNOS expression was significantly decreased. However, no significant alternations in the ultrastructure of penile cavernous tissue were seen between the two groups.

**3.2. Clinical Association between CP and ED.** The 7 studies conducted in India [25, 26], Japan [27], Taiwan [28, 29], Israel [30], and Turkey [31] reported on the association between CP and ED in humans. Of these, only the two Taiwanese studies [28, 29] used population-based data from a national database, namely, the National Health Insurance Research Database (NHIRD). The remaining five studies [25–27, 30, 31] had convenience samples ranging in size from 53 to 300 participants. All studies included men with  $\geq 18$  years of age, and the mean ages across the seven studies [25–31] ranged from 35 to 51 years.

**3.2.1. Assessment of ED.** All studies [25–31] were comparable in their assessment of ED. Five studies [25–27, 30, 31] used the

self-reported International Index of Erectile Function (IIEF) questionnaire to diagnose ED. Four [25, 27, 30, 31] of these five studies [25–27, 30, 31] used a short-form version of the IIEF called the IIEF-5 or the Sexual Health Inventory for Men (SHIM) questionnaire. One study [26] used both the IIEF-5 and a color Doppler ultrasound to diagnose ED. The method for scoring the IIEF was consistent across the five studies. The two population-based studies [28, 29] defined ED cases with the ICD-9-CM 607 diagnostic code. However, the ICD-9 code is derived from the IIEF questionnaire, and therefore using either should yield the same diagnosis.

**3.2.2. Assessment of CP.** The studies varied in their definitions of CP (Table 1). Both the population-based studies [28, 29] identified CP patients through the ICD-9-CM 523.4 diagnostic code. The Japanese study [27] used a CP self-check sheet, relying on patients to self-report CP. The remaining four studies [25, 26, 30, 31] used clinical diagnoses criteria. Of these, one study [26] diagnosed CP using probing depth (PD)  $\geq 5$  mm with clinical attachment loss (CAL)  $\geq 3$  mm and alveolar bone loss  $\geq 6$  mm, two studies [25, 30] diagnosed CP using only alveolar bone loss of  $\geq 6$  mm, and the last study [31] stratified CP into 3 levels according to PD: no CP if PD  $\leq 4$  mm, mild CP if PD  $\geq 4$  mm in  $< 15$  tooth sites with Bleeding on Probing (BoP), and severe CP if PD  $\geq 4$  mm in  $\geq 15$  tooth sites with BoP.

TABLE 1: Characteristics of the 9 studies evaluating ED and CP.

Author, year	Objective	Study population	Patients included	Assessment of ED	Assessment of CP
Keller et al., 2012 [28]	Association between ED and CP; gingivectomy and periodontal flap surgery on ED	Taiwan's National Health Insurance Research Database (NHIRD) of inpatient and outpatient medical benefit claims	32,856 ED cases; 164,280 age-matched controls; $\geq 18$ y	Self-administered IIEF-5 questionnaire and ICD-9-CM code 607.84; $\geq 2$ ED diagnoses with at least one by a urologist	ICD-9-CM code 523.4; $\geq 2$ CP diagnoses prior to ED diagnosis
Matsumoto et al., 2014 [27]	Association between ED and CP	Asahikawa city, Japan	88 adult men; mean age: 50.9 y	Self-administered IIEF-5 questionnaire	CP self-check sheet
Oğuz et al., 2013 [31]	Association between ED and CP	Patient pool of the Department of Urology at İnönü University	80 ED cases; 82 controls; 30–40 y	Clinician administered IIEF questionnaire	Severe periodontal disease was defined as $\geq 15$ tooth sites with $\geq 4$ mm PD and BoP
Sharma et al., 2011 [26]	Association between ED and CP	Outpatient section of Ankur Healthcare (andrology clinics), Rajajinagar, Bangalore, India	70 patients with vasculogenic ED; mean age: 35.3 y	IIEF-5 questionnaire and colored penile Doppler ultrasound	PD $\geq 5$ mm and attachment loss (CA loss $\geq 3$ mm at $>30\%$ sites with radiographic evidence of bone loss (distance of CEJ to alveolar bone crest of $\geq 6$ mm))
Tsao et al., 2015 [29]	Association between ED and CP; extraction on ED	Longitudinal Health Insurance Database 2000 (LHID2000) which is a randomly sampled subset of the NHIRD	5105 ED cases; 10,210 age-matched controls; $\geq 20$ y	ICD-9-CM code 607.84; $\geq 2$ ED diagnoses with at least one by a urologist	ICD-9-CM code 523.4; $\geq 2$ CP diagnoses prior to ED diagnosis
Uppal et al., 2014 [25]	Association between ED and CP	Outpatient departments of the hospitals in Ferozepur city, Punjab, India	53 patients with vasculogenic ED; $>20$ permanent teeth, no periodontal therapy in last 6 months, no aggressive periodontitis, and no systemic diseases	IIEF-5 questionnaire	PD $>5$ mm and radiographic evidence of bone loss in at least one site in the jaw with distance of CEJ to alveolar bone crest of $\geq 6$ mm
Zadik et al., 2009 [30]	Association between ED and CP	Israel Defense Forces (IDF) personnel $\geq 25$ y who filled the SHIM questionnaire during SPEC examinations	305 men who completed the IIEF-5 questionnaire and had posterior bitewing dental radiographs; mean age: 39.5 y	Clinician administered IIEF-5 questionnaire	Alveolar bone loss in at least one site in the jaw with distance of CEJ to alveolar bone crest of $\geq 6$ mm

TABLE 1: Continued.

Author, year	Objective	Study population	Patients included	Assessment of ED	Assessment of CP
Zuo et al., 2011 [32]	Biologic relationship between CP and ED (rats)	Sprague-Dawley rats purchased from the Experimental Animal Center of Luzhou Medical College	5 CP-induced cases; 5 age-matched controls; 12 weeks old	Ratio of $ICP_{max}/MAP \times 100$ ; eNOS expression; NOS and cGMP activity; ultrastructure of penile cavernous tissue	Periodontitis features including easy gum bleeding, periodontal pocket formation, alveolar bone absorption, and junctional epithelium moved to the apical root around the mandibular first molar tooth area
Eltas et al., 2013 [15]	Periodontal treatment on ED	Patient pool of the Department of Urology at İnönü University	120 patients with both CP and severe or moderate ED; >20 permanent teeth; 30–40 y	Clinician administered IIEF questionnaire	>30% of sites had PD and CA loss $\geq 4$ mm at baseline

ED, erectile dysfunction; CP, chronic periodontitis; PD, probing depth; ICP, intracavernosal pressure; MAP, mean arterial pressure; CA loss, clinical attachment loss; BoP, bleeding on probing; CEJ, cemento-enamel junction.

**3.2.3. Summary of Studies.** Uppal et al. [25] conducted a cohort study to assess the association between vasculogenic ED and CP. Patients were recruited from outpatient departments of hospitals in Ferozepur city, Punjab, India. All study subjects ( $N = 53$ ) had already received the diagnosis of vasculogenic ED and were classified into mild, moderate, and severe groupings on the basis of SHIM questionnaire scores. All subjects had ED with no other systemic diseases. Of the 53 included ED patients, 23 were mild, 17 were moderate, and 13 were severe. Between mild and moderate ED groups a significant difference in bone loss of 1.36 mm was seen. Likewise, between mild and severe ED groups a significant difference of 2.26 mm of bone loss was seen. Both bone loss and PD were positively correlated with the severity of ED, and the authors concluded that CP and ED were significantly associated.

Sharma et al. [26] conducted a retrospective cohort study in India to examine the association between CP and vasculogenic ED. Patients were recruited from an andrology clinic, and only those who were clinically diagnosed with ED through both the SHIM questionnaire and a clinical exam were selected ( $N = 82$ ). Then, only those patients with vasculogenic ED ( $N = 70$ ) were included in the study as ED cases. Patients who had received periodontal therapy within the last 6 months, used alcohol or tobacco in any form, had suffered from any acute or chronic medical conditions except ED, and were on medications that could alter the course of ED and CP were excluded from the study. A color Doppler ultrasound was used to confirm the diagnosis of vasculogenic ED and measure arterial insufficiency (peak systolic velocity  $<25$  cm/s). Patients with PD  $\geq 5$  mm and CAL  $\geq 3$  mm at  $>30\%$  sites with radiographic evidence of  $\geq 6$  mm of bone loss were diagnosed as having CP. Five patients with ED and CP were randomly selected for cardiac color Doppler to assess any changes in the vascularity of the heart in patients with ED and CP. Two of the 5 patients screened for cardiac Doppler demonstrated early cardiac vascular insufficiency. Prevalence of CP among vasculogenic ED patients increased with severity of vasculogenic ED: mild vasculogenic ED group (CP prevalence: 38.8%), mild-to-moderate vasculogenic ED group (CP prevalence: 45.8%), moderate vasculogenic ED group (CP prevalence: 76.4%), and severe vasculogenic ED group (CP prevalence: 81.8%). The positive correlation observed between CP and vasculogenic ED was not statistically significant. Although not all the patients in each ED group were affected with CP, the mean PD and mean CAL values increased with the severity of ED.

Matsumoto et al. [27] examined the relationship between CP and ED using outpatient interview sheets at dental clinics in Asahikawa city, Japan. The interview sheets for CP and ED were distributed to 300 men at hospital and dental clinics in Asahikawa. The CP self-check sheet was used to detect CP and assess its severity. The questionnaire consisted of 15 questions on CP symptoms and classified CP severity into 4 categories based on total score: a score of 0–9 indicated little possibility of periodontitis; a score of 10–30 indicated the possibility of periodontitis; a score of 31–70 required a dental check; and a score of  $\geq 71$  indicated that advanced symptoms were present and treatment was necessary. The IIEF-5

questionnaire, a short-form version of the IIEF, was used to detect ED and assess its severity. Scores  $>21$  represented normal erectile function and scores  $\leq 21$  represented ED. ED severity was classified into four categories based on the IIEF-5 scores: a score of 1 to 7 indicated severe ED; a score of 8 to 11 indicated moderate ED; a score of 12 to 16 indicated moderate-to-mild ED; a score of 17 to 21 indicated mild ED; and a score of  $\geq 22$  indicated no ED. A statistically significant correlation was observed among the following: between CP scores and the presence of ED ( $p = 0.04$ ) and between CP score and the ability to keep an erection (when looking at individual questions;  $p = 0.02$ ). However, no statistically significant correlation was noted between CP scores and the severity of ED ( $p = 0.11$ ). Correlations between CP scores, ED, and age revealed no statistically significant correlation between age and CP score ( $p = 0.06$ ), but there was a significant correlation between age and each item of the IIEF-5 questionnaire (all;  $p < 0.0001$ ).

Keller et al. [28] conducted a population-based study in Taiwan to examine the association between CP and ED using a retrospective case-control design. They used the Longitudinal Health Insurance Database 2000 (LHID2000), a random subset of the National Health Insurance Research Database, and selected 32,856 cases, all of whom were with  $\geq 18$  years of age and had received  $\geq 2$  diagnoses of ED between 2007 and 2009. A total of 164,280 controls (5 controls per case) were randomly selected and age-matched against cases. CP cases were identified only if the patients had  $\geq 2$  diagnoses of CP prior to the index date, which was the date of first ED diagnosis. Chi-square tests were used to compare demographics and comorbidities between the two groups. Conditional logistic regression analyses were performed to investigate the association between ED and previously diagnosed CP. Results revealed that cases had a significantly higher prevalence of comorbidities (hyperlipidemia, diabetes, hypertension, coronary heart disease, obesity, and alcohol abuse/alcohol dependence syndrome) ( $p < 0.001$  for all) than controls. Overall, 24,294 (12.3%) study patients had been diagnosed with CP prior to their index dates, of which 8825 were cases (26.9% of the patients with ED) and 15,469 were controls (9.4% of the patients without ED). Despite adjusting for patient's monthly income, age, geographic location, hypertension, diabetes, hyperlipidemia, coronary heart disease, obesity, and alcohol abuse/alcohol dependence syndrome, patients with ED were still 3.35 times more likely to have been diagnosed with CP prior to the index date than controls (OR: 3.35, 95% CI: 3.25–3.45,  $p < 0.001$ ). Moreover, a stronger association was observed in those with  $<30$  years of age (OR: 4.54, 95% CI: 3.81–5.40) and  $>69$  years of age (OR: 4.84, 95% CI: 4.35–5.39). Additionally, the association between CP patients receiving a gingivectomy or periodontal flap surgery and ED (OR: 1.29) was lower than that for patients with CP who did not receive treatment at all (OR: 4.33).

Tsao et al. [29] conducted a population-based study in Taiwan to examine the association between CP and ED. Medical records were taken from the Longitudinal Health Insurance Database (LHID2000), a random subset of 1 million individuals taken from the same national database

used by Keller et al. [28]. Cases of ED were between 20 and 80 years of age and were defined as being diagnosed with ED for the first time during visits to ambulatory care centers, including outpatient departments of hospitals or clinics. The only ED cases included in the study consisted of at least 2 ED diagnoses with at least 1 being from a urologist. ED diagnoses were identified in patient charts through the ICD-9-CM 607.84 diagnostic code (applies to male erectile dysfunction). ED cases had a significantly higher prevalence of other comorbidities such as hypertension, ischemic heart disease, cerebrovascular disease, diabetes mellitus, hyperlipidemia, and obesity. The only CP cases included in this study had a consensus of at least 2 different diagnoses of CP prior to the index date. CP cases were identified through the ICD-9-CM 523.4 diagnostic code (applies to chronic pericoronitis, pericementitis, simple periodontitis, and complex periodontitis). Of the 15,315 sampled subjects, 2,617 (17.09%) were diagnosed with CP prior to their index date. The prevalence of CP was significantly different between cases (23.43%) and controls (13.92%) ( $p < 0.001$ ). After adjusting for age, hypertension, ischemic heart disease, cerebrovascular disease, diabetes mellitus, hyperlipidemia, and obesity, the cases were 1.79 times more likely to have been diagnosed with CP (OR: 1.79, 95% CI: 1.64–1.96,  $p < 0.001$ ). In addition, after those with CP and history of dental extractions were stratified by age, it was found that dental extractions attenuated the development of ED in CP patients of all age groups except those with <40 years of age.

Zadik et al. [30] conducted a retrospective cohort study to examine the association between CP and ED in Israel. They collected data from medical screening examinations held between 2004 and 2005 in the Israeli Defense Force (IDF). The screening examination consisted of both medical and dental examinations and included the SHIM (short-form IIEF-5) questionnaire. 305 men were selected for the study. The SHIM questionnaire was used to detect ED and assess its severity. Posterior bitewing dental radiographs were examined to make the radiographic diagnosis of CP, which was defined as alveolar bone loss  $\geq 6$  mm. Overall, 22.9% ( $N = 50$ ) of the sampled men had ED, 16.7% ( $N = 51$ ) had mild ED, 5.9% ( $N = 18$ ) had moderate ED, and 0.3% ( $N = 1$ ) had severe ED. 4.3% ( $N = 13$ ) of the sampled men had CP. Although smoking prevalence was twice as high among men with CP, this difference was not statistically significant (45.7% versus 21.6%,  $p = 0.07$ ). Prevalence of CP was significantly greater among men with mild ED ( $p = 0.004$ ) and moderate-to-severe ED ( $p = 0.007$ ) compared to men without ED.

Oğuz et al. [31] investigated the association of CP with ED in a case-control study conducted in Department of Urology at İnönü University. The authors included 80 patients with ED (cases) and 82 age-matched male patients without ED (controls). All patients were between 30 and 40 years old. The IIEF questionnaire was used to assess the presence of ED and was administered by the same clinician to all participants. The IIEF questionnaire consists of 15 questions, of which questions 1 to 5 and 15 are used to assess the presence of ED. Scores range from 5 to 75, with those scoring  $>30$  considered to have normal erectile function and those scoring  $\leq 25$  considered to have ED. In order to

ensure that participants truly had either completely normal or impaired erectile function, those with intermediate IIEF scores between 26 and 29 were excluded from this study. Additionally, each participant underwent a comprehensive dental examination to assess CP. The Plaque Index (PI), BoP, PD, and CAL loss were assessed, and CP was diagnosed using the criteria described by Boggess et al. [33]. Patients were classified as either healthy (or no CP), mild CP, or severe CP. Compared to controls, the ED group had significantly more patients with severe periodontal disease (ED versus non-ED: 53% versus 23%;  $p = 0.003$ ). Logistic regression analysis showed a significantly positive association between ED and the severity of CP (OR: 3.29, 95% CI: 1.36–9.55,  $p < 0.01$ ). Compared to the control group, the ED group had significantly greater mean values for PI, BoP, and percentages of sites with PD  $>4$  mm and CAL loss  $>4$  mm than those of the control group ( $p < 0.05$ ). The mean values of PD and CAL loss were not significantly different between cases and controls ( $p > 0.05$ ). The decayed, missing, filled teeth scores (DMF scores) were significantly higher in the ED group than in the control group ( $p < 0.05$ ).

**3.3. Effect of Periodontal Therapy on ED.** Eltas et al. [15] conducted a randomized, single-blinded, parallel, controlled trial to evaluate the changes in the IIEF score following periodontal treatment in patients who had either severe or moderate ED with CP. They recruited 120 men between the ages of 30 and 40 who had both CP and either severe or moderate ED. These patients were recruited from the Department of Urology at İnönü University, Turkey. Patients in the treatment group ( $N = 60$ ) received periodontal treatment, while those in the control group ( $N = 60$ ) did not receive any treatment. The clinical assessments were recorded for both groups at baseline, at 1 month (R1) after the intervention, and then at 3 months (R2) after the intervention. The periodontal examination involved assessing the PI, BoP, PD, and CAL loss with CP defined as PD and CAL loss  $\geq 4$  mm in  $>30\%$  tooth sites. ED was diagnosed with IIEF scores. Patients who had other systemic diseases (such as diabetes mellitus, cardiovascular diseases, or hypertension) that could affect periodontal health or ED, who had periodontal therapy within the past 12 months, or who had been prescribed antibiotics in the past 6 months were excluded from the study. At baseline, all periodontal parameters and IIEF scores were similar in both groups ( $p > 0.05$ ). Periodontal treatment significantly improved all clinical periodontal parameters at both R1 and R2 ( $p < 0.05$ ) and improved IIEF scores at R2 ( $p < 0.05$ ). At baseline, the treatment group had 32 participants with severe ED and 28 participants with moderate ED, whereas after 3 months, the numbers were reduced to 25 and 29, respectively. In contrast, the number of participants in the control group who had severe ED ( $N = 29$ ) and moderate ED ( $N = 31$ ) remained constant across all sampling periods (baseline, R1, and R2).

## 4. Discussion

**4.1. Biological Basis for CP and ED.** Research shows that CP is associated with not only a localized increase but also

a systemic increase in inflammation [34, 35]. It is hypothesized that this proinflammatory state promotes endothelial dysfunction and injury [36, 37] through the release of inflammatory cytokines, most notably tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1, and IL-6 [38–40]. This is supported by the finding that patients with CP demonstrate higher levels of TNF- $\alpha$  compared to those with stable gingivitis [41, 42] and that TNF- $\alpha$  plays an important role in the initiation of endothelial dysfunction [43, 44]. Furthermore, patients with moderate-to-severe ED also demonstrate increased serum TNF- $\alpha$  levels [45, 46], leading researchers to hypothesize that CP-induced endothelial dysfunction can extend to the smaller penile vasculature as well as larger coronaries [24, 30, 47]. The association of CP with coronary heart diseases has already been well established [24, 48, 49]. Since vasculogenic ED is considered an early warning sign of coronary heart disease [13, 17], it is reasonable to believe that CP-induced endothelial dysfunction and atherosclerosis are manifested first in the smaller penile vasculature and later into larger coronaries and great vessels.

As described in our review, only 1 study by Zuo et al. [32] directly examined serum levels of TNF- $\alpha$  and expression of endothelial nitric oxide synthase (eNOS) in penile tissues. The authors concluded that CP induced endothelial dysfunction by decreasing both eNOS activity and vascular smooth muscle relaxation in the corpus cavernosum. More research needs to be conducted on the bacteria associated with CP which have the potential to precipitate endothelial damage as well as the effects of other enzymatic activities on the development of vasculogenic ED.

**4.2. Effect of Periodontal Therapy on ED.** Periodontal therapy results in significantly improved endothelial function [50] in patients with periodontitis and associated hypertension or cardiovascular disease [51, 52]. Furthermore, studies [53, 54] have also demonstrated that successful periodontal therapy decreases the levels of TNF- $\alpha$  in patients with progressive periodontitis. TNF- $\alpha$  is thought to be a key proinflammatory cytokine responsible for inducing endothelial dysfunction.

Based on our review, only one study [15] prospectively examined the direct effect of periodontal therapy on ED, and that study found an improvement in ED severity after periodontal therapy. The 2 retrospective population-based studies, by Keller et al. [28] and Tsao et al. [29], also found a significantly positive effect of periodontal therapy on ED presence.

It has been reported [55] that extractions due to dental infections, compared to those because of trauma or noninfectious causes, are significantly more likely to be associated with a history of nonfatal myocardial infarctions. Dental extractions, and other periodontal therapies, remove the source of inflammation and may benefit comorbidities related to the systemic inflammatory response of CP. Tsao et al. [29] reported that dental extractions in CP patients were significantly associated with reduced ED prevalence for older patients ( $\geq 40$  years) but not for younger patients ( $< 40$  years). Considering the fact that the etiology of ED in younger patients is unlikely to be vasculogenic, it can be hypothesized

that reducing periodontal inflammation in younger patients may not relieve ED symptoms.

**4.3. Considerations for Future Research on ED and CP.** ED is associated with several risk factors including age [20], cigarette smoking [56], and systemic diseases (diabetes [57, 58], hypertension, and coronary heart disease [20, 59]). However, not all of the studies [25–31] evaluating the association between ED and CP adjusted for these confounding risk factors. Only two studies, Keller et al. [28] and Tsao et al. [29], adjusted their ORs for all possible confounders. Oğuz et al. [31] adjusted their ORs for confounders such as age, BMI, income, and education level but did not adjust for medical comorbidities. Likewise, Zadik et al. [30] did not adjust for any comorbidities, claiming that in their sample of IDF personnel diabetes would be rare since it was an exclusion criterion for service.

Although ED can have multiple etiologies [12], vasculogenic ED is the most common subtype [13]. Only Sharma et al. [26], Uppal et al. [25], and Zuo et al. [32] specifically studied the relationship between vasculogenic ED and CP. None of the other studies [15, 27–31] specified the subtype of ED being studied. It is important to know whether studies are investigating the same subtype of ED since the underlying pathophysiologies, and therefore the interpretation of results, may change depending on the etiology.

Only three studies [25–27] examined CP and ED severity. Matsumoto et al. [27] reported no statistically significant correlation between the CP score and ED severity. Sharma et al. [26] observed greater PD and CAL loss scores with increasing ED severity. Uppal et al. [25] observed significant increases in both PD and CAL loss with increasing ED severity. This difference might be due to the fact that Matsumoto et al. [27] diagnosed CP with a self-report questionnaire, while both Sharma et al. [26] and Uppal et al. [25] diagnosed CP with clinical parameters.

Future research should focus on the following aspects: assessing the relationship between the duration and severity of CP and vasculogenic ED, examining whether prevention of CP reduces the incidence of vasculogenic ED, the effects of periodontal therapy on clinical and subclinical parameters of vasculogenic ED, and the association between chronic periodontitis and the various other subtypes of ED.

**4.4. Considerations for Practicing Clinicians.** Eltas et al. [15] examined the effect of periodontal therapy on ED severity and found that periodontal therapy significantly improved IIEF scores 3 months after treatment. However, since this is the only prospective study available, it cannot be affirmed that periodontal therapy always improves ED severity. Eltas et al. [15] failed to report the effect of periodontal therapy on TNF- $\alpha$  serum levels, and it is unknown whether reduced TNF- $\alpha$  levels are responsible for the ED improvement. TNF- $\alpha$  is increased in both CP and ED, and successful periodontal treatment should demonstrate a reduction of TNF- $\alpha$  levels as a proof of concept.

It would benefit patients if dentists and physicians collaborated to manage and treat ED and CP. Dentists routinely

refer CP patients to physicians for medical evaluation because CP has proven associations with several other systemic comorbidities. Including an ED screen in the dental office or in the medical office as part of the follow-up for men with CP could help clinicians detect ED at its early stages. Additionally, early vasculogenic ED may be the first sign of atherosclerosis manifested in the smaller penile vasculature and detection could portend a risk for coronary heart disease.

**4.5. Limitations within Studies.** Although all of these studies reported a significantly positive correlation between CP and ED, there exist several limitations within these studies. The nine studies were not homogenous in their diagnoses of CP. Although the majority of the studies used clinical parameters such as BoP, PD, and CAL loss, the threshold depths of diagnosing CP varied from  $>4$  mm to  $\geq 6$  mm. One study [27] used a self-report questionnaire to diagnose CP, thereby introducing the risk of bias, which may have compromised the study results. The IIEF questionnaire for diagnosing ED was unable to separate the organic and psychological causes of ED. Because it is hypothesized that the shared mechanism of CP and ED involves endothelial dysfunction, authors investigating CP and ED associations should focus on vasculogenic causes. These inconsistent disease definitions may have contributed to heterogeneity among the studies and should be standardized in future research.

## 5. Conclusion

In summary, existing research suggests that chronic periodontitis introduces a state of endothelial dysfunction which is clinically manifested as a variety of comorbid systemic conditions, such as erectile dysfunction. Although the literature reports a positive association between chronic periodontitis and erectile dysfunction, these studies are few and possess several limitations. Large, multicenter studies with longitudinal follow-ups and inclusion of all relevant confounders are needed. As erectile dysfunction may result from a variety of etiologies, future research should specify the subtype of erectile dysfunction being studied. Dentists and physicians should collaborate to manage and monitor patients with either chronic periodontitis or erectile dysfunction because of their potential association not only with each other but also with more serious systemic diseases.

## Competing Interests

The authors declare that they have no competing interests.

## Acknowledgments

The authors would like to acknowledge Dr. Satpreet Singh for his help in reviewing the paper.

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