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Original Article

ANALYSIS OF ESTROGEN DEFICIENCY ASSOCIATION WITH SALIVARY 25-HYDROXYVITAMIN D AND SALIVA FLOW RATE IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

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ABSTRACT

Objective: This study analyzes the relationship between estrogen deficiency, salivary 25-hydroxyvitamin D, and salivary flow rates in postmenopausal women with osteoporosis.

Methods: A cross-sectional study involved 52 patients with Osteoporosis at Orthopaedic Installation Putri Hijau Hospital as subjects by purposive random sampling. The inclusion criteria were participants who had menopause for at least two years, did not take (vitamin D supplements, antihypertensives, antihistamines, antidepressants, replacement estrogen hormone therapy, experience parathyroid hormone disorders, Sjogren's Syndrome, diabetes, obesity, and/or currently undergoing cancer therapy. Excluded those who vomited or were unable to sit. Saliva samples were collected using the spitting method and estrogen and 25-hydroxyvitamin D levels were calculated using an ELISA kit, and saliva flow rate using a measuring glass. The data were analyzed using the Spearman correlation test.

Results: The mean value of salivary estrogen was 8 pg/ml, salivary 25-hydroxyvitamin D was 9.17 ng/dl, and salivary flow rate was 0.177 ml/minute. Based on the results of the Spearman correlation test between salivary estrogen and salivary 25-hydroxyvitamin D, it had a significant value ($p<0.001$) in the positive direction ($r=0.925$), and salivary estrogen and salivary flow rate had a significant value ($p<0.001$) in the positive direction ($r=0.818$).

Conclusion: there is a relationship between salivary estrogen and salivary 25-hydroxyvitamin D and salivary flow rate, with a positive correlation and significant value, meaning that the lower the salivary estrogen, the lower the salivary 25-hydroxyvitamin D and salivary flow rate.

Keywords: Estrogen, Salivary 25-hydroxyvitamin D, Salivary flow rates, Osteoporosis, Post-menopausal women

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INTRODUCTION

Menopause is a natural stage in a woman's life characterized by the cessation of menstruation for 12 mo. Following this, women enter the postmenopausal phase, during which there is a reduction in the secretion of two sex hormones from the ovaries: estrogen and progesterone [1]. Reduced estrogen levels can lead to osteoporosis and oral manifestations characterized by a decrease in saliva flow rate [2]. The prevalence of osteoporosis among women in Indonesia aged 50 to 70 y and those over 70 y stands at 23% and 53%, respectively [3].

The low estrogen hormone levels that occur during the postmenopausal phase can affect a woman's quality of life [4]. Estrogen plays an important role in the metabolism of vitamin D in the kidneys. Vitamin D functions to regulate calcium absorption in the intestine. Low estrogen levels disrupt calcium homeostasis, resulting in osteoporosis and bone fractures [5]. Estrogen plays a pivotal role in vitamin D metabolism, particularly in postmenopausal women with osteoporosis. The decline in estrogen levels during menopause significantly impacts bone health and calcium regulation. Postmenopausal women often exhibit decreased levels of $1,25(OH)_2D$ due to diminished estrogen, leading to impaired calcium absorption [5]. Vitamin D deficiency plays a role in dental and oral bone pathologies (altered formation, periodontal disease, and jaw osteonecrosis) [5].

Low estrogen also influences a decrease in salivary flow rate, which can cause hyposalivation [6]. Postmenopausal women have a prevalence rate of bone fractures due to osteoporosis reaching 37.5%, the prevalence of vitamin D deficiency reaches 19% and the prevalence of hyposalivation reaches 65% [7-9].

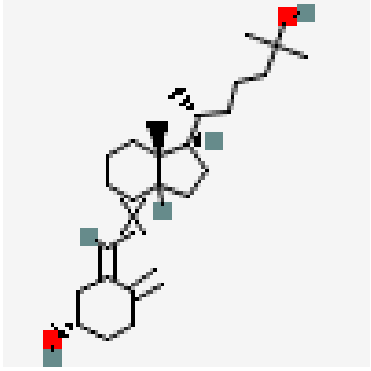

Fig. 1: Chemical structure of 25-hydroxyvitamin D3 (calcidol), used here as a representative form of 25-hydroxyvitamin *D* [37]

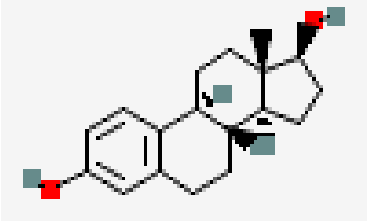

Fig. 2: Chemical structure of estradiol-the main estroge hornone in woman [38]

A decrease in estrogen levels can disrupt vitamin D metabolism, leading to an increased risk of osteoporosis.[10] Amin *et al.* found that osteoporosis in postmenopausal women can be associated with a decrease in estrogen levels [11]. Al-Obaidi *et al.* found that salivary estrogen levels were lower in postmenopausal women than in premenopausal women [12]. Al-Amiry *et al.* found that there was a positive correlation between salivary estrogen and salivary vitamin D in postmenopausal women with osteoporosis [13].

The declining in estrogen will also result in thinning and atrophy of the epithelium in the mucosa and salivary glands, resulting in a decrease in salivary flow rate. Tjahawati *et al.* found differences in salivary flow rates between groups of premenopausal and postmenopausal women, where the group of postmenopausal women had a higher flow rate [14]. Gill *et al.* found a decrease in salivary flow rate in postmenopausal women associated with lower estrogen levels [15]. Gupta *et al.* found an unstimulated salivary flow rate that was positively correlated with salivary estrogen levels in postmenopausal women [16].

Based on all of that study, Research suggests that low estrogen levels may be associated with low vitamin D levels. Estrogen and vitamin D have a complex relationship in the body, and both play crucial roles in maintaining bone health. In postmenopausal patients with osteoporosis, low salivary estrogen levels may affect salivary flow rates. Some studies indicate that decreased estrogen levels can lead to reduced saliva production and changes in saliva composition. Saliva testing may be a potential method for detecting osteoporosis, particularly in postmenopausal patients. By measuring estrogen levels and other biomarkers in saliva, medical practitioners may be able to predict osteoporosis risk and implement early interventions. Examination of estrogen and 25-hydroxyvitamin D levels through serum often causes pain in patients, so examination through saliva is needed as a non-invasive alternative. Salivary diagnostics present a significant advantage due to their noninvasive and painless nature. Their suitability for at-home collection enhances patient compliance and convenience. Moreover, saliva assays measure the free, bioactive fraction of hormones, offering a reliable indication of the body's physiological hormonal status [17]. Therefore, researchers are interested in researching the relationship between salivary estrogen, salivary 25-hydroxyvitamin D, and the salivary flow rate of postmenopausal female patients with osteoporosis.

MATERIALS AND METHODS

All protocols of this research adhered strictly to the ethical principles of The Declaration of Helsinki and received ethics committee approved by the Health Research Ethics Committee of Universitas Sumatera Utara (No. 217/KEPK/USU/2024). All participants in this study provided written informed consent and signed the consent form following the standards set by the ethics committee. This cross-sectional study was completed in January-April 2024 with samples obtained using a purposive random sampling method of 52 female patients who visited the Orthopedic Installation at the Putri Hijau Hospital in Medan included women who met the inclusion criteria: those who had been in menopause for at least two years, diagnosed with osteoporosis, not consuming vitamin D supplements, antihypertensives, antihistamines, antidepressants, not using estrogen replacement hormone therapy, and not experiencing systemic conditions such as parathyroid hormone disorders, Sjogren's Syndrome, diabetes, obesity, and not currently undergoing cancer therapy, and can be cooperative. The exclusion criteria for this study were that the subject experienced vomiting and was unable to sit.

This research data was collected by taking saliva samples using the spitting method. Researchers instructed research subjects to sit with their heads bowed and collect saliva samples using a graduated cylinder. Saliva without stimulation is collected in the mouth with the lips closed. Then, spit it into the cylinder every 1 minute for 5 min to measure the flow rate then calculate the average. Examination of salivary estrogen levels and salivary 25-hydroxyvitamin D requires a minimum of 2 ml of saliva sample. After the saliva samples were collected, they were brought using a cooler box filled with ice packs to the Terpadu Laboratory of the Medical Faculty of Universitas Sumatera Utara. This integrated laboratory served as the site for saliva sample storage for Estrogen and salivary 25-hydroxyvitamin D level testing, as it is equipped with adequate facilities and certified under ISO/IEC 17025:2017. Thereafter, the saliva was centrifuged for 10 min at 2500 rpm. Researchers store the saliva samples at a temperature of-20 °C, which can last up to 6 mo. After all of the saliva samples were collected, levels of salivary estrogen were calculated by using EA0025Hu, human estrogen, E Elisa Kit, and salivary 25-hydroxyvitamin D by using e1543Hu, human Vitamin D, VD Elisa Kit, which brand from Bioassay Technology Laboratory.

Estrogen levels in adult women before menopause are 30-400 pg/ml. Normal vitamin D levels are 20-30 ng/ml, and normal unstimulated saliva flow rate is 0.25-0.35 ml/min.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0. Data normality was assessed using the Kolmogorov-Smirnov test, and variance homogeneity was evaluated with Levene's test. Both salivary estrogen ($p=0.001$), salivary 25-hydroxyvitamin D ($p=0.007$), and salivary flow rates ($p=0.000$) were not normally distributed ($p<0.05$), necessitating non-parametric tests, and data were analyzed using the Spearman correlation test.

RESULTS AND DISCUSSION

The demographic data of the subjects shows that the group of postmenopausal women at the orthopedic surgery polyclinic in Putri Hijau hospital, Medan, with the largest number of osteoporosis sufferers, is in the 55-59 y age range, with a percentage of 32.7%. (table 1) These results are in line with Priya *et al.*, who found that the group of women suffering from osteoporosis had an age range of 55-60 y with a percentage of 36.6% [18]. The results of this study differ from Dieny *et al.*, who found that the largest group of osteoporosis sufferers was over 70 y old [19]. The difference occurs because, based on data from the Central Statistics Agency (Badan Pusat Statistik Sumatera Utara) in 2023, the life expectancy in North Sumatra for women is only 72 y, therefore, there are fewer patients with an age above 70 y. In addition, several subjects aged over 70 y were excluded due to physical conditions such as being unable to sit and experiencing vomiting when saliva samples were taken.

Table 1: Demography of postmenopausal women with osteoporosis based on menopausal stage

Age	Frequency	Percentage (%)
55-59	17	32.7%
60-64	12	23.1%
65-69	11	21.2%
70-74	12	23.1%
total	52	100%

This study found that in postmenopausal women, the average salivary estrogen level for osteoporosis sufferers was 0.008 ng/ml, with the lowest value being 0.004 ng/ml and the highest being 0.017 ng/ml. The mean salivary 25-hydroxyvitamin D was 9.17 ng/ml, with the lowest value being 4.17 ng/ml and the highest being 16.79 ng/ml. The average saliva flow rate was 0.17 ml/minute, with the lowest value being 0.08 ml/minute and the highest being 0.3 ml/minute (table 2).

Table 2: The difference in the biomarker saliva level in postmenopausal women with osteoporosis

Subject	n	Variable	Average	Min	Max	Standard deviation
Postmenopausal women	52	Salivary estrogen (ng/ml)	0.008*	0.004	0.017	0.030
		Salivary 25-hidroxyvitamin D (ng/ml)	9.17*	4.17	16.79	3.33
		Salivary flow rate (ml/min) (min/ml)	0.17*	0.08	0.3	0.06

*Normally salivary estrogen postmenopausal: 0,01-0,005 ng/ml, *Normally salivary 25-Hidroxyvitamin D: 20-30 ng/ml, *Normally unstimulated salivary flow rate: 0,25-0,35 ml/min

Table 3: Correlation between salivary estrogen with salivary 25-hydroxyvitamin D and saliva flow rate in postmenopausal women with osteoporosis

Subject	n	Variabel		r	p
Postmenopausal Women	52	Salivary Estrogen	25-Hidroxyvitamin D	0.925*	<0.001*
		Salivary Estrogen	Salivary Flow Rate	0.818*	<0.001*

*p=0.000 significant value based on Spearman test, *r=positive correlation

Based on the Spearman test, it was found that there was a significant relationship between saliva estrogen and vitamin D ($p<0.001$; $p<0.05$) with a very strong degree of relationship and a positive correlation ($r=0.925$). The lower the salivary estrogen levels relates to the lower of salivary 25-Hydroxyvitamin D levels. The relationship between saliva estrogen and saliva flow rate is significant ($p<0.001$; $p<0.05$) with a very strong degree of relationship and a positive correlation ($r=0.818$). The lower the salivary estrogen level also decline the salivary flow rate (table 3).

The results of this study found that the average salivary estrogen level in postmenopausal women with osteoporosis was low, 0.008 ng/ml. A study of Tivis *et al.* reported that the normal salivary estrogen is 0,5-4,39 ng/ml [20]. Gupta *et al.* found that salivary estrogen levels are low in postmenopausal women [16]. Arsani *et al.* found that estradiol levels tend to be lower at late stage of perimenopause compared to early age of perimenopause women [21]. Soundrya *et al.* found that salivary estrogen levels in the group of postmenopausal women are lower than in the group of premenopausal women [22]. The menopausal phase is a natural physiological process in women where there are few primary ovarian follicles, so the number is insufficient to respond to the effects of Follicle Stimulating Hormone (FSH). On the other hand, there is no increase in Luteinizing Hormone (LH) levels, and ovulation does not occur, resulting in cessation of menstruation and decreased estrogen secretion [23].

The results of this study found that the average salivary 25-hydroxyvitamin D level in postmenopausal women with osteoporosis was reduced (9.17 ng/ml), which is normally 20-30 ng/ml. Al-Amiry and Najem also reported that postmenopausal women with osteoporosis had low salivary vitamin D levels [13]. Low levels of Vitamin D can affect calcium absorption in postmenopausal women, resulting in an increased risk of osteoporosis [24]. Postmenopausal women are susceptible to vitamin D deficiency due to increasing age, less exposure to sunlight, and lack of consumption of foods containing vitamin D [24]. Karampela *et al.* also identified increased body weight as another potential confounding factor influencing vitamin D deficiency. Vitamin D deficiency can be associated with various health conditions during menopause, such as vasomotor symptoms, vaginal atrophy, sexual dysfunction, and osteoporosis [25].

The results of this study found that there was a relationship between salivary estrogen and salivary 25-Hydroxy Vitamin D with a significant value ($p<0.001$) and a positive correlation ($r=0.925$), which reports that as salivary estrogen levels progressively decrease, a concomitant decline in the 25-hydroxyvitamin D concentrations is also observed. Al Amiry *et al.* found a positive correlation between salivary estrogen levels and salivary vitamin D in postmenopausal women with osteoporosis [13]. In postmenopausal individuals with osteoporosis, decreased salivary estrogen levels may compromise salivary flow rates. Studies suggest that estrogen depletion can lead to diminished saliva production and alterations in saliva composition. The impact of estrogen deficiency in postmenopausal women are reduced active vitamin D levels and increased bone resorption [25]. Estrogen functions to stimulate 1-α hydroxylase in the metabolism of the active form of vitamin D, as 1,25-hydroxyvitamin D in the kidneys. Due to diminished estrogen, leading to impaired calcium absorption [26]. In postmenopausal women, reduced vitamin D also causes increased secretion of parathyroid hormone, which affects bone remodeling. Calcium resorption will exceed calcium absorption into the bones, resulting in reduced Bone Mineral Density (BMD), osteoporosis, and bone fractures [26, 27].

The results of this study found that the average unstimulated salivary flow rate in postmenopausal women with osteoporosis was 0.17 ml/minute, which means the average salivary flow rate is low. The unstimulated salivary flow rate is normally 0.25-0.35 ml/minute. Poudel *et al.* and Foglio Bonda *et al.* emphasized that the average unstimulated saliva flow rate in postmenopausal women is low [28, 29]. The decrease in saliva flow rate in postmenopausal women occurred due to degeneration of the salivary glands [30]. Salivary glands in postmenopausal women experience a reduction in acinar cell volume, loss of secretory tissue, and increased adipose tissue [31].

The results of this study reported that there is a relationship between salivary estrogen and salivary flow rate, with a significant value ($p<0.001$) and a positive correlation ($r=0.8188$), which means that the lower the salivary estrogen level, the lower the salivary flow rate. The results of this study are in line with Gill *et al.*, who affirm a decrease in the rate of unstimulated saliva flow in women after menopause, which was related to hormonal changes that occurred during this period [32]. Ciesielska *et al.* found a decrease in saliva flow rate in postmenopausal women compared to premenopausal women [33].

Low estrogen levels affect oral conditions in postmenopausal women because there is Estrogen Receptor β (Erβ) in the epithelial tissue in the mouth. A decrease in estrogen levels will result in thinning and atrophy of the epithelium in the mucosa and salivary glands [31]. This situation causes complaints of a dry mouth (xerostomia), difficulty in wearing removable dentures, difficulty chewing, a burning sensation, impaired taste, and causes cervical caries and periodontal disease [34]. Low estrogen levels also affect the density of the jawbone and alveolar bone. This will cause increased tooth mobility and the risk of tooth loss, which can affect the saliva flow rate [31].

Other studies also reported that biochemical alterations are characterized in osteoporotic as well as osteopenic patients. Monitoring of these parameters may be beneficial while giving the treatment to these patients for the prevention of other life-threatening risks [35]. Kumar *et al.* also found that the osteoporotic population taking calcium along with physiotherapy showed an improvement in the total quality of life [36].

Salivary diagnostics may offer a promising approach for detecting osteoporosis, particularly in postmenopausal women. By quantifying estrogen levels and other biomarkers in saliva, clinicians may be able to predict osteoporosis risk and initiate timely interventions.

However, there are limitations of this study, further investigation is warranted to elucidate the relationship between low salivary estrogen, bone mineral density minerals and osteoporosis, as well as to develop reliable and efficacious saliva-based diagnostic methodologies.

CONCLUSION

This study concludes that there is a relationship between salivary estrogen and salivary 25-hydroxyvitamin D, and salivary flow rate, with a positive correlation and significant value, which means that the lower the salivary estrogen as the sign that the decrease in salivary 25-hydroxyvitamin D and salivary flow rate. These findings underscore the importance of conducting longitudinal research employing salivary biomarkers as a noninvasive method for assessing osteoporosis risk and progression.

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AUTHORS CONTRIBUTIONS

All authors significantly contributed to the conception, design, data acquisition, analysis, and interpretation. They were involved in drafting and revising the article for important intellectual content. All authors agreed to submit the work to the current journal, approved the final version for publication, and agreed to be accountable for all aspects of the research.

CONFLICT OF INTERESTS

Declared none

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