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RESEARCH ARTICLE

The correlation between serum zinc and vitamin D/25(OH)D in women with recurrent aphthous stomatitis

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is an oral mucosal disease which was more prevalent in women than men. Study has shown that zinc deficiency associated with the occurance of RAS. Other study also have shown that vitamin D deficiency contributed in RAS. However, there is no study yet that reveal the association between serum zinc and vitamin D/25(OH)D in women with RAS. To investigate the association between serum zinc and vitamin D/25(OH)D in women with RAS. Thirty two women patients with RAS who meet the inclusion criteria participated in this study. The inclusions criteria was non pregnant women who have been diagnosed RAS and did not have other oral diseases. The exclusions criteria were those who have systemic diseases, taking medications including multivitamin, and have bad habits (i.e. smoking). Data concerning characteristic of subjects, severity of RAS, serum vitamin D/25(OH)D, and zinc were collected and presented descriptively. The correlation between serum zinc and vitamin D/25(OH)D was analyzed using Pearson correlation test with 95% confidence interval. This study has been approved by Medical and Health Ethics Committe, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta. All subjects of this study have low mean value of serum vitamin D/25(OH)D (11.08 ± 3.11 ng/mL) and categorized with vitamin D deficiency. The subjects also have low mean value of serum zinc (54.78 ± 9.19 µg/dL) and seventy percent subjects have mean value of serum zinc below normal. The result of Pearson correlation test showed that there was a significant positive correlation between mean serum zinc and vitamin D/25(OH)D ($r= 0.351$, $p<0.05$) in women with RAS. Serum zinc associated with vitamin D/25(OH)D and play role in pathogenesis of RAS.

Keywords: recurrent aphthous stomatitis; serum; vitamin D; women; zinc

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a disease in oral mucosal and the etiology is not clear.[1] The prevalence is 5% to 66% with the 20-25% is the avarage prevalence in the community.[2-4] The clinical signs of RAS may be single or multiple ulcers in mucosal, with oval, yellowish base and erythematous surrounding area, accompanied with pain. The recurrent ulcers may heal in 7-14 days. There are clinical type of RAS: minor RAS (the ulcer size < 10 mm), mayor RAS (the ulcer size > 10 mm) and herpetiform type RAS (the ulcer size is 2-3 mm with clustered multiple form ulcers).[1,2,4-6] There are several factors has been known associated with RAS such as age, family history, food and drugs hypersensitivity, gender, hormonal, nutritional defficiency, trauma, stress, bacteria. All those factors cause an abnormality of immune response of oral mucosa and result in tissue destruction mediated by CD8 T cell lymphocyte.[1,4,5]

The prevalence RAS is higher in women than men.[7,8] It is suggested that RAS associated wth the hormonal change. Studies have shown that RAS associated with imbalance progesterone and estrogene in menstrual cycle specially in luteal phase.[1,9] Another change during menstrual cycle may also zinc losses. It was reported that the avarage zinc loss during menstruation was 6 µg/day in normal menstrual cycle.[10] A study has revealed that serum zinc may influenced by estradiol in

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menstrual cycle. The fluctuation of zinc plasma concentration may be influenced by the fluctuation of estradiol during menstrual cycle in women.[11] Another study also reported that women who have premenstrual syndrome tend to have low plasma zinc concentration compared with normal women.[12]

Zinc is an important trace element factors for growths, reproduction in human and categorize as micronutrients. Zinc may play role in human metabolism as a vital micronutrients for more than 300 enzyme, for stabilization of DNA, for gene expression, and neuronal signaling. The human body contains 2-3 gr of zinc and the recommended daily intake of zinc is about 12 mg/day and may increase up to 19 mg/day for pregnancy and lactation.[13] Another important role of zinc for human body is in immunity system. Zinc has been known as immunomodulator for immune system and essential for cell maturation, differentiation, progression, and function of immune cells. Zinc also involved in killing harmfull pathogen, cytokine production as well as reactive oxygene species (ROS) production, so, the condition of zinc defficiency may affects maturation and function of T and B cells which favor of Th2 cell driven allergic reaction. In regard in innate immunity, zinc was important in maturation of monocytes. In zinc defficiency, the neutrophil function such as phagocytosis, oxidative burst, degranulation, chemotaxis, was impaired. The natural killer (NK) cells function was impaired when zinc was absent.[14]

Although the zinc deficiency may cause a disease acrodermatitis enteropathica which characterized by thymic atrophy, lymphopenia, impaired cell mediated immune response.[15,16] Study also found that zinc deficiency also associate with the occurance of RAS. It was shown that subjects with history of racurrent aphthous stomatitis have low plasma zinc concentration compared with normal subjects.[17] The role of zinc in RAS also supported by a study that zinc therapy may reduce the recurrency of RAS.[18] Another important of nutrition factors in RAS is vitamin D. Recent study has revealed that RAS patients have low level of serum vitamin D/25(OH)D compared with healthy control.[19,20] It is suggested that vitamin D may have important role in RAS pathogenesis. As a steroid hormone, vitamin D has been known has many functions such as involved in calcium and phoshate metabolism, and an important role as immunomodulatory function in both innate and cellular immunity.[21-23] Vitamin D in human body mainly synthesis in the skin. Food is also a source of vitamin D. Vitamin D is metabolized in liver to undergone hydroxylation to 25(OH)D then convert to the active form vitamin D3/1,25(OH)2D3 in kidney.[24]

With the evidence that zinc deficiency and vitamin D deficiency may involve in RAS and since there was a report that vitamin D associated with zinc in children and adolsecent.[25] There is possibility also that vitamin D associated with zinc in RAS because recent study revealed that zinc may be activated by vitamin D in caco-2 cell lines by increasing the expression of ZnT10 protein expression.[26] The aim of this sudy is to investigate the association between serum zinc and vitamin D/25(OH)D in women with RAS.

MATERIALS AND METHODS

The participants of this study were women who had been diagnosed RAS in the Department of Oral Medicine of Dental Hospital Dental Hospital Prof. Soedomo, Universitas Gadjah Mada, Yogyakarta. Those who agree to participate were informed about this study. The inclusion criteria were patients with RAS, age 18 - 30 years old, with 1st to 3rd days onset of recent oral ulcers. The exclusion criteria were those who have systemic diseases or conditions, taking medications both orally or topically and multivitamins, have bad habits (i.e smoking). This study was approved by the Ethical Committee for Research of the Faculty of Medicine of Universitas Gadjah Mada, Yogyakarta, Indonesia number KE/FK/1170/EC/2016. Informed consent was obtained from all participants. In Addition, the information of age, education level, ethnicity, gender/sex, marriage status, predisposing factors were obtained by using a questionnaire.

A venapuncture was performed to obtain all participants blood sample (± 3 cc for each subject) to determine serum vitamin D/25(OH)D and zinc.

Vitamin D/25(OH) was determined by ECLIA methods (electro-chemiluminescence, Cobas, Roche Diagnostic International Ltd) vitamin D deficiency when the vitamin D (25-OH)D < 20 ng/ml, vitamin D insuficiency (21-29 ng/mL), normal serum vitamin D (25-OH) (> 30 ng/mL),[21] zinc was determined by ICP-MS (Inductively Coupled Plasma Mass Spectrometry), Roche Diagnostic International Ltd) methods. The normal value for serum zinc was 60-130 µg/ml according laboratory reference normal value.

The demographic of women with RAS was analyzed and presenting descriptively. The Shapiro Wilk test was used in order to know whether the data were in normal distribution. The correlation between serum vitamin D/25(OH)D and zinc was analyzed using Pearson correlation test when the data normally distributed. All statistical analysis with 95% Confidence Interval (CI) was performed.

RESULTS

There were 32 women with RAS participated in this study. The mean age of this study subjects was 21 years old. Most of this study subjects were Javanese (71%), college students (93.75%), not marrried yet (100%). Many subjects have the size of oral ulcers less than 10 mm (93.74%) and number of ulcers less than 10 ulcers (84%). Most of subjects stated hormonal was the predisposing factors. The most location of the oral ulcers were buccal and labial mucosa. All participants reported that the oral ulcers accompanied with pain, and based on VAS score indicated mild pain (Table 1).

All of RAS subjects have low serum level of vitamin D/25(OH)D with the mean value of Vitamin D/25(OH)D was 11.08 ± 3.11 ng/ml and categorized with vitamin D deficiency (<20 ng/ml). The average of zinc serum level was 54.78 ± 9.19 µg/ml. Both serum zinc and vitamin D/25(OH)D data were in normal distribution after analyze using Shapiro Wilk test. Pearson correlation test showed that there was a positive significant correlation between serum vitamin D/25(OH)D and zinc (Table 2).

Table 1 . The characteristic of the study participants

Variable	RAS subjects (n =32)
Age : (mean/SD)	21.21 (2.03)
Education level : n (%)	
High education level	30 (93.7)
Ethncity : n (%)	
Javanese	23 (71)
Marriage status : n (%)	
Not married yet	32 (100)
Predisposing factor* : n (%)	
Stress	11 (34)
Hormonal	14 (43)
Hormonal and stress	6 (18)
Unknown	2 (5)
Oral ulcer characteristic	
Ulcer numbers : n (%)	
<10	27 (84.4)
>10	5 (15.6)
Ulcer size : mm (n%)	
>10	2 (6.3)
<10	30 (93.7)
Pain scale (VAS) score : mean (SD)	4.88 (2.2)
Ulcer locations : n (%)	
Floor of the mouth	1 (2.2)
Tongue	4 (8.7)
Gingiva	6 (13.0)
Labial mucosa	23 (50)
Buccal mucosa	10 (21.7)
Soft palate	1 (2.2)
Vestibulum	1 (2.2)

mm: milimeter; n: number of subjects; VAS: visual analog scale; *patients anamnesis

Table 2. The correlation between serum vitamin D/25(OH)D and zinc in the RAS subjects

Serum markers	Mean (SD)	r value	p value
Vitamin D/25(OH)D	11.08 (3.11) ng/ml	0.351*	0.049*
Zinc	54.78 (9.19) µg/ml		

ml: mililiter; p: significancy with p<0.05; *Pearson correlation test; r: correlation coefficients; SD: standard deviation; ng: nanogram; µg/ml: microgram

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DISCUSSION

This study is the first study which shown the correlation between serum zinc and vitamin D/25(OH)D in RAS. Recurrent aphthous stomatitis is the most prevalent oral mucosal disease in community. Several factors may predispose for the development of RAS. The genetic factors is the main factor that contribute for the RAS.[1] However, studies have reveal that RAS tend to be more found in women than man, specially in the young adult women.[2] Several theories have been proposed for the explanation the pathogenesis of RAS in women. Except the genetic factor, the imbalance of hormonal change due to menstrual change also have been accepted to be one of the predisposing factors. The fluctuation of estrogen and progesterone before menstrual cycle in luteal phase result in the immune system dysregulation including oral mucosal system which cause tissue damage and inflammation.[27] Other factors such as stress also contribute to the development of RAS. Psychological and physical stress have been known as the predisposing factors for RAS,[9] as have been shown in our result that the most subjects was college students which may have an stressfull life during their study. This study is similar with other study which shown that both stress and hormonal were the most contibuting factors for the RAS.[7]

Our study also shown that the minor RAS type was the dominant type found in this study. This was indicated by the result of this study which shown that many subjects have oral ulcer with less than 10 mm in every episode of RAS. Recurrent aphthous stomatitis also have variation of oral ulcers number but most of minor RAS have less than 10 ulcers in every episode.[6] Only herpetifrom RAS and herpes simplex infection may have number of ulcers more than 10 in oral muocsal in every episode.[4] It was well known that there were differences between viral infection such as herpes simplex infection with RAS, such as RAS may be found more in non keratinized mucosal in oral cavity than keratinized and this is contrast with viral (herpes simplex) infection which was more likely found in both keratinized and non keratinzed mucosa.[6] Our study shown that most of oral ulcers of our subjects found in oral non keratinized mucosa. Since RAS is an acute type oral mucosal disease, the oral ulcers may accompanied by pain due to inflammation.[28] The severity of RAS depend on the ulcers number, size and the other factors that may exagerate the inflammation. This is indicated by our study response for VAS score that shown VAS score indicated the pain associated with oral ulcers although the score was not high due to variation of severity of oral ulcers and individual response.

Zinc and vitamin D have been known have an essential role in immune system.[14,23] The immune dysregulation of oral mucosa is the primary mechanism of pathogenesis of RAS.[1,2] Vitamin D/25(OH)D has been known as important nutrient for bone metabolism and required for calcium metabolism together with parathyroid hormone.[24] Vitamin D is derived from two important source. First it is from UVB mediated synthesis in the skin. The photolytic convert 7-dehydrocholesterol to produce pre-vitamin D3, then slowly isomerized to vitamin D3. Second, vitamin D obtained from food intake. Vitamin D which derived from dietary, vitamin D2 (ergocalciferol), obtained from plant such as fungi/yeast and vitamin D3 (cholecalciferol) which obatined from animal.[23,24] In the circulation vitamin D bind to vitamin D binding protein or albumin then metabolized in liver and undergo hydroxylation to 25(OH)D. The most reliable parameter of vitamin D in human is 25(OH)D. Subesequently, Vitamin D/25(OH)D metabolized in the kidney by enzyme (1-α-hydroxylase) into calcitriol or 1,25 dihydrovitamin D(1,25(OH)2D). Calcitriol is the active form of vitamin D which play imprtant role in skeletal and immune system function.[23,24,29-31]

Few studies has investigated the serum level of vitamin D/25(OH)D in RAS patients and most of studies were cross sectional which may not explain the causal and effect correlation to meet the conclusion that vitamin D may be an etiology factor for RAS, although some benefecial effect the treatment vitamin D for apthous stomatitis in children has been revealed.[19,20]

The role of vitamin D in RAS may relate with vitamin D as immunomodulator. Vitamin D may

activate innate and adaptive/cellular immunity, since studies have found vitamin D receptor (VDR) expressed in neutrophil, macrophage, dendritic cells and in lymphocyte (T and B cell). Vitamin D may activate antimicrobial factors through toll like receptors (TLRs) especially TLR2 and TLR4,[30-33] which probably explain the role of low level vitamin D involve in RAS through the failure of regulation of TLR2 and TLR4 by vitamin D. In cellular mediated immunity, vitamin D particularly 1,25(OH)2D may have antiinflammatory activity. The supression vitamin D reducing the T helper type 1 (Th1) cell production and increased the T helper type 2 (Th2) proliferation by increasing the production of IL-4, IL-5 and IL-10.[30,33] Vitamin D may inhibit proliferation of B cell and reduce immunoglobulin production, promote apoptosis of immunoglobulin-producing B cells.[21] The low level of vitamin D in all RAS subjects in our recent study may explain low level of vitamin D involve in pathogenesis in RAS because the failure of immunomodulator function of vitamin D on celllular mediated immunity. It has been known that RAS was a disease of T cell mediated response with the TNFα involvement, and CD8 T cell stimulation and produce acute inflammation.[2,3]

This study shown that serum zinc associated with serum vitamin D/25(OH)D in RAS patients. It may explain both zinc and vitamin D involve in immune dysregulation in RAS. Therefore, the condition of our RAS patients which have vitamin D deficiency may impair the immunity and this impairment may cause by the low level of serum zinc level. It may be true since our result shown that more than half or seventy RAS patients have the mean value of zinc below normal value of serum zinc. The correlation of zinc and vitamin D also can be explained by the important role of vitamin D receptor which in normal condition was depend on intracellular zinc concentration, so zinc have to help vitamin D to activate vitamin D receptor in order to work in cell with vitamin D. Another important role the correlation of zinc and vitamin D is both zinc and vitamin D have a positive effect each other on absosption in metabolic pathway,[25] however the obvious mechanism how zinc influence the absorption vitamin D is still unclear, but a study shown that systemic level of zinc may be regulated by vitamin D.[26] Although RAS have several conditions as presdiposing factors, in this study, stress, hormonal and genetic may involve in pathogenesis of RAS. The exact mechanism of the role of hormonal in vitamin D in RAS is still inconsistent. Hormonal change may contribute on the pathogenesis of RAS,[34] but studies showed different results. One study shown that vitamin D was not affected by the estradiol fluctuation in follicular phase of menstrual cycle,[35] on the contrary, other study showed there was a negative association between vitamin D/25(OH)D and progesterone and estrogen in luteal phase in young female.[36] Hence, there is a difficulty for explanation of the role of hormonal change on the vitamin D in this study which is the limitation of this study, therefore further study needed to investigate the association of vitamin D and hormonal change in women with RAS. The conclusion of this study was the association between zinc and vitamin D/25(OH)D may have potential role for the explanation the pathogenesis zinc and vitamin D in RAS.

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