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SERUM LEVELS OF ASYMMETRIC AND SYMMETRIC DIMETHYLARGININE IN WOMEN WITH VITAMIN D DEFICIENCY AND HISTORY OF PREGNANCY LOSS – A PILOT STUDY

SERUMSKI NIVOI ASIMETRIČNOG I SIMETRIČNOG DIMETILARGININA KOD ŽENA SA NEDOSTATKOM VITAMINA D I ISTORIJOM POBAČAJA – PILOT STUDIJA

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Summary

Background: Vitamin D deficiency has been reported to be associated with pregnancy loss. Asymmetric dimethyl-L-arginine (ADMA) and symmetric dimethyl-L-arginine (SDMA) are arginine analogues that have direct and indirect effects on nitric oxide (NO) synthesis and endothelial dysfunction. This study aimed to evaluate ADMA and SDMA levels among women with history of pregnancy loss compared to women without history of pregnancy loss and all participants were suffering from vitamin D deficiency.
Methods: To investigate the relationship between vitamin D deficiency and ADMA and SDMA, both groups of women were experiencing vitamin D deficiency. All women enrolled in this study had a vitamin D level below 75 nmol/L and were not pregnant. ADMA and SDMA levels were investigated in 28 women without a history of pregnancy loss and 19 women with a history of pregnancy loss.
Results: No statistically significant differences were found in ADMA and SDMA levels among the two groups. The correlation analysis showed that vitamin D deficiency was not significantly inversely correlated with ADMA and SDMA in women without a history of pregnancy loss, but was significantly correlated with SDMA in women with a history of pregnancy loss.
Conclusions: Vitamin D deficiency, in women with or without a history of failed clinical pregnancies, has no effect on the circulating levels of ADMA and SDMA. Further studies are needed to investigate any possible link between these parameters.

Keywords: ADMA, SDMA, vitamin D deficiency, pregnancy loss

Kratak sadržaj

Uvod: Nedostatak vitamina D doveden je u vezu s pobačajima. Asimetrični dimetil-L-arginin (ADMA) i simetrični dimetil-L-arginin (SDMA) analozi su arginina koji direktno i indirektno utiču na sintezu azot-oksida (NO) i endotelnu disfunkciju. Cilj ove studije bio je da se odrede nivoi ADMA i SDMA kod žena sa istorijom pobačaja u poređenju sa ženama bez istorije pobačaja a sve učesnice su patile od nedostatka vitamina D.
Metode: Da bi se ispitao odnos između nedostatka vitamina D i ADMA i SDMA, obe grupe žena patile su od nedostatka vitamina D. Sve žene uključene u ovu studije imale su nivoe vitamina D ispod 75 nmol/L i nisu bile trudne. Nivoi ADMA i SDMA određeni su kod 28 žena bez istorije pobačaja i 19 žena sa istorijom pobačaja.
Rezultati: Nisu nađene statistički značajne razlike u nivoima ADMA i SDMA između dve grupe. Korelaciona analiza pokazala je da nedostatak vitamina D nije bio u značajnoj obrnutoj korelaciji sa ADMA i SDMA kod žena bez istorije pobačaja, ali jeste bio u značajnoj korelaciji sa SDMA kod žena sa istorijom pobačaja.
Zaključak: Nedostatak vitamina D kod žena sa i bez istorije neuspešnih kliničkih trudnoća nema uticaja na cirkulišuće nivoe ADMA i SDMA. Potrebne su dalje studije kako bi se istražile potencijalne veze između ovih parametara.

Ključne reči: ADMA, SDMA, nedostatak vitamina D, pobačaj

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Introduction

Pregnancy loss, also known as miscarriage, is an outcome of pregnancy that results in a dead-born child. The majority of miscarriages occur before the 12th week of gestation. Many pregnancies fail before being clinically recognized, whereas approximately 10–15% of clinically recognized pregnancies terminate with spontaneous loss (1, 2). Recurrent spontaneous abortion (RSA) is a negative pregnancy outcome, defined as two or more consecutive clinical pregnancies that terminate before 20 weeks of gestation (3, 4). However, causes of spontaneous pregnancy loss are unknown, but are thought to be related to hormonal problems, chromosomal abnormalities, uterine abnormalities, infections, and autoimmune disorders.

Vitamin D deficiency in pregnant women may be a factor that increases the risk of obstetrical complications, resulting in RSA or first trimester pregnancy loss. However, the effect of vitamin D on pregnancy is still unclear (5–7). Vitamin D is a lipid-soluble secosteroid hormone that plays a significant role in mineral homeostasis and bone metabolism (8, 9). Vitamin D converts to its active form, 1,25-dihydroxy vitamin D_3, through 1-α-hydroxylase and 25-hydroxylase. Vitamin D functions by combining with the nuclear vitamin D_3 receptor (VDR). Vitamin D regulates cell proliferation and differentiation, modulates the immune response, and may control human reproductive processes (10, 11). Conversely, vitamin D deficiency contributes to several chronic diseases and is associated with infertility, preeclampsia, bacterial vaginosis, polycystic ovary syndrome, gestational diabetes, obstetrical outcome, and male gonadal function (12–16).

Vitamin D deficiency is a non-traditional cardiovascular risk factor that can be treated with oral supplementation. Cardiovascular risk factors, such as high blood pressure and abnormal blood lipid levels, can increase the risk of endothelial dysfunction. Decreased nitric oxide (NO) levels impair endothelium-dependent vasodilation, and result in endothelial dysfunction (17–19). Asymmetric dimethyl-L-arginine (ADMA) is an endogenous inhibitor of NO synthase (NOS) and considered an independent risk factor for cardiovascular diseases. ADMA inhibits NO synthesis by inhibiting NOS activity, leading to endothelial dysfunction (20, 21). Circulating ADMA levels fluctuate in several diseases, including diabetes, obesity, hypertension, hyperlipidemia, myocardial infraction, fertility, Alzheimer's dementia, and depression (21–31). The ADMA isomer, symmetric dimethyl-L-arginine (SDMA), does not directly affect NOS activity but may interfere with NO synthesis and endothelial dysfunction by competing with L-arginine transportation. However, SDMA is considered a sensitive marker for renal function. ADMA is eliminated through urinary excretion and is metabolized by dimethylarginine dimethylamino-hydrolase (DDAH), whereas SDMA is only renally excreted (32–34).

Since vitamin D deficiency is associated with endothelial dysfunction markers, this study aimed to investigate ADMA and SDMA levels in women that suffer from vitamin D deficiency and had experienced a miscarriage at least once in their lives.

Materials and Methods

Participants

Women aged between 20 and 54 years, with vitamin D levels below 75 nmol/L, and with or without a history of pregnancy loss were invited to participate in this study. Blood samples were collected from non-pregnant women after fasting. Serum samples were centrifuged at 3000 rpm for 10 min to separate cells and the serum was stored at –20 °C until further analysis.

All participants were informed about the study during their visit to King Abdullaziz University Hospital and each participant signed a written informed consent. Blood samples were collected with approval of the Ethics Board of King Abdulaziz University (Reference number 93-15).

Biochemical analyses

ADMA and SDMA levels were measured using competitive ELISA (DLD Diagnostika, Germany). Vitamin D concentrations were measured by immunochemiluminescent assay (Siemens, U.S.), whereas glucose and cholesterol concentrations were determined using automatic colorimetric methods.

Statistical analysis

Version 22 of the Statistical Package for the Social Sciences (PSS) was used to perform the statistical analyses. Data are expressed as mean ± standard deviation (SD) and the Pearson correlation coefficient was used to assess the significant correlation between vitamin D, ADMA, and SDMA.

Results

The study population characteristics are shown in *Table I*. By study design, all participants were women with deficient or insufficient vitamin D levels and identified as one of two groups: women with uncomplicated pregnancies, and women with a history of 1–4 pregnancy losses. None of the measured variables, including median age, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), glucose, cholesterol, vitamin D, ADMA, or SDMA, were statistically significantly different between the

women either with or without a history of pregnancy loss. Vitamin D concentrations were deficient in both groups (53.61 ± 24.36 and 53.57 ± 20.64 nmol/L for women with and without a history of miscarriages, respectively). No significant differences were observed in ADMA levels between women with and without a history of pregnancy loss (0.69 ± 0.09 and 0.64 ± 0.09 μmol/L, respectively). SDMA levels were statistically meaningless for women both with and without a history of miscarriage (0.94 ± 0.23 and 0.86 ± 0.16 μmol/L, respectively) (*Figure 1*).

To find a link with spontaneous abortion, the correlation between vitamin D concentration and methylarginine (ADMA and SDMA) was analyzed in women suffering from vitamin D deficiency. *Figure 2* shows the scatter plots of vitamin D and ADMA concentrations in women with and without a history of pregnancy loss and vitamin D deficiencies. As expected, vitamin D levels were negatively correlated with ADMA for both groups, but the obtained results were not significantly correlated. No difference was found in ADMA levels between women with or without a history of pregnancy loss.

Similar to ADMA, SDMA levels were negatively and insignificantly correlated to vitamin D levels in women without a history of miscarriage. In contrast, SDMA levels were positively and significantly correlated with vitamin D ($p < 0.05$) in women with a history of pregnancy loss (*Figure 3*). *Table II* summarizes the Pearson correlation analysis performed in this study.

Table I Biochemical characteristics of study population. Results are presented as mean ± SD.

	Women without Pregnancy Loss History (n=28)	Women with Pregnancy Loss History (n=19)
Age (Years)	35.93 ±11.91	39.16 ± 10.02
BMI (kg/m^2)	26.12 ± 6.37	28.80 ± 5.49
SBP (mmHg)	120.09 ± 23.89	126.14 ± 21.77
DBP (mmHg)	73.62 ± 17.22	95.71 ± 38.61
Glucose (mmol/L)	4.81 ± 0.63	5.32 ± 1.40
Cholesterol (mmol/L)	4.66 ± 1.02	4.19 ± 0.28
Vitamin D (nmol/L)	53.57 ± 20.64	53.61 ± 22.89
ADMA (μmol/L)	0.643 ± 0.09	0.689 ± 0.09
SDMA (μmol/L)	0.856 ± 0.16	0.935 ± 0.23

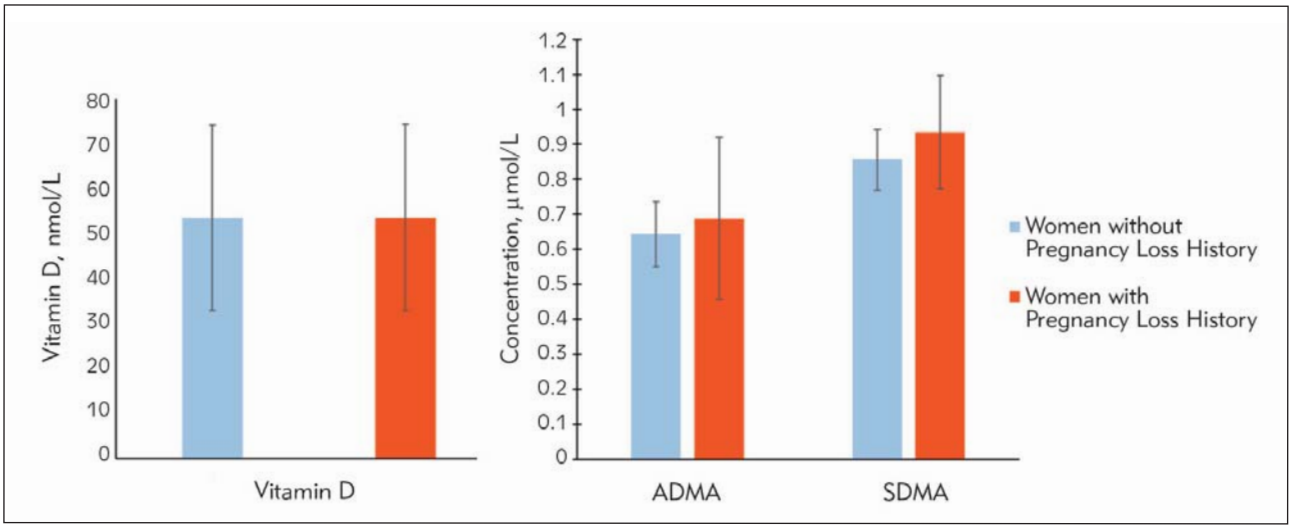

Figure 1 Concentrations of vitamin D, asymmetric dimethyl-L-arginine (ADMA), and symmetric dimethyl-L-arginine (SDAM) in women with and without a history of pregnancy loss.

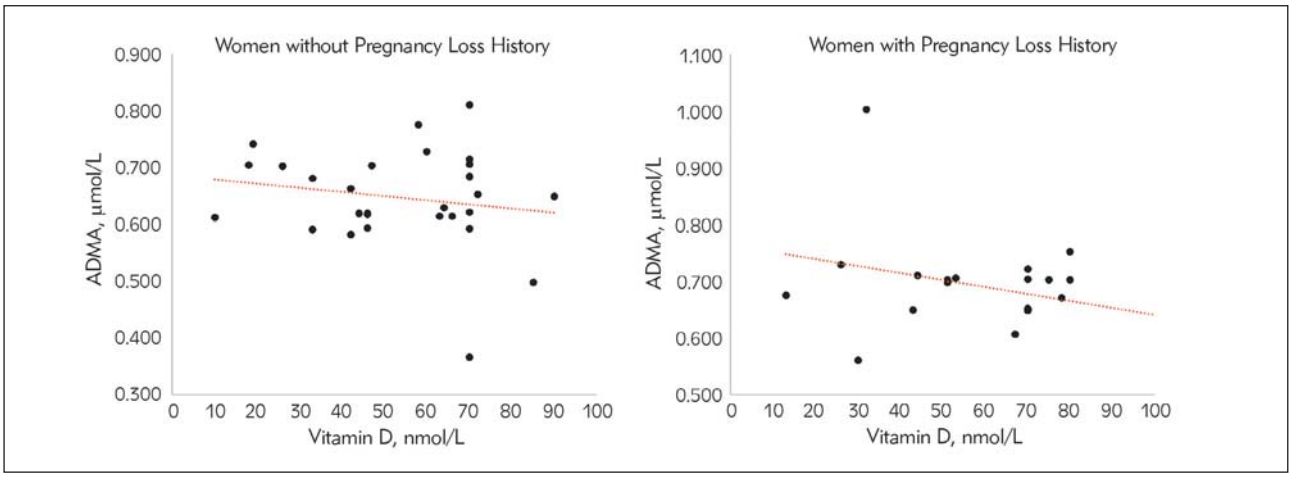

Figure 2 Correlation between vitamin D and ADMA concentrations in women with and without a history of pregnancy loss.

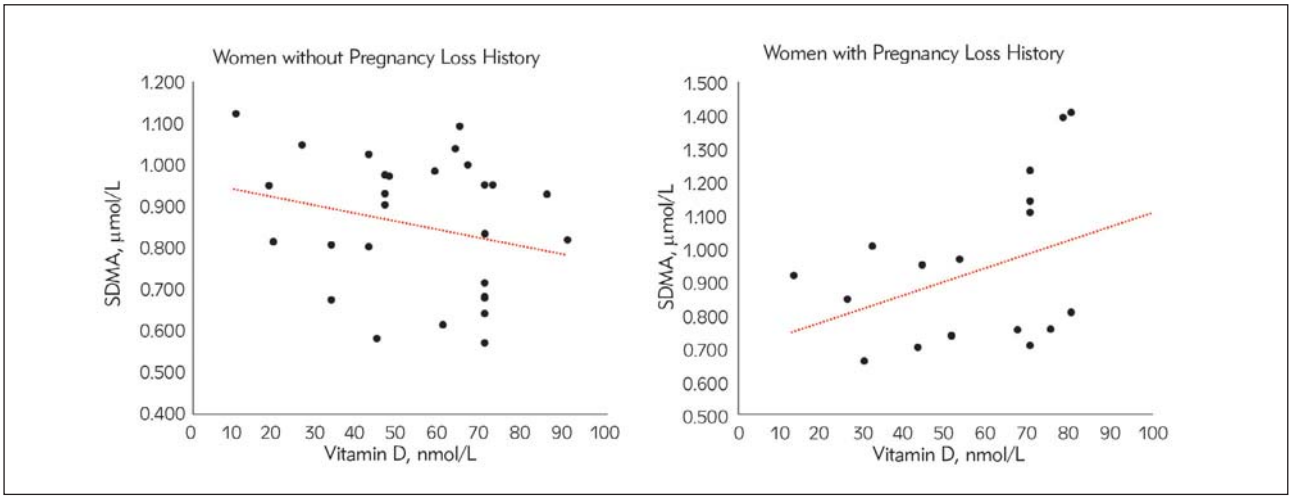

Figure 3 Correlation between vitamin D and SDMA concentrations in women with and without a history of pregnancy loss.

Table II Bivariate analysis of asymmetric dimethyl-L-arginine (ADMA) and symmetric dimethyl-L-arginine (SDMA) levels associated with vitamin D deficiency.

	Women without Pregnancy Loss History (n=28)		Women with Pregnancy Loss History (n=19)	
	p	r	p	r
ADMA	-0.176	0.185	-0.301	0.105
SDMA	-0.250	0.199	0.407 *	0.042

* Correlation is significant at the 0.05 level.

Discussion

This study attempted to investigate the relationship of ADMA and SDMA concentrations with vitamin D deficiency in women with and without a history of pregnancy loss. In the Pearson correlation analysis, ADMA and SDMA levels were statistically insignificant and negatively correlated with vitamin D deficiency in both groups. The exception were SDMA levels in women with a history of pregnancy loss, where the correlation with vitamin D was significant and positive. Moreover, none of the measured variables showed a significant difference between the two groups of women.

Notably, a fluctuation in the measured methylarginine concentrations in the same disease has been reported in several studies. Several factors affect the circulating levels of arginine and its derivatives, including age, body mass index (BMI), diet, season, and gene polymorphism. In this paper, age and BMI were matched in both groups; therefore, ADMA and SDMA values were non-significant between groups. Dietary differences were not excluded as a possible factor affecting ADMA and SDMA concentrations. Samples were collected throughout the year, so the seasonal fluctuation may have impacted the obtained results. Previous studies reported that normal variation in diet does not influence circulating levels of arginine

and methylarginines, even with complete exclusion of arginine from the diet or with oral supplementation of exogenous arginine (34, 35). In one study, a fluctuation in the ADMA levels was observed, and ADMA was found to be inversely associated with a seasonal fluctuation in vitamin D levels (36). The current study is mainly limited by collecting samples randomly throughout the year, and the small sample size, due to the restricted number of women suffering from vitamin D deficiency and having a history of pregnancy loss.

The relationship between vitamin D concentration and the incidence of heart disease has been investigated in several population studies (17, 19). Moreover, a direct association between vitamin D deficiency and endothelial dysfunction in mild to moderate chronic kidney disease patients was demonstrated by Chitalia et al. (17). Although several studies reported a significant correlation between vitamin D deficiency and endothelial dysfunction, the mechanism has not yet been comprehensively studied (35–37). Methylarginines (ADMA and SDMA) are important biomarkers for cardiovascular disease (21), progression of renal failure (40, 41), and death (42, 43). Hence, these two biomarkers may influence NO and cause endothelial dysfunction in several diseases.

A significant independent association between vitamin D deficiency and elevated levels of ADMA has been observed in previous studies (17, 36, 43). Patients with chronic kidney disease that were treated with Paricalcitol, a vitamin D receptor agonist, showed short-term significant reduction in ADMA concentration (44). Since vitamin D levels are inversely correlated with ADMA, this phenomenon can be explained by the antioxidant activity of vitamin D that is associated with a decrease in lipid peroxidation and an improvement in endothelial function (43). Thus, antioxidant activity improves DDAH activity and reduces type 1 protein arginine methyltransferase (PRMT) activity, subsequently enhancing ADMA degradation which reduces its production (44, 45). In comparison, a meta-analysis of 51 studies found a non-significant effect between vitamin D and cardiovascular diseases (46). Moreover, previous studies found that vitamin D levels were not significantly associated with ADMA and SDMA levels. Maaty et al. (47) reported on a non-significant association between ADMA, SDMA, and vitamin D. Although they found that vitamin D participates in activating the NO system, vitamin D did not influence the endothelial function by modulating ADMA or SDMA levels (47). An insignificant reduction of ADMA and SDMA concentrations by oral vitamin D supplementation in patients with arterial hypertension was observed in a study performed by Grübler et al. (48). These results may be attributed to different ethnicities and different frequencies of polymorphisms of vitamin D genes, such as vitamin D receptors (VDR), which may influence the ADMA and SDMA levels in different studies.

Changes in methylarginine concentrations were small in response to pregnancy; plasma concentrations of ADMA and SDMA declined in early pregnancy. In normal pregnancies, maternal ADMA levels were lower than in non-pregnant women. This finding suggested that ADMA may act as a key regulator for vasodilation and blood pressure in normal pregnancy (49). Saarelainen et al. (50) assumed that ADMA regulates blood pressure in pregnancy, and changes in maternal arginine or ADMA levels were not correlated to endothelium-dependent vasodilation. Rijvers et al. (51) suggested that ADMA and SDMA play a modest role in the pathogenesis of hypertensive pregnancy in women at high risk of recurrent hypertensive disorder. However, Hou et al. (52) demonstrated that vitamin D deficiency is associated with miscarriages. They reported that women with normal pregnancies have higher vitamin D concentrations than women with first trimester miscarriages. Hence, this study attempted to find a link between vitamin D deficiency and methylarginines in women with a history of pregnancy loss. The obtained data showed slightly higher ADMA and SDMA levels in women with a history of pregnancy loss than women without a history of pregnancy loss, although this difference was not statistically significant, suggesting no appreciable effect of ADMA or SDMA function and metabolism on pregnancy loss. In one study, ADMA and SDMA concentrations were measured in women with preeclampsia (53). ADMA was slightly elevated in maternal circulation, whereas SDMA was significantly elevated in maternal and fetal circulatory systems, which may be attributed to a reduction of renal clearance. Hence, SDMA could be considered as a marker of mild renal dysfunction in preeclampsia. In another study, maternal ADMA and SDMA levels were not elevated in moderate preeclampsia, whereas ADMA was elevated in severe preeclampsia (54).

Conclusions

To the best of the author's knowledge, this is the first attempt to study the effect of a history of pregnancy loss on circulating ADMA and SDMA levels in women suffering from vitamin D deficiency. Although the main findings of this study were negative, as the obtained results showed no significant correlation between ADMA or SDMA and vitamin D deficiency, the possible link between vitamin D deficiency and endothelial dysfunction in women with a history of pregnancy loss requires further investigation.

Conflict of interest statement

The author stated that she has no conflicts of interest regarding the publication of this article.

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