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Original Research

The Association between Vitamin D/25(OH)D and Reproductive Hormone in Young Women with Recurrent Aphthous Stomatitis: An Observational Study

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Abstract

Aim: To investigate the association between vitamin D/25-hydroxyvitamin D [25(OH)D] level and reproductive hormone in women with recurrent aphthous stomatitis (RAS). The reproductive hormonal change suggested contributing to development of RAS in women. Studies have also shown that vitamin D deficiency may contribute to the development of RAS. So far, there is no study that reveals the association between vitamin D/25(OH)D and reproductive hormone in RAS. **Materials and Methods:** A cross-sectional study was performed on 38 female patients with RAS without any systemic history, any habit, or on any medications. All subjects with RAS underwent intraoral examination and hormonal level assessment to examine reproductive hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol, and progesterone), cortisol, and vitamin D/25(OH)D. The demographic characteristics of oral ulcers, predisposing factors, and pain (visual analog scale [VAS]) scores of RAS were also obtained from all participants. The characteristics of subjects, severity of RAS, FSH, LH, estradiol, progesterone, cortisol, and vitamin D/25(OH)D were presented descriptively. **Results:** All subjects had mean value of estradiol (93.99 ± 81.34 pg/mL), progesterone (0.73 [0.44 to 3.73 ng/mL]), FSH (4.24 ± 1.90 mIU/mL), LH (8.12 ± 5.76 mIU/mL), cortisol (8.13 ± 2.70 μg/mL), and had low mean value of serum vitamin D/25(OH)D (10.88 ± 3.21 ng/mL) which was categorized with vitamin D deficiency. The result of Pearson correlation test showed a significant positive correlation between mean LH and vitamin D/25(OH)D ($P < 0.05$). **Conclusion:** All subjects with RAS have vitamin D deficiency and vitamin D is correlated with LH.

Keywords: Female, Luteinizing Hormone, Recurrent Aphthous Stomatitis, Vitamin D/25(OH)D

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Introduction

Several studies have shown that recurrent aphthous stomatitis (RAS) is more prevalent in women than men.[1-3] One of the precipitating factors of RAS in women might be menstrual/hormonal change.[4-6] Although the role of menstrual cycle as the precipitating factor of RAS is still conflicting, women with RAS may relate to the fluctuation of reproductive or sex hormone (progesterone and estrogen) in luteal phase of menstrual cycle.[6-8] Both sex hormones are regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The mechanisms of reproductive hormone of women in development of RAS may be caused by the influence of both progesterone and estrogen, which disrupt both innate and cell-mediated immunity.[7-9] Furthermore, hormonal change during menstrual cycle may induce the elevation of cortisol and stress response in women.[10] Some evidences also revealed that RAS is associated with stress.[3-5,11] Stress may involve in RAS pathogenesis by modified immune response in

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oral mucosal but the exact mechanism is still unclear.[6] Stress may induce the release of cortisol. Cortisol is a hormone that is produced by adrenal cortex in response to stress through hypothalamus–pituitary–adrenal (HPA) axis. Studies have shown that cortisol level in patients with RAS is higher than that of healthy controls, meaning that stressful condition may induce the increasing of cortisol production by cortex adrenal.[12,13]

A study has shown that patients with RAS have low level of serum vitamin D.[14] Vitamin D is also influenced by the fluctuation of sexual hormone in menstrual cycle.[15,16] This is supported by the study that revealed that women with premenstrual syndrome have low serum vitamin D than women without premenstrual syndrome.[17,18] The role of vitamin D in oral mucosal disease is shown by a study that low vitamin D was found in children with periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome.[19] However, none of the studies showed the association between vitamin D and reproductive hormone levels in women with RAS. Although the vitamin D has a negative association with estrogen and progesterone in young women,[20,21] vitamin D may associate with the reproductive hormone change in RAS. The pathogenesis of RAS would be more complex as stress may also predispose for the development of RAS. Therefore, there may be a role of vitamin D in the development of RAS in young women, which is induced by hormonal change in menstrual cycle and cortisol change that is indicator of stress. In such condition, vitamin D and hormonal change may contribute to the development of RAS in women. The aim of this study was to evaluate the association between serum vitamin D/25-hydroxyvitamin D [25(OH)D] level, reproductive hormones (estrogen, progesterone, FSH, and LH), and cortisol level in women with RAS.

Materials and Methods

Study design

This was a cross-sectional analytical study performed on all consecutive patients with RAS attending Departments of Oral Medicine and Dental Public Hospital, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Indonesia from September 2016 to November 2016.

Sampling criteria

A simple random sampling technique was performed. The inclusion criteria of the study were female patients older than 18 years, those who diagnosed with RAS and who had oral ulcers no more than 3 days, those who did not have other systemic diseases, those who did not consume any medications (including contraceptive and hormonal therapy), and those who did not have hysterectomy. The exclusion criteria of the study were patients with RAS who had irregular menstrual cycle, those who had smoking habit, those wearing prosthesis or orthodontic, those who were pregnant and lactation, and those who did not agree to participate in this study. All participants who matched the criteria were informed about the study and written consent was taken from each participant with explanation of purpose of the study.

Study method

Initially, information about age, education level, married status, and ethnicity were obtained by questionnaire. The demographic data collected and the pain score using a visual analog scale (VAS) with 0–10 scale was used to examine the severity of RAS. They were asked to rate the severity of pain on a 10-point scale, ranging from 0 (none) to 10 (most severe). Intraoral examination was performed on all patients to obtain the data about number, size, and locations of ulcers. During intraoral examination, the data of predisposing factors of RAS were also obtained from the patients.

All participants underwent a venipuncture to obtain a blood sample. The blood sample was taken from median cubital vein on the patient's upper right limb. A ethylenediaminetetraacetic vacutainer was used to collect the blood sample to determine FSH, LH, progesterone, estradiol, and serum cortisol. The electrochemiluminescence immunoassay analyzer (ECLIA) method that was the standard examination for those parameters was applied according to manufacturer's instructions. The values of FSH = 1.7–7.7 mIU/mL, LH = 1.0–11.4 mIU/mL, progesterone = 1.7–2.7 ng/mL, estradiol = 43.8–211, and normal serum cortisol (morning value) = 4.30–22.40ug/dL were considered to be normal levels. Vitamin D/25(OH)D (ECLIA Method, Cobas, Roche Diagnostic International Ltd, USA) deficiency was determined when the vitamin D/25(OH)D level was <20 ng/mL. Vitamin D insufficiency was determined when the vitamin D/25(OH)D level was 21–29 ng/mL and when the vitamin D/25(OH)D level was > 30 ng/mL, it was considered to be in normal level. All blood examination was conducted in Pathology Clinic Laboratory at Prodia Laboratory, Dr. Sardjito Hostpital.

Statistical analysis

The demographic data and serum level of vitamin D and reproductive hormone of patients with RAS were analyzed using descriptive statistics. The Kolmogorov–Smirnov test was used to test whether the data were normally distributed. The correlation between vitamin D/25(OH)D level, reproductive hormones (estrogen, progesterone, FSH, and LH), and cortisol was analyzed by Pearson correlation test for normal distributed data and Spearman correlation test when the data were not normally distributed. Linear regression with reproductive hormone, cortisol, and age were considered predictors for vitamin D. In order to have sizeable correlation, We proposed the coefficient correlation = 0.5 and alpha at 0.05

with the power 80%. Data were analyzed using Statistical Package for the Social Sciences software program, USA, version 17.0 with 95% confidence interval (CI).

Results

There were 38 patients with RAS who fulfilled the inclusion and exclusion criteria during this study period. Most of the subjects were college students (97%), Javanese (76%), and not married yet (100%). Stress, hormonal, and unknown factors were the predisposing factors of patients with RAS. All subjects had oral ulcers of size <10 mm (100%), which were categorized as minor type RAS. The most sites of the location of the oral ulcers were buccal and labial mucosal. All RAS subjects reported oral ulcers accompanied by pain but moderate pain in category. Our subjects with RAS had mean value of estradiol = 93.99 ± 81.34 pg/mL, progesterone = 0.73 (0.44–3.73 ng/mL), FSH = 4.24 ± 1.90 mIU/mL, LH = 8.12 ± 5.76 mIU/mL, and cortisol = 8.13 ± 2.70 µg/mL. All subjects had low mean value of serum vitamin D/25(OH)D (10.88 ± 3.21 ng/mL), which was categorized with vitamin D deficiency [Table 1]. Only vitamin D/25 (OH) had an a positive significant association with LH ($P < 0.05$) [Table 2]. Linear regression showed that 30.8% variability in vitamin D/25(OH) in our subjects RAS was explained by other parameters ($F = 2.297$ and $P = 0.060$) [Table 3].

Discussion

This is the first study that showed the correlation between vitamin D/25(OH)D and reproductive hormone in women with RAS. We found that vitamin D/25(OH)D is correlated with LH in women with RAS. Many factors may be as predisposing factors for the development of RAS including nutritional factors and hormonal change. Although genetic factor is the main factor for the development of RAS,[4] both vitamin D and LH may contribute to development of RAS. This study showed that all women with RAS had low level of vitamin D/25(OH)D. Studies have shown that the prevalence of RAS in women is higher than men.[21] e explanation of the high prevalence of RAS in women may be caused by the imbalance of hormonal change of menstrual cycle. The fluctuation of estrogen and progesterone luteal phase of menstrual cycle results in the dysregulation of immune response, which induces tissue destruction and causes inflammation of oral mucosal.[22] Stress may also contribute to the development of RAS; physically and psychologically stresses have been known as the predisposing factors of RAS. Our result showed that most subjects were college students who may tend to have a stressful condition during their daily life. This study result was in line with other study that showed that both hormonal and stress were dominant predisposing factors for RAS.[11] Although the mean serum cortisol level of

Table 1: The characteristics of recurrent aphthous stomatitis subjects

Variable	Value
Number of subjects	38
Age: mean (SD)	21.16 (1.96)
Ethnicity: Java (%)	76%
Married status	
Not married (%)	100%
Education level: *n* (%)	
High education level	37 (97)
Predisposing factor*: *n* (%)	
Stress	10 (28)
Hormonal	10 (26)
Hormonal and stress	16 (42)
Unknown	2 (5)
Oral ulcer characteristic	
Ulcer numbers: *n* (%)	
<10	38 (100)
>10	–
Ulcer size: mm (*n* %)	
<10	38 (100)
>10	
Pain scale (VAS) score: mean (SD)	4.86 (2.28)
Ulcer locations: *n* (%)	
Floor of the mouth	4 (10)
Tongue	10 (27)
Gingiva	10 (27)
Labial mucosa	27 (72)
Buccal mucosa	16 (43)
Soft palate	3 (8)
Hormone status	
Estradiol: mean (SD) pg/mL	93.99 (81.34)
Progesterone: median IQR ng/mL	0.73 (0.44 to 3.73)
FSH: mean (SD) mIU/mL	4.24 (1.90)
LH: mean (SD) mIU/mL	8.12 (5.76)
Serum cortisol: mean (SD) µg/dL	8.13 (2.70)
itamin D: mean (SD) ng/mL	10.88 (3.21)

IQR = interquartile range, *n* = number, SD = standard deviation, S = visual analog scale, pg = picogram, ng = nanogram, FSH = follicle-stimulating hormone, LH = luteinizing hormone, mL = millimeter, dL = deciliter

Table 2: The correlation between vitamin D/25-hydroxyvitamin D, reproductive hormone, and cortisol

Correlation	Vitamin D (*r*)	*P* value
Estradiol	0.49	0.772
Progesterone	–0.108#	0.519#
FSH	0.199	0.233
LH	0.321	<0.05*
tisol	–0.096	0.566

FSH = follicle-stimulating hormone, LH = luteinizing hormone, *P* = probability, *r* = correlation coefficient

*Significant with $P < 0.05$

#Analyzed using Spearman correlation test

Table 3: Linear regression between reproductive hormone and cortisol toward vitamin D/25-hydroxyvitamin D

Variables	β (unstandardized coefficient)	95% CI (β)	SE (β)	β (standardized coefficient)	*P* value
Estradiol	−0.007	−0.028 – 0.015	0.010	−0.172	0.523
Progesterone	−0.216	−0.544 – 0.112	0.161	−0.279	0.188
FSH	−0.467	−1.342 – 0.489	0.429	−0.277	0.285
LH	0.266	−0.041 – 0.573	0.151	−0.478	0.087
Cortisol	−0.206	−0.592 – 0.180	0.189	−0.174	0.285
Age	−0.657	−0.113 – (−1.202)	0.267	−0.403	<0.05*
(Constant)	27.56	13.978 – 41.161	6.664		0.000

FSH = follicle-stimulating hormone, LH = luteinizing hormone, CI = confidence interval, SE = standard error

*Significant with $R^2 = 0.308$; $P = 0.060$

our subjects was normal, it may indicate that the stress level may not give a significant impact to the cortisol level because only small number of subjects (28%) which claimed stress as predisposing factors. Other reason that probably explained the normal level of serum cortisol was the result from an adaptive mechanism of human body to the stress. In acute stress, there will be an adaptive mechanism of HPA axis to the stress.[23]

Minor type of RAS was the most type RAS found in our study, which indicated that many subjects have oral ulcers of size <10 mm in every episode of RAS. There were also variations in the numbers of oral ulcers in this study, but most of the oral ulcers were minor type of RAS that had ulcers of size <10 mm in every episode of RAS. Only herpetiform RAS and Primary Herpes Simplex virus infection may have oral ulcer with number > 10 ulcers in every episode.[24] However, there were differences between viral infections such as herpes simplex virus infection and RAS. RAS is mostly found in nonkeratinized mucosal in oral cavity as compared to keratinized mucosal. This is in contrast with viral (herpes simplex virus) infection, which was more likely found in both keratinized and nonkeratinized mucosal and preceded by vesicles and prodromal symptoms development.[25] In our study, most of oral ulcers of study subjects were found in nonkeratinized oral mucosal without any systemic feature and were not preceded by vesicles eruption. Both buccal and labial mucosal were the most site of oral ulcers in this study subjects. RAS is an acute-type oral mucosal disease; hence, the oral ulcers may be accompanied by pain. This condition had been shown by our subject's response for VAS score. This pain is a nociceptive pain which is caused by inflammation.[26] The severity of RAS may be indicated by pain sensation and influenced by the number and size of oral ulcers. Other factors include local trauma that may aggravate the inflammation. The mean VAS score of this study subjects indicated that the pain associated with oral ulcers was moderate due to variation of severity of oral ulcers.[27,28]

Vitamin D/25(OH)D has been known as an important nutrient not only for bone metabolism, required for calcium metabolism together with parathyroid hormone,[29] but also play a role in immune system function.[29-33] Not many studies have investigated the role of vitamin D/25(OH)D in RAS. Most of studies of the role of vitamin D in RAS were cross-sectional and have different results. A study reported that patients with RAS have lower serum vitamin D than healthy controls.[14] Another study revealed no difference in the serum vitamin D between patients with RAS and healthy controls.[34] Therefore, those studies may not explain the cause and effect of vitamin D in RAS. It was difficult to raise a conclusion that vitamin D was the etiology of RAS. However, studies have shown some beneficial effects of vitamin D for treatment of aphthous stomatitis.[18]

The role of vitamin D in RAS may be related with the function of vitamin D as immunomodulator. Vitamin D may activate vitamin D receptor (VDR) expressed in neutrophils, macrophages, dendritic cells, and lymphocytes (T and B cells). In cellular-mediated immunity, vitamin D particularly $1,25(OH)_2D$ may have anti-inflammatory activity. Vitamin D may reduce the production of T helper type 1 (Th1) cell and may lead to the increase of the T helper type 2 (Th2) proliferation by increasing interleukin (IL)-4, IL-5, and IL-10 production.[32-35] Vitamin D may inhibit proliferation of B cell and reduce immunoglobulin production, promoting the apoptosis of immunoglobulin-producing B cells.[36] It is well known that RAS is a type of disease of T-cell-mediated response with the involvement of tumor-necrotizing factor-α (TNF-α) and CD^8 T cell stimulation, and produces acute inflammation in oral mucosal.[21,37] The decreased vitamin D in all subjects with RAS of our study may partially explain that the low level of serum vitamin D may involve in the development of RAS because of the failure of vitamin D as immunomodulator on cellular-mediated immunity.

The result of this study only showed a significant positive correlation between vitamin D/25(OH)D with LH and none of reproductive hormone and cortisol as predictors for vitamin D/25(OH)D, only age as predictor for vitamin D.[38] There was no correlation between vitamin D/25(OH)D with the FSH, estradiol, and progesterone, although hormonal change may involve in the pathogenesis of RAS. A study showed that patients with RAS had low level of progesterone.[39] Other study showed that vitamin D was not affected by the estradiol fluctuation in follicular phase of menstrual cycle in women.[16] Moreover, a study showed a negative correlation between vitamin D/25(OH)

D with progesterone and estrogen in luteal phase in young women.[20] The different result of those studies indicated that the hormonal change in women may be fluctuating, which may affect the vitamin D level or vice versa. Interestingly, in this study we only showed that there was a correlation between vitamin D/25(OH)D with LH. On the contrary, a study showed that there was not a significant correlation between vitamin D/25(OH)D with LH but there was a positive correlation between vitamin D/25(OH)D with FSH in women with adequate ovarium reserve pattern.[40] Other study did not show any correlation between vitamin D/25(OD) and FSH and LH in nonobese, overweight, and obese women.[41] However, other study showed different results that revealed that vitamin D/25(OH)D has an inverse correlation with FSH. Low level of vitamin D may give adverse effects on ovarian reserve in women.[15] Vitamin D decreases FSH receptor (FSHR) gene expression in human luteinized granulosa cells.[42] Another study showed that there was an inverse correlation between vitamin D/25(OH) D with LH in infertility men.[43] A recent study showed that infertile women with vitamin D deficiency (<10 ng/mL) had lower LH level (6.8 ± 1.3 IU/L) and LH level (5.7 ng/mL) than infertile women with vitamin D deficient. Only FSH level was found to be significantly different between infertile women with vitamin D deficiency and vitamin D insufficiency.[44] On the contrary, in our subjects with RAS FSH level was 4.24+ IU/mL and LH level was 8.12+5.76 (IU/mL) and a significant correlation was observed between LH and vitamin D concentration. The different results may be caused by the different conditions of the subjects. None of those studies explained the mechanism of vitamin D influence FSH and LH.

Other studies have shown that vitamin D has a correlation with progesterone and estrogen. Vitamin D supplementation may increase progesterone production.[42] It is known that vitamin D/25(OH) is effective to regulate T cell when progesterone is available. The progesterone may have immunomodulatory function of vitamin D/25(OH)D due the induction of progesterone to VDR.[45] A study revealed a positive correlation between vitamin D/25(OH)D with estradiol but did not show a correlation between vitamin D/25(OH)D with LH.[46] The relationship between vitamin D with progesterone and estradiol might be also explained by an intervention study that showed that vitamin D supplementation decreased progesterone and estradiol in women during luteal phase of menstrual cycle.[20] Moreover, vitamin D may have progesterone activity involving in menstrual cycle and pregnancy.[47] Unfortunately, we failed to show the correlation between vitamin D/25(OH)D with progesterone and estrogen. We did not further discuss the correlation between LH and cortisol as we did not find any relationship between vitamin D and cortisol. Although there was evidence that LH may bound with adrenal LH receptor, it may increase adrenal function and indirectly increase adrenocorticotropic hormone (ACTH) and result in increased cortisol secretion.[48]

The correlation between vitamin D with reproductive hormone still showed conflicting results because of not only different subjects of those studies but also different study designs, which indicated that there were complex mechanisms involved in regulation of vitamin D to reproductive hormone. Therefore, it is unknown whether the correlation between vitamin D and LH in this study may or may not contribute to explain the pathogenesis of vitamin D in RAS in young women. Furthermore, Some limitations presents in our current study make our results can not be generalized since a small number of subjects involved, and the examination of reproductive hormone and vitamin D only in one spot time, therefore it needs further study with involve more variables and more subjects.

It can be concluded that there is a positive correlation between vitamin D/25(OH)D with LH in women with RAS with vitamin D/25(OH)D deficiency.

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Conflicts of interest

There are no conflicts of interest.

Authors contributions

Hendri Susanto: Research concept and design, writing article, data analysis & interpretation. Puput Kadarwati: Data collection & assembly data. Sri Budiarti: Writing the article, critical revision of the article. Supriatno: Writing the article, critical revision of the article. Taufan Bramantoro: Writing the article, data analysis & interpretation, critical revision of the article.

Ethical policy and Institutional Review board statement

This study was approved by the Ethical Committee for Research of the Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia (KE/FK/1170/EC/2016). All the procedures were performed as per the ethical guidelines laid down by Declaration of Helsinki (1975).

Declaration of patient consent

All participants who matched the criteria were informed about the study and written consent was taken from each participant with explanation of purpose of the study.

Data availability statement

The data that support the study results are available from the corresponding author (Dr. Hendri Susanto, e mail: drghendri@ugm.ac.id) on request.

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