

ORIGINAL ARTICLE

The Relationship Between Interleukin-1 β Levels and Sociodemographic Factors With Periodontal Status in the Menopausal Transition

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ABSTRACT

Introduction: Before menopausal or in perimenopausal period, there will be fluctuations in women reproductive hormones, resulting in disruption of the balance of pro-inflammatory and anti-inflammatory cytokines that disrupt the body including periodontal tissue. This study aims to analyze the relationship between Interleukin-1 β (IL-1 β) level and sociodemographic factor, i.e. age and education level with periodontal status in the menopause transition period. **Methods:** A cross-sectional study involving 82 women suffering periodontitis in Jakarta, Indonesia. Age, education level and perimenopausal status are obtained through anamnesis; the periodontal status examination is done by measuring pocket depth, attachment loss, gingival recession, oral hygiene index, while IL-1 β level is obtained through blood tests. **Results:** This study showed that the majority of subjects willing to participate in this study aged ≤ 50 years (87.8%), and education level was upper Junior High School (57.3%). Based on the Spearman correlation test it was found that the IL-1 β level had a significant correlation with gingival recession ($p=0.003$), whereas education level had a significant correlation with attachment loss ($p=0.016$), gingival recession ($p=0.007$) and oral hygiene index ($p=0.004$) but age does not have a significant correlation with periodontal status ($p>0.05$). **Conclusion:** Only gingival recession was a factor associated with IL-1 β , whereas attachment loss, gingival recession and oral hygiene index were factors related to education level. Further research is needed to determine the factors other than cytokines and sociodemography that most play a role in influencing periodontal conditions in women who enter the menopausal transition.

Keywords: Menopause; Periodontal; IL-1 β level; Age; Education

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INTRODUCTION

Menopausal problems are essential to discuss because of all associated with menopause implementing prophylactic measures so that women can live healthy and enjoyable. Before menopause, women will experience menopausal transition, known as perimenopause, which is when the condition of endocrinological, biological, and clinical approaching menopause begins (1).

Perimenopause is a period of dynamic and female physiological phenomenon characterized by the

emergence of a variety of physical symptoms due to a decrease in ovarian steroid hormones, and it's caused by reduced ovarian function. Although these symptoms are not life-threatening, they can affect the physical and mental conditions that will affect the quality of life of perimenopause (2). The menopausal transition is usually experienced by women aged 50 years. When women enter perimenopause changes fluctuation of estrogen and follicle-stimulating hormone (FSH) so that women will experience some symptoms. The symptoms vary widely among individuals, and this is related to the condition of aging, menopause, and the fluctuation of social phenomena (3,4). This indicates that the menopausal transition is a natural consequence and progressive condition in women's lives that can affect the physical condition, including the health of the oral cavity.

Periodontitis is a periodontal disease induced by a specific bacterial biofilm on the surface of the tooth which triggers a response immunoinflammatory on bone tissue. The process of bone resorption in women aged > 40 years is more active than bone formation so that this causes bone mass to be lower. Bacteria are necessary for the initiation of the disease process in which proteolytic enzymes of the host will mediate the direct damage to periodontal tissues. The progression of periodontitis is influenced by various factors such as genetics, general health, smoking, and nutrition. Furthermore, age, education, and socioeconomic factor is also a factor that can affect the disease (5,6).

Periodontitis is an imbalance of host response to periodontopathogen, causing periodontal tissue damage to the onset of clinical signs. The quality of the inflammatory immune response against bacterial determines the severity and extent of disease. One of the main cytokines identified in chronic periodontitis disease by the influence of the activity of immune cells is IL-1 β . Interleukin-1 β is a pro-inflammatory cytokine and a key in the initiation and regulation of immune response in the periodontium. This cytokine involved in the pathogenesis of inflammation-induced bone resorption. Interleukin-1 β also mediate tissue damage by stimulating prostaglandin E2 and collagenase (7,8).

The decline in ovarian function is associated with increased pro-inflammatory cytokines. Pro-inflammatory cytokines that increase could trigger further periodontal destruction because of these cytokines will inhibit collagen synthesis and stimulate cellular matrix degradation in addition to the action that can stimulate the formation of new osteoclasts to increase bone resorption(9,10). Previous research revealed that fewer oral discomfort experienced in the premenopausal than perimenopause and postmenopause (11). Palomo et al, 2013 showed that women at risk for systemic disease if not pay attention to periodontal health, especially in postmenopausal, so it is important for the early detection and treatment of periodontal on the menopausal transition so that further damage can be prevented in the postmenopausal period (12).

The emergence of various changes that occur in menopause, including changes in the oral cavity such as reduced salivary flow, thinning of the gingiva and reduced density of alveolar bone, makes it necessary to have an examination from the start, namely before entering menopause. In the period before menopause (perimenopausal), hormonal changes begin to occur, which also affect the increase in pro-inflammatory cytokines, one of which is IL-1 β (7,8).

The increase in IL-1 β cytokines will trigger damage, including damage to the oral cavity, so in this study,

an examination of IL-1 β and periodontal conditions were carried out to see whether there was a relationship between IL-1 β and sociodemographic factors with periodontal status during the menopause transition. The purpose of this study was to see the relationship between IL-1 β and sociodemography so that it is hoped that the results of this study can be a guide to assist in the treatment of periodontal disease, which is prone to occur during menopause.

MATERIALS AND METHODS

This is a cross-sectional study of the women who enter menopause transition, aged 45 years and over and suffering periodontitis in Jakarta, Indonesia. Before conducting the study, researchers have obtained permission from the Research Ethics Committee of Faculty of Dentistry (KEPKG), Universitas Indonesia No.36/Ethical Approval/FGUI/V/2018. All subjects had been approved and signed informed consent before participating in the study. All subjects had been approved and signed informed consent before participating in the study. The inclusion criteria in this study were women aged 45 years and over, had not entered menopause, suffered from periodontitis. Subjects who are pregnant, suffering systemic diseases such as diabetes mellitus, smoking and periodontal treatment within six months, excluded in this study.

The demographic data and information about the subject of menopausal status were obtained through an interview. Subjects who entered the menopausal transition are women who have not entered menopause and often have amenorrhea (no periods) where this condition lasts for at least 60 days until menopause and has acknowledged that she has experienced at least three symptoms of menopause (13).

Checking the status of periodontal pocket depth is done through examination, gingival recession, clinical attachment loss, and oral hygiene index using the dental mirror and prob UNC-15 Color-Coded Probe (@ Hu-Friedy) with a black band for each millimeter up to 15 millimeters(14), dental explorer and tweezers. Before examining the periodontal parameters, namely attachment loss, pocket depth, gingival recession, the inter-examiner examination was performed using ICC>0.70, while the oral hygiene index inter-examiner was tested using Kappa>0.75 Examination of pocket depth, gingival recession, and clinical attachment loss made on the six sides of the teeth in the oral cavity.

Pocket depth is measured by inserting prob along the gingival groove as measured from the gingival margin to the bottom of the pocket. Gingival recession is a picture that shows the exposure of the root surface of a tooth due to the movement of the gingival margin to the apical. Gingival recession is measured from the cemento-enamel junction to the gingival margin

(15,16). Clinical attachment loss measured from the cemento-enamel junction to the bottom of the pocket, when a gingival recession, then the calculation of loss of attachment is obtained by summing the pocket depth with gingival recession (17). Examination of the oral hygiene index by Greene and Vermillon did by summing the debris index and calculus index to measure the subject of oral hygiene status of the subject (18,19).

The level of IL-1 β is done by taking a blood sample from the subject of the veins in the morning. The sample was then placed in a tube and stored at a temperature of -800C. IL-1 β examination performed by ELISA (kit Quantikine @ HS ELISA; R & D Systems, A brand biotech USA) with a concentration in accordance with the manufacturer's instructions.

Test for normality in the research conducted by the Kolmogorov-Smirnov test, while for the bivariate analysis was done by using Spearman's correlation test with the provisions of a correlation between two groups was considered to be statistically significant when $p < 0.050$.

RESULTS

A total of 82 subjects ready to participate in the study, where the majority of subjects willing to participate in this study aged under 50 years (87.8%), and education level was upper Junior High School (57.3%). (Table I) Table two shows that the clinical attachment loss has the highest average value (2.64mm), while the gingival recession has the lowest average value (0.85mm).

Table I : Demographic Data from Study Participant

Variables (n = 82)	n (%)
Age (Years)	
≤50 years	71 (87.8%)
> 50 years	10 (12.2%)
Education Level	
Upper Junior High School	47 (57.3%)
Junior High School and Lower	35 (42.7%)
Number of Children	
≤ 2	38 (46.3)
> 2	44 (53.7)

Spearman correlation test showed that there was no correlation between IL-1 β to clinical attachment loss ($p = 0.088$), pocket depth ($p = 0.697$), and the oral hygiene index ($p = 0.117$), but there is a significant relationship between IL-1 β with gingival recession ($p = 0.003$). Age did not have a significant relationship with periodontal status ($p > 0.050$), but the level of education has a significant relationship with clinical attachment loss ($p = 0.016$), gingival recession ($p = 0.007$) and the index of oral hygiene ($p = 0.004$), but did not have a relationship with pocket depth ($p = 0.254$). (Table III).

Table II : Periodontal Status and Interleukin-1 β Levels of the Subjects

Variables (n = 82)	Mean (SD)	Median (Min-Max)
Periodontal Status		
Clinical Attachment Loss (mm)	2.64 (0.78)	2.56 (0.78-4.98)
Pocket Depth (mm)	1.79 (0.42)	1.74 (0.70-3.32)
Gingival Recession (mm)	0.85 (0.58)	0.75 (0.01-2.47)
Oral Hygiene Index	1.84 (0.89)	1.70 (0.44-4.65)
IL-1 β (pg / ml)	0.89 (2.05)	0.27 (0.05-16.68)

DISCUSSION

Caries and periodontal disease is a common disease of the oral cavity and the main problem in the oral health problems that will affect the quality of life of sufferers. Periodontal disease is a chronic inflammation that occurs due to the dominant response of Gram-negative bacteria-derived from dental plaque. The influence of sex steroid hormones on the periodontium can worsen a good plaque control. Changes in the oral cavity that occurs due to hormonal changes cannot be separated from the physiological process of aging, such as thinning of the gingival epithelium and thus susceptible to inflammation; on the other hand, salivary flow rate and composition also affect the condition of the oral cavity (20,21).

The research was carried out on women who will enter the menopausal transition or perimenopause, for women in the menopausal transition will experience a variety of symptoms that would interfere with her life as things that happen in postmenopausal, this is

Table III : Correlation between Periodontal Status with IL-1β, Age, and Education Level of Women in Menopausal Transition

Variables (n = 82)	IL-1beta		Age		Education Level		
	correlation coefficient	p value	correlation coefficient	p value	correlation coefficient	p value	
Periodontal Status							
Clinical Attachment Loss	-0.190	0.088	0.144	0.197	-0.267	0.016 *	
Pocket Depth	-0.044	0.697	0.031	0.782	-0.127	0.254	
Gingival Recession	-0.324	0.003 *	0.209	0.059	-0.298	0.007 *	
Oral Hygiene Index	-0.174	0.117	0.043	0.702	-0.316	0.004 *	

Spearman’s correlation test (* significant p <0.050)

in line with research conducted by Hakimi et al, 2010 against women perimenopause and postmenopausal in Iran and show that some of the symptoms of perimenopause did not differ significantly with postmenopausal and symptoms after the menopausal transition will not be reduced even increased a few years after menopause (22).

The onset of symptoms in perimenopausal due to fluctuations in reproductive hormones will cause complaints included in the oral cavity. This is because the estrogen in this case estradiol is potential for women. Estradiol levels will decrease after menopause and were replaced by estrone derived from androstenedione. Circulation levels of estrone in postmenopausal higher than estradiol, which is about 30 to 70 pg/ml. Women entering menopause will experience a decline in ovarian function that estrogen and progesterone hormone production will decline. Reduced levels of estrogen and progesterone levels in perimenopause cannot be distinguished, both of these hormone receptors are in the gingival tissue (23,24). Lack of estrogen can cause loss of keratin, the thinner gingival tissue, decreased salivary gland function and modulate periodontal pathogens are like *Porphyromonas gingivalis*, *Prevotella intermedia*, and it contributes to increased severity of periodontitis (25).

This research was conducted in subjects aged 45 years and above; this is in line with research Żoźnierzuk-Kieliszek et al, 2012 (26). Some of the conditions of the subject cannot be included in this study because it can lead to bias in the study as subjects who are pregnantly excluded in this study because during pregnancy there is a change of periodontal tissue due to hormonal changes and it's lead to changes in the immune system such as the occurrence of gingival enlargement and

gingivitis due to gingival capillary permeability and changes in the bacterial composition (27).

The majority of subjects in this study are aged ≤50 years (87.8%) (Table I), it indicates that the subject entered the menopausal transition is under 50 years old and most subjects over the age of 50 years have entered menopause. The age of menopause is between 45 and 55 years (28).

Generally, the first hormonal changes of perimenopause are the increased levels of FSH. Increased FSH levels will cause an exponential decrease gonadotropin-sensitive ovarian follicle when we get closer to menopause. This condition will affect the variability in estrogen levels and an increase in anovulatory cycles, which eventually will cause a reduction in the estrogen. Lack of estrogen plays a role in the pathobiology of periodontal diseases, but estrogen is not the only factor that plays a role in the occurrence of periodontal disease (29,30).

Subjects in this study have more education level upper junior high school (57.3%). (Table I) The education level affects how the subject faces the symptoms that arise during the menopausal transition and afterwards. Research conducted by Ziagham et al, 2015 showed that there is a significant relationship between the level of education with depression, women who have a high level of education have an average value lower depression scores; on the other hand, the high severity of depression is associated with increased symptoms of menopause (31). Some biomarkers that can be used in detecting psychological stress are also the same as markers for periodontal damage such as the hormone cortisol, IL-1β, and IL-6. Stressors can directly affect immune cells and modulate secretion from pro-inflammatory cytokines, one of which is IL-1β (32).

The number of children held by the subject of menopause affects the subject. This is in line with research Shin et al, 2017 who demonstrated that an increase in the number of pregnancies associated with older age at menopause (33). In this study, the majority of subjects had a number of children, more than two people (53.7%). (Table I).

Clinical loss of attachment is one of the signs of periodontitis and, in this study, had the highest average value compared to another periodontal status. Attachment loss occurs through the destruction of the periodontal ligament and alveolar bone adjacent to it so that it leads to gingival recession and pathological periodontal pocket depth. The degree of attachment loss describes the severity and can be used as an indicator in determining the severity of the periodontal disease (34). In general, since 1999, the American Academy of Periodontology categorizes the severity of periodontitis by attachment loss is mild when attachment loss occurs 1 to 2 mm, moderate when 3 to 4 and severe when ≥ 5 mm (35). Mean attachment loss of subjects in this study included in mild. The majority of subjects in this study have a level of education upper junior high school, so this may be one reason that the average clinical attachment loss of the subjects in this study included in the mild category.

The gingival recession has the lowest average value in this study. The unveiling of the root surfaces of teeth or gingival recession can affect the lives of sufferers by causing complaints such as the emergence of a sense of pain and also interfere with aesthetics. Gingival prevalence increases with age, but it need not be seen as a consequence of aging (36).

Table three shows that clinical attachment loss, pocket depth, and the oral hygiene index have no correlation with IL-1 β ($p > 0.050$), but IL-1 β has a significant correlation with the gingival recession ($p = 0.003$) (Table III). In periodontal disease, the balance between pro and anti-inflammatory directed pro-inflammatory activity. IL-1 β acts regulate matrix metalloproteinases (MMP) and downregulated the production of tissue inhibitor of metalloproteinases and also as a potent stimulator of bone resorption. Interleukin-1 β may also stimulate the proliferation of keratinocytes, fibroblasts, and endothelial cells, and to increase the synthesis of fibroblasts collagenase, hyaluronate, fibronectin, and prostaglandin E2 (PGE2) (37).

Prostaglandin E2 is derived from arachidonic acid metabolism found in the inflamed side, this molecule is closely related to tissue damage. Kumar et al, 2013 in their study, showed that the increase of PGE2 in line with the progression of periodontal disease where PGE2 levels were positively correlated with gingival index, plaque index, pocket depth, and attachment

loss (38). Prostaglandin E2 helps the regulation of IL-1 β and are involved in inflammatory reactions and periodontal tissue damage (38,39). Although in this study, the correlation coefficient between IL-1 β with gingival recession is negative, the magnitude of the correlation is weak (-0.324) (40).

Age did not have a significant correlation with periodontal status ($p > 0.05$). This is possible because age is not considered as an etiologic factor in periodontitis apart from periodontitis associated with systemic disease (41). Although bacterial plaque is an important factor, it is not enough proficiency level in explaining the development of the periodontal disease. Various factors such as age, systemic conditions, smoking, educational level, socioeconomic issues also play a role in the progression of periodontal disease (42). The increased severity of periodontal disease and bone loss with age-related to the length of time periodontal tissues exposed to bacterial plaque, so that it reflects the cumulative history of the oral cavity subject (43). However, this is different from the research conducted by Abbass et al, 2020 which reveals that age is a factor related to the occurrence and severity of the periodontal disease (44).

Factor level of education has a significant relationship with clinical attachment loss, gingival recession and the index of oral hygiene ($p < 0.050$), where correlation coefficient was negative, and there were means that the higher of education level, the lower the attachment loss, gingival recession and the index of oral hygiene (Table III). This is consistent with the meta-analysis study conducted by Boillot et al, 2011 who demonstrated that education as a factor predictor of chronic periodontitis and low education levels are associated with increased risk of periodontitis (45). Research conducted by Celeste et al, 2019 showed that education has a negative correlation with the severity of periodontitis (46). Education can affect health either directly, such as through employment status and income earned or indirectly is through a healthy lifestyle.

Some of the risk factors for periodontitis are systemic disease, smoking, psychological factors and oral hygiene and hormonal influences. The decrease in reproductive hormones at the time of menopause will cause changes in the levels of host cytokines and microorganisms in the oral cavity. Imbalance of these two factors can increase periodontal destruction. Menopause appears as a problem because of the conditions of rapid globalization and urbanization. Increased awareness and long-lived individuals, as well as economic conditions and education have improved, causing women to become more positive attitudes in facing menopause. However, most still do not realize the implications of short-term and long-term debilitating conditions associated with

middle age and old age due to a lack of awareness and unavailability or the increasing cost of medical support and social systems (1,47).

There is a necessity of a multidisciplinary approach to the problem of menopause that is by putting more emphasis on promotive and preventive interventions so that the subject is better prepared in dealing with symptoms that will be experienced, including symptoms in the oral cavity and clinicians who perform oral care must be more careful and give more care motivation for patients undergoing menopausal and postmenopausal transitions to have regular dental health checks (1,20).

The limitation in this study is that the study conducted by the cross-sectional method that needs to be done longitudinal studies to learn more about other factors associated with periodontal status and checks the status of perimenopause subject only done using interviews, may in advanced research be added hormone reproduction assays to better explain the menopausal status of the subject.

CONCLUSION

The conclusions in this study are only gingival recession was a factor associated with IL-1 β , whereas attachment loss, gingival recession and oral hygiene index were factors related to education level. Further research is needed to determine the factors other than cytokines and sociodemography that most play a role in influencing periodontal conditions in women who enter the menopausal transition.

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