

Original Article

CORRELATION BETWEEN ESTRADIOL SERUM LEVELS WITH XEROSTOMIA INVENTORY SCORE ON MENOPAUSAL WOMEN

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ABSTRACT

Objective: Menopause is a condition of permanent cessation of menstruation for 12 consecutive months. This occurs due to the loss of follicular ovarian activity so that estrogen levels decrease in the body. Menopause can occur at various ages, where the average age of menopause is 51-55 y. Menopause can affect oral tissues as well as other organ systems and cause xerostomia. Some of the symptoms of xerostomia include burning feelings, taste abnormalities, dysarthria, dysphagia, dysgeusia, and halitosis.

Methods: This study uses a case series design to assess the correlation between estradiol levels and the incidence of xerostomia in menopausal women. The incidence of xerostomia using the Xerostomia Inventory (XI) Score. This research was conducted in several places, namely H. Adam Malik General Hospital Medan and the hospital network of the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Sumatra Utara. The study population was all postmenopausal women at the H. Adam Malik General Hospital in Medan and the Obgyn FK USU network hospital that met the study inclusion-exclusion criteria. This research was conducted in February with a minimum sample of 38 people.

Results: In this study, 38 samples were obtained. Based on the results of the study, it was found that the most age groups were in the range of 56-60 y, the duration of menopause in the 5-10 y group, and the highest Body Mass Index (BMI) was obesity. The mean value of estradiol in menopausal women was 23.61±8.37 pg/ml; the mean value of XI score in menopausal women was 24.29±9.44. The correlation of estradiol levels and XI scores in menopausal women is a strong negative correlation that is -0.651 (p value<0.05). Correlation value of XI score and obesity in menopausal women is a low positive correlation with r = 0.342 (p value<0.05) while the value of correlation XI score with menopausal women who are not obese is a strong positive correlation with r = 0.793 (p value<0, 05).

Conclusion: Changes in the oral cavity are caused by aging and hypoestrogenism. The mean age of postmenopausal women was 56.98±4.35, with a mean BMI of 28.24±4.41. Estradiol levels in menopausal women are lower than women of reproductive age in each phase of the menstrual cycle. Significant reduction in estrogen production during menopause causes a decrease in salivary flow, leading to hyposalivation and symptoms of xerostomia.

Keywords: Menopause, Xerostomia, Estradiol

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INTRODUCTION

According to the World Health Organization (WHO) in 2005, menopause is the cessation of menstrual cycles forever for women who previously menstruated every month, due to the number of follicles experiencing atresia continues to increase until follicles are no longer available, marked amenorrhoea in the last twelve months in a row, and not caused by pathological conditions. The diagnosis of menopause is made after amenorrhoea is present for at least the last 12 mo, FSH levels>40 mIU/ml and estrogen levels<30 pg/ml. The National Institute for Health and Care in 2015 recommends diagnosis of menopause in women aged 45 y and over who have not had a menstrual episode for at least 12 consecutive months and are not using hormonal contraception [1-5].

Estradiol levels in postmenopausal women are lower compared to women of reproductive age in each phase of the menstrual cycle. In menopausal women, estradiol and estron are derived from adrenal androgen conversion in the liver, kidneys, brain, adrenal glands, and adipose tissue. The process of aromatization that occurs in the peripheral is related to a woman's body weight. Obese women have higher estrogen levels compared to thin women because of increased peripheral aromatization. Circulating estradiol levels after menopause are around 10-20 pg/ml, mostly derived from peripheral

conversion of estrone, mainly from peripheral conversion from androstenedione. Circulating estrogen levels in menopausal women are higher than estradiol, around 30-70 pg/ml. The average postmenopausal estrogen production rate ranges from 45µg/24 h [6-8]

Oral mucosa is histologically similar to that of the vaginal mucosa, both of which are arranged by layered squamous epithelium layers and show desquamative growth patterns. Therefore, the oral mucosal environment naturally responds to the hormone estrogen which circulates through the proliferation and maturation of the epithelium [9]. Based on *in vitro* studies, estrogen can affect populations of two main cells in the gingival tissue, such as keratinocytes and fibroblasts. Based on further observations, the estrogenic effect on the oral mucosa is seen mainly from inflammatory changes in periodontal tissue, including gingivitis and fibrous hyperplasia. However, desquamative gingival lesions often occur in women. Estimation of estrogen expression is related to age and can affect the keratinization of the oral cavity mucosa, considering that the oral mucosal epithelium contains cytokeratin 5 and 14 in the basal layer [9, 10].

Xerostomia is a perception of dry taste in the mouth and is associated with the decreased salivary flow. Reduced salivary flow by 40-50%

certainly makes xerostomia more symptomatic. Dry mouth taste can affect the quality of life and interfere with daily functional activities such as chewing, swallowing, and talking. Reduced salivary volume, accompanied by the antibacterial effect of saliva, can facilitate infection, tooth decay, and other periodontal diseases [11-13].

There are three scoring systems known for the evaluation of xerostomia-hyposalivation, including the Xerostomia Index (XI), Clinical Oral Dryness Scale (CODS), and European League Against Rheumatism SS Patient-Reported Index (ESSPRI). In the process, hyposalivation is usually assessed in conditions without stimulation of saliva (unstimulated whole saliva flow [UWS]), and by stimulation of saliva (stimulated whole saliva flow (SWS), stimulated parotid flow (SPF)); tests with salivary stimulation are minimally exposed to variations than conditions without stimulation, although more difficult to do [12, 14].

Xerostomia Inventory (XI) Score is a validated questionnaire containing eleven statement items designed by Thomson *et al.* The main purpose of this scoring system is to assess the individual's individual risk of dental caries from xerostomia. When first tested in normal elderly patients, the XI score was found to be unrelated to the hyposalivation condition (UWS, SWS, or SPF). This questionnaire is not appropriate for use in patients with apraxia, terminal illness, cognitive impairment, fever, dehydration, Sjogren's syndrome, and a history of previous head-neck radiotherapy [12, 14, 15].

Epidemiological studies prove the incidence of xerostomia increases with age. According to the hypothesis, this is more due to the functional capacity of the remaining salivary glands that are able to compensate for the loss of acinar tissue. Decreased salivary flow has several negative effects on oral health such as increased risk of dental erosion, demineralization, dental caries, periodontitis, intraoral infections such as oral candidiasis, halitosis, burning sensation, difficulty chewing, vocal dysfunction, dysgeusia (taste disorders) and dysphagia (difficult to swallow) [16-18].

The number of symptoms and oral clinical signs was found more in postmenopausal women (43%) than other premenopausal women (6%). The main concern of this disorder is anhedonia towards food (the inability to enjoy food and drink) which results in weight loss due to drastic reduced calorie and nutritional intake. This prevalence increases with age, more often suffered by those aged 65 y and over. Cell growth and function is regulated by the hormone estrogen, mediated by estrogen receptors, ER α and ER β . Estrogen does play an important role in oral cavity homeostasis and salivary glandula. Maturation of oral cavity epithelialization tends to decrease in postmenopausal women, causing atrophic epithelium so

it is susceptible to inflammation. This underlies why postmenopausal women often complain of burning mouth sensations. Salivary function is also partly regulated by the expression and levels of the hormone estrogen in the blood [11, 18, 19].

MATERIALS AND METHODS

Methods

This study using a case series design to assess the correlation between estradiol levels and the incidence of xerostomia in menopausal women. The incidence of xerostomia using the Xerostomia Inventory (XI) Score. This research was conducted in several places, namely, H. Adam Malik General Hospital Medan and the hospital network of the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Sumatra Utara. The study population was all postmenopausal women at the H. Adam Malik General Hospital in Medan and Department of Obstetrics and Gynecology FK USU network hospital who meet the research criteria as mentioned above. The steps taken in the sample are history taking, including name, age, parity, education, and profession. Then do a physical examination, including awareness, weight and height. The research procedure was that the blood was taken from the vein medianacubiti as much as 3 cc to measure estradiol levels. Blood samples are sent to clinical laboratories in the city of Medan. The condition of oral xerostomia is evaluated through the Xerostomia Inventory (XI) Score. Then the data is tabulated and analyzed statistically.

RESULTS

A total of 38 samples were found that met the inclusion criteria, and agreed to participate. From table 1 we found the age characteristics, the most age group of menopausal women in this study was in the range of 56-60 y by 22 people (57.9%), followed by the age range of 51-55 y by 13 people (34.2%), the age range of 45-50 y by 2 people (5.3%), and >60 y consisting of only one person (2.6%). Based on the duration of menopause, the majority group came from the group of 5-10 y with a total of 24 people (63.2%), followed by the group <5 y with a total of 11 people (28.9%), and finally those who had experienced menopause for more than ten years with a total of 3 people (7.9%). In terms of body mass index, this category is divided into four groups, including underweight, normowight, overweight, and obesity. The BMI group had at most 20 people with obesity (52.6%), normowight of 8 people (21.1%), and finally underweight of 1 person (2.6%).

Table 1: Characteristic of subject

Variable	n	Percentage
Age (years old)		
45-50	2	5.3
51-55	13	34.2
56-60	22	57.9
60-65	1	2.6
Duration of menopause (Years)		
<5	11	28.9
5-10	24	63.2
>10	3	7.9
BMI		
Underweight	1	2.6
Normoweight	8	21.1
Overweight	9	23.7
Obesitas	20	52.6
Total	38	100

From table 2 we found that the mean value of estradiol in this study was 23,61 \pm 8.37 pg/ml with a minimum value of 13 and a maximum value of 37.

Table 2: Average value of estradiol levels in menopausal women

Parameter	mean \pm SD	Median	Min	Max
Estradiol	23.61 \pm 8.378	19	13	37

From table 3 we found that the mean value of in this study was 24.29 \pm 9.44 with a minimum value of 11 and a maximum value of 36

Table 3: Average value of Xerostomy inventory score in menopausal women

Parameter	mean±SD	Median	Min	Max
XI Score	24.29±9.44	28.5	11	36

From table 4 we found there was a strong negative correlation between estradiol and XI Score was -0,651 with a p value <0,05 which shows that with high XI Score the estradiol level will decrease.

Table 4: Correlation of estradiol and Xerostomy Inventory Score in menopausal women

Variable	r	p
Estradiol XI Score	-0,651	<0,05

From table 5 shows the low positive correlation value between XI Score and obesity with r = 0,342 with p value <0,05 which shows that with more obese a woman, value of XI Score will also increase.

Table 5: Correlation of Xerostomy Inventory Score and obesity in menopausal women

Variable	r	p
XI Score	0.326	<0,05

From table 6 we found a strong positive correlation between XI Score and non-obese BMI with r= 0,793 with p<0,05 which shows that women who are not obese have an XI Score that does not increase.

Table 6: Correlation of Xerostomy Inventory Score and non obese in menopausal women

Variable	r	p
XI Score	0.793	<0,05

DISCUSSION

Menopause affects oral tissue in the same way as changing other systems. Changes in the oral cavity are caused by aging and hypoestrogenism. From the results of this study, it appears that the majority of menopausal women aged 56-60 y (57.9%) with menopause duration of 5-10 y (63.2%), and included in the category of obesity (52.6%). In contrast to this study, Kaur *et al.* showed the average age of natural menopausal women was 47.46±2.61 while in surgical menopause women were 48.42±2.60. Whereas the duration of the second menopause seemed almost the same as the duration of 1.4 and 1.58 y, respectively. The results of this study are not in line with the study above. It appears that the two sample groups with normowight with mean Body Mass Index are 22.95±1.65 and 23.02±1.45, respectively [20]. In line with this study, Gholizadeh, *et al.* The mean age of postmenopausal women was 56.98±4.35, with a mean BMI of 28.24±4.41 [21]. Research by Gao, *et al.* found the average age of postmenopausal women was 56.9±3, with a BMI of 27.6±2.4 kg/m² [22]. Research by Jones showed the average age of postmenopausal women was 59.6±4.8 y with BMI 26.1±5.2 kg/m² [23]. Whereas research by Puspita *et al.*, found the average age of menopausal women was 53.45±3.09 with BMI 25.38±4.12 and the majority of menopause duration >5 y with 40.4% [24]. Research by Hosseini in 2011, showed the average age of menopausal women with xerostomia was 57, 41±7.71 with BMI 23.8±2.1 and duration of menopause 9.1±7.3 y [25].

In this study, the average estradiol level was 23.61±8.37 pg/ml. In a study by Kaur, *et al.* found an average level of serum estradiol in women with surgical menopause of 20.49±3.16 pg/ml while in natural menopause, it was 27.41±5.08 g/ml. Whereas in the study of Gholizadeh, *et al.*, the mean estradiol appeared to be lower with a level of 17.22±11.07 [21] In a study by Gao, *et al.* the average estradiol in postmenopausal women was found to be 18.2±4.6 [22]. Research by Jones found the mean estradiol level of 16.2 pmol/l (9.4-24.2) [23]. Puspita *et al.* who conducted research in several hospitals in Medan, North Sumatra found the average levels of estradiol in menopausal women was 18.62±16.85 ng/ml. Low serum levels of estradiol are commonly found in postmenopausal women due to Estradiol (E2, or 17β-estradiol) is a steroid hormone derived from target cholesterol in various tissues in the female reproductive organs. In women, estradiol is synthesized mainly by ovarian

follicles. In postmenopausal women, the average concentration of serum estradiol reaches 10-20 pg/ml. Estradiol levels in menopausal women are lower than women of reproductive age in each phase of the menstrual cycle [24].

The prevalence of discomfort in the mouth was found to be significantly higher in perimenopausal and postmenopausal women (43%) than in premenopausal women (6%). In a study from Turkey, Yalcin *et al.* investigated the saliva of a small group (n = 14) of menopausal women and the same number of premenopausal controls and found that the rate of salivary flow decreased in menopausal women and increased with the use of HRT, while the pH concentrations of saliva, electrolytes and calcium were not affected [26].

Salivary composition in postmenopausal women depends on estrogen, low calcium concentrations during ovulation occur when estrogen levels are high and appear to be lower during pregnancy than during labor. In addition, hormone replacement therapy can reduce symptoms of dry mouth and improve oral health. In addition to estrogen deficiency causes calcium levels to decrease, conversely PTH levels appear to rise. With an increase in PTH in response to hypocalcemia, the condition of eucalcemia will only be achieved with reduced renal calcium excretion and stimulation of renal conversion from 25-hydroxyvitamin D to 1.25-dihydroxyvitamin D. It also increases calcium absorption in the intestine. In Singh's study, a positive correlation (P<0.05) was seen between salivary calcium and XI score [27]. Sewón *et al.* also showed similar results. A study from Iran on the flow rate and salivary composition of 42 postmenopausal women with or without xerostomia (21 cases, 21 controls) showed that the average calcium concentration was significantly higher in cases than in controls. Salivary β-estradiol concentrations were analyzed and it was observed that in the case group had significantly lower concentrations and hormone production than the control group [26].

Xerostomia and burning mouth are the main oral symptoms of menopause. Related to this, the climacteric period lasts long and involves a series of events such as loss of female reproductive capacity and changes in important sex hormones that are marked by a decrease in progesterone, and especially estrogen levels. Partial or total reduction in estrogen production during menopause and significant climacteric causes a decrease in salivary flow, leading to

hyposalivation and symptoms of xerostomia. Decreased salivary flow during menopause results from blocking of salivary gland function, which may be due to physiological changes associated with age and/or hormones as demonstrated by the detection of sex hormone receptors in the oral mucosa and salivary glands. Although several studies have shown that xerostomia may not be associated with a decrease in salivary flow rate, in fact this is a process associated with low estrogen levels. However, the prevalence of oral symptoms, especially xerostomia, has been shown to be greater in postmenopausal women than in premenopause [12]. In this study the average Xerostomy Inventory (XI) Score was 24.29 ± 9.44 . Research by Kaur, *et al.* The mean XI score in the premenopausal group was 12.5 while the XI score in the postmenopausal group appeared to be twice as high as 30.24 [17]. In Singh's study, the average XI score for menopausal patients with xerostomia was 22.10 ± 4.9 [27]. A study by Hosseini in 2017 showed a prevalence of severe xerostomia of 15% in postmenopausal women, whereas no premenopausal subjects experienced severe xerostomia. The incidence of hyposalivation in postmenopausal women was significantly higher than in premenopausal women ($P < 0.005$). In premenopausal women, the risk of hyposalivation is 27.5 (AR = 25.5), whereas during menopause, the risk of hyposalivation increases to 3.7 times higher (RR = 3.7). And in studies by Minicucci, *et al.* there was no correlation between the Xerostomia Inventory and the Visual Analogue Scale questionnaire in the three groups observed and salivary flow seemed lower in the menopause group [12].

A case-control study was carried out on 64 postmenopausal women aged 42-75 y with or without selected xerostomia (32 as cases and 32 as controls) and conducted at the Oral Medicine Clinic, Tehran University of Medical Sciences. Xerostomy Inventory Score (XI) is used as an index of the severity of xerostomia. Saliva 17β -estradiol was measured by an enzyme immunoassay kit. The unstimulated mean salivary flow rate and 17β -estradiol concentration were significantly lower in cases than controls. There was a significant negative correlation between XI score and overall unstimulated salivary flow rate and also the concentration of 17β -estradiol in menopausal women. There seems to be a negative correlation between the severity of xerostomia and 17β -estradiol saliva in postmenopausal women [28]. This finding is in line with this study which found a strong negative correlation between estradiol and XI score was -0.651 with a value of $p < 0.05$ which indicates that with high levels of XI score, estradiol levels will decrease.

In table 4.1.5, it is seen that a low positive correlation value between XI score and obesity with $r = 0.342$ with a value of $p < 0.05$ which indicates that with a woman's obesity, the XI score will also increase. In table 4.1.6, we can see a strong positive correlation between the XI score and non-obese BMI with $r = 0.793$ with a p value < 0.05 which shows that women who are not obese have an XI score that does not increase. Xerostomia is the main complaint of most elderly individuals and is closely related to menopause [25]. In the study by Hosseini it appears that women who complain of oral dryness have a mean BMI of 24.8 ± 2.1 kg/m² which is included in the norm weight category, while BMI in women without oral dryness complaints appears more low with 24.2 ± 2.5 kg/m² [28]. Research by Tremblay shows a BMI of more than 25 kg/m² in adults and childhood obesity related to the occurrence of hypo salivation [29]. A study at Andalas University showed the results of a linear regression test known that the rate of salivary flow = $0.404 - 0.008 * (\text{BMI})$. Regression coefficient of IMT 0.008 states that each addition of 1 Body Mass Index (BMI) will reduce salivary flow rate by 0,008 ml/min. This study concludes that there is a meaningful relationship between BMI and salivary flow rate [30].

CONCLUSION

The most common age group is 55-60 y with a total of 22 people (57.9%), the most menopause is 24 people (63.2%), and the highest BMI is the obese group with 19 people (50%). The mean value of estradiol levels in this study was $23.61 \pm 8,378$ pg/ml. The mean value of XI score in this study was 24.29 ± 9.44 . It is estimated that a strong negative ($r = -0,651$) is significant between estradiol levels and XI scores which means the lower the estradiol levels, the higher the XI score. It is estimated that positive is moderate ($r = 0.342$),

which is significant between XI and BMI scores, which means that the higher the BMI (obesity), the higher the XI value. It is estimated that there is a strong positive ($r = 0.793$), which is significant between the XI score and the non-obese BMI, which means that the higher the BMI (not obese), the XI score is also not increased.

RECOMMENDATION

Need to do further research on the symptoms of xerostomia in menopausal women, given that sometimes the symptoms are not realized in menopausal women and also about xerostomia in menopausal women using other parameters so that it can improve the diagnosis.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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