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An Insight into the Role of Periodontitis as a Potential Risk Factor for Development of Erectile Dysfunction

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ABSTRACT

Erectile dysfunction (ED) is one of the common sexual disorders affecting many men worldwide. Owing to shared common risk factors, periodontitis is related to ED. However, the prevalence of periodontitis among Malaysian patients with ED is currently unknown. This study aimed to investigate the prevalence of periodontitis in patients with ED in Malaysia and the factors associated with this relationship. Forty-one subjects aged 27–59 years old were recruited to participate in this study. The International Index of Erectile Function (IIEF-5) was used in assessing the presence of ED. Their periodontal health was assessed through comprehensive periodontal examination including plaque index, bleeding on probing and clinical attachment level. The subjects were categorised according to the severity of their periodontal health and ED. A questionnaire on general health and oral habits was administered. The prevalence of periodontitis (95.5%) among subjects with ED was significantly higher than those without ED (52.6%). Subjects with ED had the worst periodontal health, as indicated by the mean clinical attachment loss and percentage of sites with bleeding on probing. No differences in oral hygiene habits were found between subjects with and without ED. The prevalence of periodontal disease among Malaysian patients with ED was high. Periodontitis was positively associated with the severity of ED, supporting a dose-dependent association between the two diseases. Oral hygiene habits were not significantly related to any periodontitis parameters nor were significantly different between subjects with and without ED.

Keywords: *Erectile dysfunction; International Index of Erectile Function; men's sexual health; periodontitis; periodontal disease*

INTRODUCTION

Erectile dysfunction (ED) is a common sexual health disorder affecting men. It is formally defined as persistent penile flaccidity and inability to attain and maintain an erection sufficient for sexual satisfaction (Dean & Lue, 2005). It is associated with multifactorial factors, psychogenic (Rosen, 2001; Bilal & Abbasi, 2020) and organic (Ritchie & Sullivan, 2011; Irfan *et al.*, 2020b). Organic ED encompasses neurogenic (Thomas & Konstantinidis, 2021), endocrinologic (Kouidrat *et al.*, 2017), vasculogenic (Kirby *et al.*, 2005) and drugs (Irfan *et al.*, 2020b). Penile erection is a vascular event that requires an intact endothelium to occur (Irwin, 2019). Given that the physiology of erection depends on vascular changes, any factors that cause endothelial dysfunction in small vessels of the penis may affect penile erection. Accordingly, many known cardiovascular risk factors, such as hypertension and diabetes, is also associated with the development of ED (Gratzke *et al.*, 2010). The other risks of ED include hypertension (Wang *et al.*, 2021), hormone imbalance (Kouidrat *et al.*, 2017), alcohol (Khoo *et al.*, 2008), drugs (Teoh *et al.*, 2017) and smoking (Lam *et al.*, 2006; Kovac *et al.*, 2015). Moreover, the prevalence and degree of ED (minimal, moderate and complete) seem to increase with age (Low *et al.*, 2006; Khoo *et al.*, 2008; Eisenberg & Meldrum, 2017).

While penile Doppler examination may facilitate the differential diagnosis of ED, the severity of the disorder can be objectively measured using the International Index of Erectile Function (IIEF-5) questionnaire or complete IIEF (Rosen *et al.*, 1999). The validated IIEF-5 questionnaire evaluates the self-reported indicators of male sexual function, encompassing erectile strength, orgasm, desire, satisfaction with intercourse and overall satisfaction. Owing to its sensitive nature, ED may be underdiagnosed in some countries. Many studies reported the high prevalence of ED, indicating that ED is a significant public health problem that considerably affects men's quality of life (Khoo *et al.*, 2008; Capogrosso *et al.*, 2017; Irfan *et al.*, 2020a; Elterman *et al.*, 2021). Currently, more than 150 million people worldwide have ED (Irwin, 2019), presenting a 52% prevalence across all severities in the United States (Rosen, 2001) and a 30% prevalence of ED across eight European centres (Irfan *et al.*, 2020a) and affecting more than 63% of men aged 50–80 years old across Asian countries (Ho *et al.*, 2011; Irfan *et al.*, 2020a). In Malaysia, the prevalence of ED is 81.5% in a primary healthcare setting (Low *et al.*, 2006; Ab Rahman *et al.*, 2011).

Periodontal disease is a common bacterial-induced gingival inflammation and has been one of the significant oral health problems worldwide. In the United States alone, recent reports estimate that 64.7 million adults, 47% of the adult population, suffer from periodontal disease; 38.5% have moderate to severe disease (Kellesarian *et al.*, 2018). In Malaysia, the National Oral Health Survey of Adult has reported that 94% of adults are affected by periodontal disease; this rate is higher than in developing and third world countries (Oral Health Division, Ministry of Health Malaysia [OHD-MOH], 2013). Of this figure, 18% of the adult population suffers from the most severe form of periodontal disease. Hence, the disease has been considered a national burden (Mohd Dom *et al.*, 2016). Like ED, periodontal disease significantly affects a patient's quality of life and financially affects patients and the public healthcare system (Eltas *et al.*, 2016; Ferreira *et al.*, 2017).

Periodontal disease occurs in two variants: first, gingivitis, which is gingival bleeding without any loss of attachment of the tissues and second, periodontitis, which involves disease progression into the cementum, periodontal ligament and alveolar bone. Periodontitis is caused by the immuno-inflammatory reaction to primarily anaerobic bacteria found in the subgingival plaque. Evidence strongly supports that periodontitis is a risk factor for certain systemic diseases, such as diabetes mellitus (Stöhr *et al.*, 2021)

and cardiovascular disease (Sanz *et al.*, 2020). Moreover, diabetes and smoking have been identified as modifiers for periodontitis severity (Jepsen *et al.*, 2018; Papapanou *et al.*, 2018).

ED and periodontitis share the same risk factors, and thus many studies (Zadik *et al.*, 2009; Sharma *et al.*, 2011; Matsumoto *et al.*, 2014; Tsao *et al.*, 2015), including systematic reviews (Wang *et al.*, 2016; Liu *et al.*, 2017; Kellesarian *et al.*, 2018; Zhou *et al.*, 2019; Farook *et al.*, 2021), have been conducted to demonstrate the existence of the link between ED and periodontitis or the role of periodontitis as a potential risk factor for the development of ED. Uncontrolled periodontitis increases the risk of systemic inflammation due to the translocation of pathogenic bacteria from the oral cavity into the blood circulation (i.e., bacteraemia). Along with the translocation of bacteria, various types of cytokines and inflammatory markers are released into the systemic circulation, including interleukin-1, interleukin-6, interleukin-8, tumour necrosis factor and prostaglandin E_2. These circulating cytokines and inflammatory mediators destroy the vascular endothelium, thereby leading to endothelial dysfunction. The role of the reactive oxygen species (ROS) produced during periodontitis progression in the oral tissues has been proposed. ROS released to tissues can reduce the bioavailability of nitric oxide. This effect exacerbates endothelial dysfunction and impairs the mechanisms associated with muscular contractions, leading to ED (Bizzarro & Loos, 2019).

To date, the possible relationship between periodontal disease and ED has been investigated by multiple meta-analyses, which found significant positive associations between these two conditions (Wang *et al.*, 2016; Liu *et al.*, 2017; Kellesarian *et al.*, 2018; Zhou *et al.*, 2019; Farook *et al.*, 2021). In Asia, studies from Taiwan (Keller *et al.*, 2012; Tsao *et al.*, 2015), Korea (Lee & Jeong, 2020), India (Sharma *et al.*, 2011; Uppal *et al.*, 2014) and Japan (Matsumoto *et al.*, 2014) have shown positive relationships with varying prevalence ranging from 12.3% to 81.8%. However, evidence on this relationship in the Southeast Asia population is limited. Given the significant genetic or hereditary components of periodontal disease and ED, this relationship in the Malaysian population is of great interest. Hence, we aimed to investigate the prevalence of periodontitis in patients with ED in Malaysia and the factors associated with this relationship.

MATERIALS AND METHODS

A cross-sectional study was performed, and patients referred to the Urology Clinic at Hospital Canselor Tuanku Mukhriz (HCTM), Malaysia, were invited to participate in the study. Ethical approval was obtained from the Research Ethics Committee of Universiti Kebangsaan Malaysia under the code UKM 1.5.3.5/138/FGG-001-2012. The recruited subjects have consented verbally and in writing before the periodontal examination was conducted.

The inclusion criteria were as follows:

1. Age of less than 60.
2. Dentate patients with at least 20 teeth present.
3. Able to provide verbal and written consent.

The exclusion criteria were as follows:

1. Patients who received any periodontal treatment within the previous six months.
2. Any treated or untreated malignancy.
3. Patients with systemic diseases that are unstable.
4. Patients treated for ED.
5. Intake of any form of antibiotics in the last three months.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for the preparation of this manuscript.

Assessment of Erectile Dysfunction

All patients admitted to the Urology Clinic during the recruitment period were invited to participate in the study. Verbal and written consent was obtained from each subject. The subjects were invited to complete the IIEF-5 form (Rosen *et al.*, 1999). The completed forms were numbered and placed in a brown envelope by an assigned nurse. The assessment of IIEF-5 forms for ED status was carried out by ZMZ.

International Index of Erectile Function (IIEF-5)

The assessment tool for ED was the IIEF-5. The simplicity and clarity of the questionnaire had been pre-tested in 10 subjects of comparable age who were not involved in this study. The five questions in IIEF-5 were scored from one point to six points and arranged as an ordinal scale ranging from one (represent as lowest score) to five (represent the maximum score). The total score ranged from 1 to 25. A score of 21 is the cut-off point in determining whether a person has an ED. Subjects who scored 1–21 were considered to have ED and subdivided into four stages (mild ED, mild to moderate ED, moderate ED and severe ED). Those who scored more than 21 were considered free from ED.

Periodontal Clinical Assessment

The subjects were invited to undergo an oral examination carried out by a single examiner (ZMS) and blinded from the ED status throughout the study. ZMS was calibrated against a gold standard, a periodontist (MR) and tested for intra-examiner reliability before the study. The parameters recorded included plaque index (PI), bleeding on probing (BOP), probing pocket depth, gingival recession and clinical attachment level (CAL). Six teeth had been chosen for PI based on Ramfjord Teeth (Ramfjord, 1959).

The subjects were categorised as having periodontal health and periodontitis. Additionally, periodontitis was classified based on stages defined by severity: mild periodontitis (Stage I), moderate periodontitis (Stage II) and severe periodontitis (Stage III/IV) as outlined by the Consensus Report of Workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Papapanou *et al.*, 2018).

Statistical Analyses

Results were analysed using SPSS statistical package (version 25.0, for Windows, USA). Shapiro-Wilk test was used in assessing the normality of data distribution. All periodontal parameters were expressed as mean ± standard deviation. Mann-Whitney test was used in determining differences among the groups (ED and non-ED). Categorical data were analysed using the chi-square test. A *p-value* of <0.05 was considered statistically significant. The relationships between ED and periodontitis and other variables were assessed using multiple logistic regression to obtain the odd ratio (OR) and the confidence interval (CI). The following characteristics were examined as predictors: diagnosis of periodontitis, smoking (yes/no), diabetes (yes/no), age and plaque level (low/moderate/high).

RESULTS

Patients were randomly selected during their clinical sessions in the Urology Clinic for 10 months. Fig. 1 shows the flowchart of the study methodology and the number of subjects at every stage. Of the 64 male patients invited, only 41 were finally included in the study. The subjects were aged 27–59 years old, with a mean age of 40.7 years old (±11.39). The demographic data of the subjects are presented in Table 1.

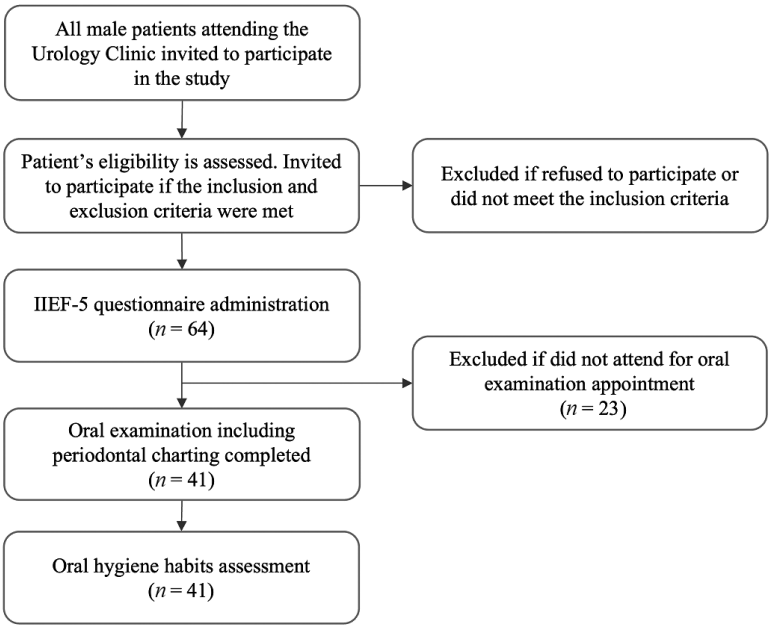

Fig. 1 Flowchart of the research activities.

Table 1 Demographic characteristics of the subjects

Characteristics	IIEF-5 score > 21 (*n* = 19)	IIEF-5 score < 21 (*n* = 22)	*p*-value
Age; Mean (SD)	35.11 (7.57)	45.55 (12.05)	0.002*
Education level; *n* (%)			
Primary	8 (42.1)	10 (45.5)	0.829
Secondary/Tertiary	11 (57.9)	12 (54.5)	
Health problems; *n* (%)			
Yes	5 (26.3)	11 (50)	0.121
No	14 (73.3)	11 (50)	
Diabetes mellitus; *n* (%)			
Yes	0 (0)	14 (63.6)	0.03*
No	19 (100)	8 (36.4)	
Smoking; *n* (%)			
Yes	5 (26.3)	5 (22.7)	0.79
No	14 (73.7)	17 (77.3)	

Note: * Indicate statistically significant.

As shown in Table 1, age and diabetes mellitus appeared statistically associated with ED. There were up to 95.5% of subjects with ED had periodontitis, whereas only 52.6% of those without ED had periodontitis. The Fisher's Exact test showed an association between periodontitis and ED (p = 0.001, two-tailed, n = 22).

Periodontitis and ED

Comparison between the periodontal parameters were made between the subjects who had ED (IIEF-5 score < 21) and no ED (IIEF-5 score > 21). In general, the subjects with ED had significantly worse periodontal health, as indicated by their mean CAL and percentage of sites with BOP (Table 2).

Table 2 Clinical parameters of periodontal health according to IIEF-5 score

Clinical parameters	IIEF-5 score > 21 (*n* = 19)	IIEF-5 score < 21 (*n* = 22)	*p*-value
Periodontitis			0.001*
Yes	10 (52.6)	21 (95.5)	
No	9 (47.4)	1 (4.5)	
Mean CAL (mm)	1.86 ± 0.68	2.2 ± 0.77	0.021*
Mean PD (mm)	1.78 ± 0.56	1.89 ± 0.63	0.278
% Sites exhibit BOP	19.96 ±18.03	31.28 ± 12.39	0.021*
% PI	44.28 ± 20.05	66.25 ± 23.76	0.02*

Note: * Indicate statistically significant.

Table 3 Analysis relationship between periodontal status and ED severity

Category	Non-ED *n* (%)	Mild ED *n* (%)	Mild to moderate ED *n* (%)	Moderate ED *n* (%)	Severe ED *n* (%)	*p*-value
Periodontitis	10 (24.4)	6 (14.6)	8 (19.5)	6 (14.6)	1 (2.4)	0.031*
Periodontally healthy	9 (22.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	

The relationship between periodontal status and ED severity was further analysed in the subjects with or without periodontitis. Pearson's chi-square test showed an association between periodontitis diagnosis and severity of ED (p = 0.031, two-tailed, n = 41), as shown in Table 3.

A logistic regression model was used to investigate the association between ED diagnosis and diagnosis of periodontitis and other variables. Smoking and plaque levels were not included in the final model as they were not significantly associated with ED. The logistic regression model was statistically significant, χ^2 (2, N = 41) = 16.417, p-value = < 0.001. The model explained 44.1% (Nagelkerke R2) of the variance in ED diagnosis and correctly classified 73.2% of cases. Patients with ED were more likely to have periodontitis (OR = 21.35, 95% CI [1.817, 250.962]) while controlling for diabetes.

Oral Hygiene Practices

No significant differences in oral hygiene practices, including the frequency of tooth brushing and the type of toothpaste used, were found between subjects with and without ED. All subjects were using fluoridated toothpaste, as recommended by their clinicians regardless of their ED status. No difference in the number of subjects claiming that they routinely visit dental clinics between the two groups.

DISCUSSION

While the association of periodontal disease and ED may have been investigated in other countries, to the best of our knowledge, this study is amongst the first in Malaysia. The high prevalence of periodontitis (95.5%) in subjects with ED in this study supports the relationship between these diseases. Other studies which reported similar results include Taiwan (Tsao *et al.*, 2015) and India (Sharma *et al.*, 2011; Uppal *et al.*, 2014). However, this rate was higher compared to other studies in this region (Keller *et al.*, 2012; Matsumoto *et al.*, 2014; Lee & Jeong, 2020). Following regression analysis, our study correctly classified 73.2% of periodontitis cases in the ED group. We reported that patients with ED were more likely to have periodontitis (OR = 21.35,

95% CI [1.817, 250.962]) while controlling for diabetes. This abnormally large odds ratio and wide CI could contribute to sparse data bias as the sample size was relatively small.

Vice versa, a European study has reported that 74% of the ED cases were diagnosed with chronic periodontitis compared to 58% of non-ED cases (Martín *et al.*, 2018). They reported that patients with periodontitis were 2.17 more likely to have erectile dysfunction (OR = 2.17; 95% CI = 1.06–4.43; $p = 0.03$) independently of other confounders, compared to periodontally healthy men. The evidence was further reiterated by a recent systematic review which showed that periodontitis was associated with an increased risk of ED (OR = 2.56, 95% CI = 1.70–3.85) as compared with the non-periodontitis subjects (Farook *et al.*, 2021). Further studies are recommended to clarify the mechanisms of interaction between these diseases and to strengthen the evidence that periodontitis increases the occurrence of ED, and periodontitis might have important clinical implications for development of ED especially in young adults.

It has been reported that ED and periodontitis may share many common risk factors, including age, smoking, diabetes and depression (Low *et al.*, 2006; Khoo *et al.*, 2008). The mechanism accounting for the relationship between these two diseases is systemic inflammation induced by periodontal pathogens. This type of inflammation contributes to endothelial dysfunction and atherosclerosis and occurs first in small vessels, such as penile vasculature, and large arteries, such as the coronary arteries (Matsumoto *et al.*, 2014). Patients with periodontitis have significantly high levels of C-reactive protein, elevated levels of serum IL-6 with lower levels of interleukin-4 and interleukin-18, high levels of thrombotic factors, such as fibrinogen, and elevated dyslipidaemia according to their measured serum total cholesterol levels, low-density lipoproteins (LDL), triglycerides, very-low-density lipoproteins, oxidised LDL and phospholipase A2 (Sanz *et al.*, 2020). Periodontitis may also reduce testosterone levels (Zhou *et al.*, 2019). As stated in Table 1, this study recruited higher number of ED patients with diabetes mellitus (*p-value* = 0.03), and most of them were older than 45 years old age (p-value = 0.002). Therefore, the high prevalence of periodontitis in subjects with ED could be attributed by the shared risk factors of the subjects included in this study. ED presents in mostly middle-aged man with other co-morbid (Gratzke *et al.*, 2010; Kouidrat *et al.*, 2017). Meanwhile older age has become predictor of tooth loss in periodontitis patients (Eke *et al.*, 2016; Papapanou & Susin, 2017; Helal *et al.*, 2019) and diabetes mellitus is modifiable risk factor for periodontitis (Genco & Borgnakke, 2020; Polak *et al.*, 2020).

Poor oral hygiene increases the risk of developing periodontitis and is a potential confounding factor in investigating the relationship between periodontitis and systemic diseases. Other studies investigating periodontitis and ED did not report the contribution of oral hygiene to this relationship (Sharma *et al.*, 2011; Keller *et al.*, 2012; Oğuz *et al.*, 2013). In this study, the plaque index, a measure of oral hygiene status, was significantly higher in the ED group. This result potentially contributes to the high prevalence of periodontitis in the ED group.

The detection of ED and assessment of its severity was conducted using the IIEF-5 questionnaire. No validated IIEF-5 questionnaire for the Malaysian population is currently available. Hence, this study used the five-item abridged version developed by Rosen *et al.* (1999), similar to the other studies included in those meta-analyses (Wang *et al.*, 2016; Liu *et al.*, 2017; Kellesarian *et al.*, 2018; Zhou *et al.*, 2019; Farook *et al.*, 2021). As a result, it can introduce a degree of bias as the questionnaire may not necessarily suit the Malaysian population. Other limitations in this study include the small sample size. Recruitment is problematic because studies

on ED is influenced by cultural taboo. Men affected especially younger individuals are reluctant to discuss sexual problems because ED implicates that their masculinity has been reduced or lost (Ho *et al.*, 2011; Nordin *et al.*, 2019). Difficulty in recruiting appropriate age limit and controlling the confounding factors prior had an impact on sample size and overall analyses, resulted in large CI of our regression analyses. A multicentre study or large scale, population-based study should be more appropriate to increase the sample size and public awareness on both diseases. A case-control design with matched age and oral hygiene would be the better research design to improve this study. The molecular biological studies also might be appropriate to further investigate inflammatory mediators involved in both diseases. More intervention studies and a longitudinal follow-up is warranted to investigate whether periodontal treatment can improve ED severity.

CONCLUSION

Within the limitation of this study, a high prevalence of periodontitis among Malaysian patients with ED was demonstrated. Oral hygiene habits were not significantly related to any periodontitis parameters nor it significantly different between those with and without ED. Due to the predomination of periodontitis in ED patients, it can be suggested that dentists could highlight the possible risk development of ED in periodontal patients. However, molecular or population-based studies are warranted to establish the associations.

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