Original Article

Relationship between vitamin d status and cortisol in girls with primary dysmenorrhea

Dinara Kulzhanova[1], Ainur Amanzholkyzy[2], Ainur Donayeva[3], Zhanslu Sarkulova[4], Marat Sarkulov[5], Tokshilykova Ainur[6], Yersulu Sagidanova[7], Farida Balmaganbetova[8], Samat Saparbayev[9], Akzhunis Mannapova[10], Natalya Zagorulya[11], Saule Kubekova[12], Assel Baubekova[13]

ABSTRACT

Background & Aims

Many adolescent girls and young women experience painful periods, medically known as primary dysmenorrhea (PD). Vitamin D deficiency and high cortisol levels seem to be connected and may even worsen the symptoms of PD. The aim of this research was to determine possible relationship between vitamin D and salivary cortisol levels in adolescent girls with PD.

Methodology

A total of 191 adolescent girls with PD aged 13-16 years were examined. All participants were randomly divided into two groups: the main group (n =96), which took vitamin D 4000 IU per day for three months and the control group (n =95), which took placebo. Further laboratory tests were carried out to determine the level of 25(OH) vitamin D in the blood serum and 4 samples of saliva to evaluate cortisol levels during the day before and after the intervention.

Results & Conclusion

After the intervention in the main group, an average negative relationship was revealed between the content of 25(OH) vitamin D in the blood with morning (r=-0.4, p=0.001) and daytime (r=-0.25, p=0.041) levels of cortisol in the saliva of adolescent girls with PD, while no significant relationships were identified in the control group. We found that higher vitamin D levels were linked to lower cortisol levels in their saliva, especially in the mornings. This suggests a potential benefit of vitamin D in reducing stress hormones in these girls.

Keywords

Primary dysmenorrhea; adolescent girls; vitamin D; cortisol

INTRODUCTION

Primary Dysmenorrhea (PD) is a prevalent condition affecting many adolescent girls and young women. It manifests as severe pain in the lower abdomen during menstruation, often

1. Dinara Kulzhanova (Mail; kulzhanova.dinara@bk.ru) Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
2. Ainur Amanzholkyzy (Mail; a.ainur.82@mail.ru). Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
3. Ainur Donayeva (Mail; ainur.donayeva@mail.ru) . Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
4. Zhanslu Sarkulova (Mail: Slu2008@mail.ru), Department of anesthesiology and reanimatology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
5. Marat Sarkulov (Mail: tair.sark@mail.ru). Departments of urology and andrology, including children's, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
6. Tokshilykova Ainur (Mail: Ainur.t_83@mail.ru) Department of anesthesiology and reanimatology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan.
7. Yersulu Sagidanova (Mail; sagidanova.e@mail.ru) Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan.
8. Farida Balmaganbetova (Mail; 10farik@bk.ru) Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan.
9. Samat Saparbayev, Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan.
10. Akzhunis Mannapova Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
11. Natalya Zagorulya, Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
12. Saule Kubekova, Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
13. Assel Baubekova, Department of Obstetrics and Gynecology, Astana Medical University, Astana, Kazakhstan.

Correspondence

Dinara Kulzhanova (Mail; kulzhanova.dinara@bk.ru) Department of normal physiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

DOI: https://doi.org/10.3329/bjms.v24i2.81716

accompanied by other symptoms like nausea, vomiting, diarrhea, headaches, and fatigue. Importantly, these symptoms occur in the absence of any underlying pelvic organ abnormalities[1]. It occurs in 50-90% of adolescent girls in the first two years after menarche[2-6].

The exact causes of PD remain unclear, with multiple contributing factors at play. Due to its significant prevalence among young women globally, PD warrants further investigation.

Hormonal imbalance is a potential contributing factor, not the sole cause, of PD[7,8]. Fluctuations in hormone levels throughout the menstrual cycle have prompted research into the connection between cortisol levels and specific menstrual phases. High cortisol levels are potentially linked to heightened pain sensitivity, which could worsen PD symptoms[9].

Studies suggest a possible link between low vitamin D levels and primary dysmenorrhea[10, 11]. Research indicates that vitamin D deficiency might be associated with higher cortisol levels [12]. This connection could be explained by vitamin D's role in supporting the proper function of the hypothalamus and pituitary gland, which regulate cortisol production. Finnish research suggests vitamin D might lower the production of cortisol by affecting the related genes and make cells less responsive to cortisol by reducing receptor activity[13]. Polish studies indicate vitamin D may speed up the breakdown of cortisol in the body and consequently, contribute to lower overall cortisol levels [14]. Studies from Iran suggest vitamin D supplements might help lower cortisol levels in individuals with vitamin D deficiency. A specific study showed an 18% decrease

Block diagram CONSORT 2010

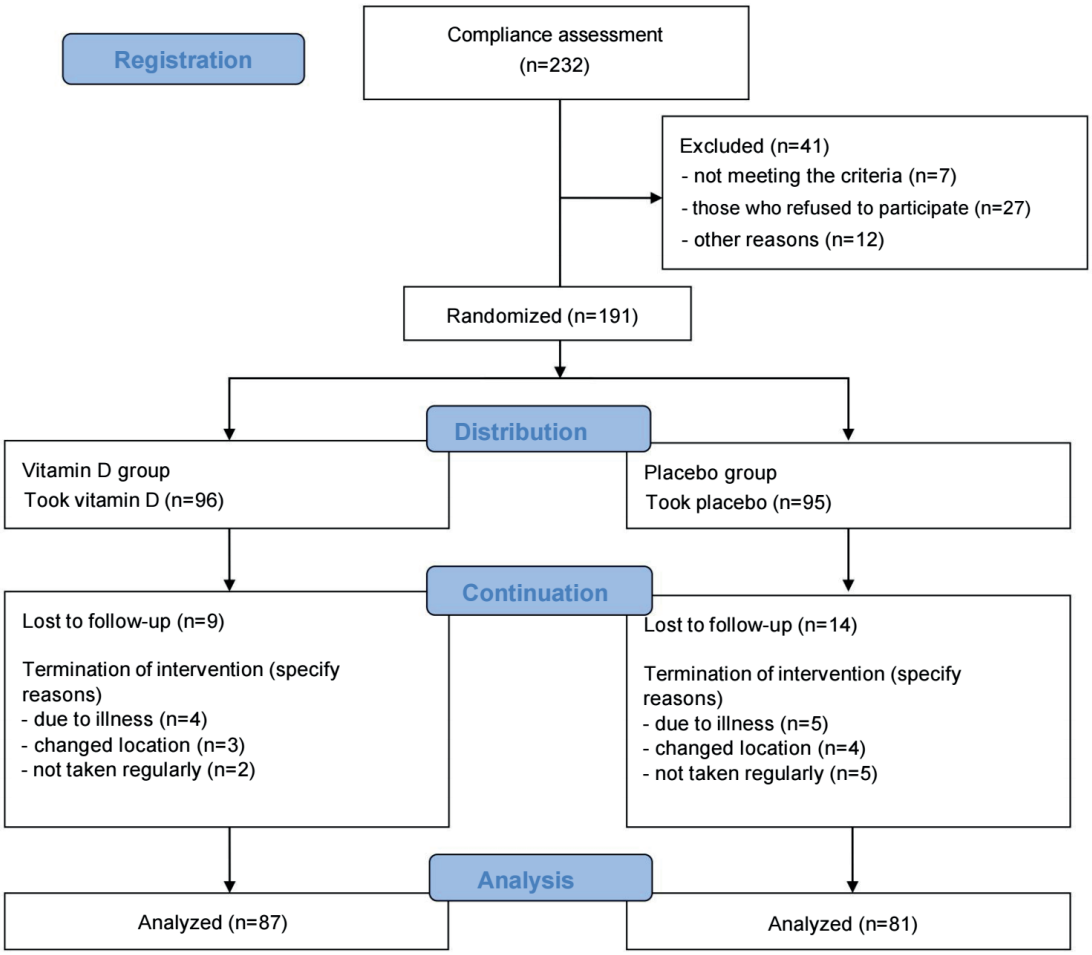

Figure 1. Study flowchart

in blood cortisol levels after 8 weeks of daily 2,000 IU vitamin D supplementation in deficient individuals [15].

Studies suggest vitamin D supplementation might be beneficial for managing PD in adolescents.

Vitamin D deficiency may be linked to elevated cortisol, and supplementation could help regulate it. Additionally might directly contribute to lessening the severity of pain experienced during PD [16].

The aim of this research was to determine possible relationship between vitamin D and salivary cortisol levels in adolescent girls with PD.

MATERIALS AND METHODS

Study disign

This study is in double-blind randomized placebo-controlled trial.

Setting and time of the study

The study carried out at the Regional Perinatal Center in Aktobe, Kazakhstan between

January 2022 and November 2023., after receiving ethical approval from the West Kazakhstan Medical University's local ethics committee (meeting No. 9, November 19, 2021).

Participants

The study involved adolescent girls aged 13-16 diagnosed with PD. Out of 191 girls initially enrolled, 168 completed the study as shown in figure 1 [17].

All participants (girls and their parents) were fully informed about the study's details, the absence of any risks involved and their right to freely decline participation at any stage. Only adolescents meeting the set criteria (inclusion/exclusion) and who provided written consent were included in the survey.

Sample size was calculated by power analysis with significance level α=0.05 and power β=0.8. Participants were randomly assigned to two groups by random number generator. The main group (n = 96) received a daily dose of 4000 IU vitamin D for three months, while the control group (n = 95) received a placebo (inactive pills).

Laboratory sample analysis

Blood and saliva samples were collected to assess relevant biological markers. 25(OH) vitamin D levels in blood serum were measured using an electrochemiluminescent immunoassay, which is performed on an automatic immunoassay analyzer "Cobas E411" ("Rosh Diagnostics GmbH", Germany). Cortisol levels in saliva were determined by an enzyme-linked immunosorbent assay using a modular analyzer Cobas-6000 ("Rosh Diagnostics AG", Switzerland). Mixed oral saliva samples are collected using a specialized SaliCaps kit within 5 min, the tube can be stored at +2 - +8°C. Saliva portions are collected at the following time intervals:

Morning (8:00-10:00 AM)

Afternoon (12:00-2:00 PM)

Evening (6:00-8:00 PM)

Night (10:00 PM-12:00 AM)

These measurements were taken both at the beginning of the study and after three months of receiving either vitamin D or placebo.

Cortisol levels in saliva naturally fluctuate throughout the day in a pattern that follows body's circadian rhythm. Reaching their peak in the morning, tending to steadily decline during the evening and continue to be low at night.

Statistical analysis

All data obtained were analyzed by the statistical program SPSS version 26 (IBM SPSS Statistics, USA). Quantitative variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as numbers and percentages. Differences between groups were tested by the Mann -Whitney and Fischer-exact test respectively. The Wilcoxon signed-rank test for related samples was used to compare the differences between Vitamin D and salivary cortisol levels before and after intervention. Spearman's correlation test was used to detect relationships between variables. The level of significance was set at 0.05 ($p < 0.05$).

ETHICAL CLEARENCE

The study was approved by the West Kazakhstan Medical University's local ethics committee (meeting No. 9, November 19, 2021).

RESULTS

The study involved 191 adolescent girls with primary dysmenorrhea, selected according to inclusion and exclusion criteria. For various reasons, not all

participants reached the end of the study. Some of them were excluded during the study due to illness, irregular intake of vitamin D and placebo, and also because of change of residence. A total of 168 teenage girls with primary dysmenorrhea (PD) were involved in the study. The average age of the participants was 14.16 ± 1.18 years old. Importantly, there were no significant differences between the groups in terms of their average vitamin D (25(OH) vitamin D) levels and cortisol levels in their saliva. This means the groups were well-matched at the beginning of the study.

Out of 168 teenage girls with primary dysmenorrhea (PD) participating in the study, only one had a normal vitamin D level based on the initial 25(OH) vitamin D test. The vast majority (99.4%) of the participants had inadequate vitamin D levels. This includes 28 girls with insufficient levels and a concerning 139 with deficiency.

Three months of vitamin D supplementation in the main group significantly improved vitamin D status. The percentage of participants with normal levels increased to 46%, while those with insufficient levels rose to 43.7%. Deficiency rates dropped to 10.3%. In contrast, the control group showed minimal improvement, with only 1.2% reaching normal levels, 13.6% having insufficient levels, and a persistent deficiency in 85.2%. This suggests that vitamin D supplementation effectively increased vitamin D levels and shifted participants from deficiency towards sufficiency.

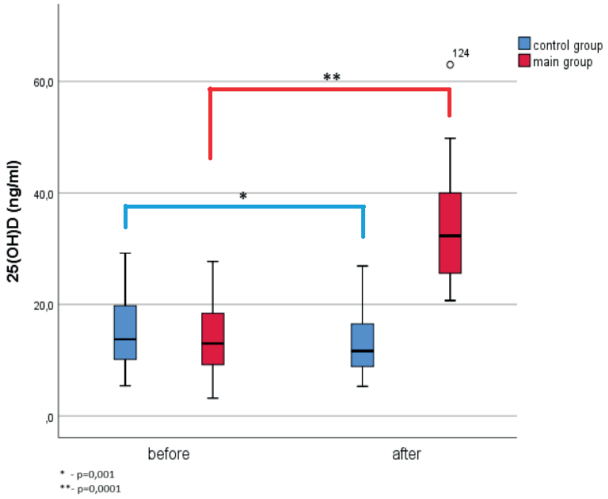

Figure 2. Vitamin D levels before and after intervention

Analysis of vitamin D levels (25(OH) vitamin D) revealed a significant difference between the groups before and after the intervention (Figure 2). In the main group, three months of vitamin D supplementation significantly increased blood serum 25(OH) vitamin D levels compared to baseline ($p<0.000$). Conversely, the control group experienced a significant decrease in their vitamin D levels over the same period. Notably, following the intervention, the vitamin D content in the main group was 2.5 times higher than that of the control group.

While all the adolescent girls with primary dysmenorrhea (PD) had salivary cortisol levels within the normal range initially, a closer look revealed abnormal cortisol levels in a significant portion of the participants. Morning cortisol was elevated in 21% of the girls, followed by evening cortisol (17.4%). Disruptions in daytime (3%) and night cortisol (10.2%) were observed less frequently. These findings suggest a potential link between PD and a disrupted circadian rhythm of cortisol production in some adolescent girls.

Vitamin D supplementation in the main group appeared to influence cortisol levels. The percentage of participants with normal morning and evening cortisol levels increased by 9.2% and 5.7%, respectively. Conversely, daytime and night cortisol levels decreased slightly (by 5.8% and 3.4%, respectively). Interestingly, the control group receiving a placebo also showed changes in cortisol levels. While the number of girls with normal morning cortisol levels rose more substantially (15%), afternoon, evening, and night cortisol levels all showed modest decreases (3.7%, 5%, and 6.2%, respectively).

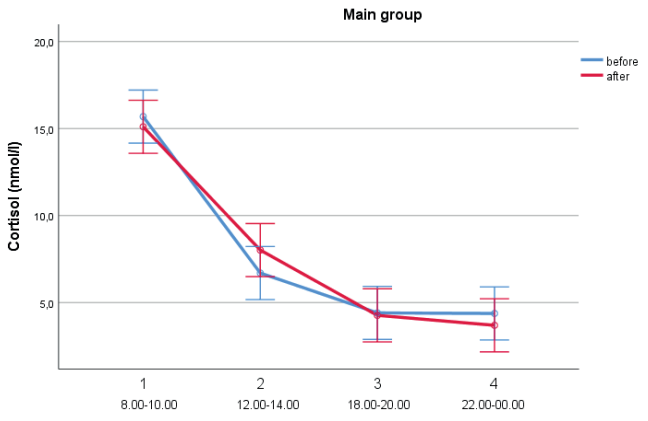

Figure 3. Cortisol levels before and after intervention in the main group

An analysis of cortisol levels throughout the day in both groups showed a general trend of decrease following the intervention. However, these decreases

were not statistically significant. In the main group (Figure 3), cortisol levels in the morning (15.68±8.99 to 15.10±8.09 nmol/l, p=0.8), evening (4.41±2.92 to 4.26±3.95 nmol/l, p=0.3), and night (4.37±7.84 to 3.69±4.92 nmol/l, p=0.6) showed slight reductions compared to baseline levels. However, these changes were not statistically significant. Interestingly, daytime cortisol levels (6.69±5.05 to 8.01±5.59 nmol/l) showed a small increase, but again, this was not statistically significant (p = 0.1).

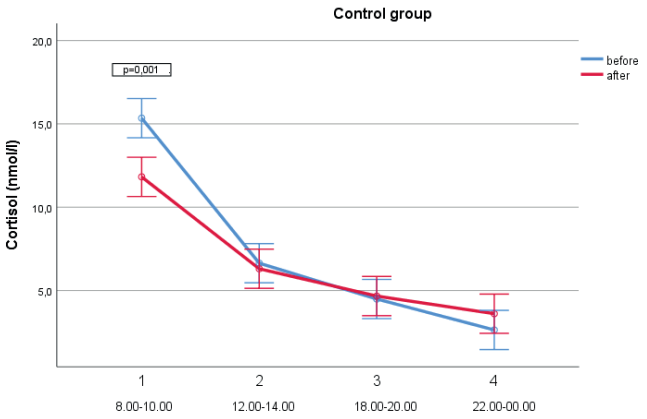

Figure 4. Cortisol levels before and after intervention in the control group

The control group showed a significant decrease in morning cortisol levels in saliva (Figure 4). The average level dropped from 15.34 nmol/L ± 7.32 to 11.82 nmol/L ± 7.28 (p=0.001). Daytime cortisol levels also decreased slightly, from 6.64 nmol/L ± 6.72 to 6.31 nmol/L ± 4.24 (p=0.8). However, evening and night cortisol levels showed slight increases. Evening cortisol went from 4.49 nmol/L ± 3.98 to 4.66 nmol/L ± 4.01 (p=0.8), and nighttime cortisol increased from 2.63 nmol/L ± 2.24 to 3.61 nmol/L ± 4.76 (p=0.2). The changes in evening and night cortisol levels were not statistically significant.

Following the intervention, morning salivary cortisol levels showed a significant difference between the groups (p = 0.001). Specifically, the control group exhibited lower morning cortisol levels compared to the main group. No statistically significant differences were observed in cortisol levels at other times of the day (Figure 5).

The analysis of the main group, where girls with PD took vitamin D for three months, showed a moderate

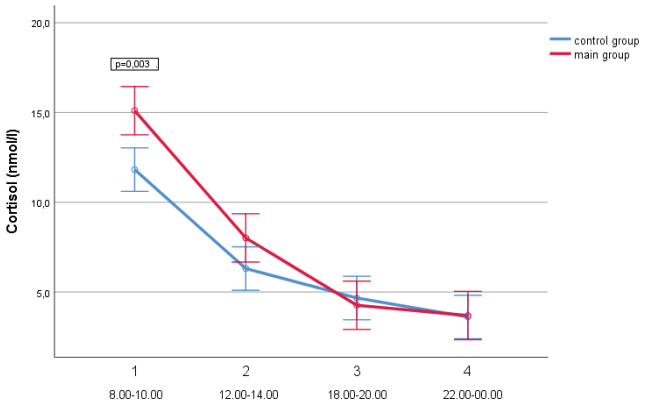

Figure 5. Cortisol levels after intervention in two groups

negative association between their blood levels of 25(OH) vitamin D and cortisol levels in their saliva, both in the morning (r= -0.4, p=0.001) and daytime (r= -0.25, p=0.041). This means that higher vitamin D levels tended to be linked with lower cortisol levels. Interestingly, no such relationship was found in the control group (Figure 6).

DISCUSSION

A study by Indian researchers found that 70% of women, regardless of whether they received vitamin D or a placebo, had a vitamin D deficiency. Their average vitamin D levels increased significantly in the vitamin D group (from 16.87 to 41.93) but remained unchanged in the placebo group (16.16 to 17.45) [18]. Our study, however, shows a different picture. In our study of adolescent girls with primary dysmenorrhea, a much higher percentage (85.2%) had vitamin D deficiency. Interestingly, the placebo group in our study even showed a slight decrease in vitamin D levels (from 15.14 to 12.97). These contrasting results suggest potential differences between adolescent girls and adult women in vitamin D metabolism or the effectiveness of the intervention.

A study on women with dysmenorrhea by researchers in Turkey found lower average vitamin D levels (8.2 ± 2.7 ng/L) and a high deficiency rate of 80% [10]. Our study on adolescent girls with dysmenorrhea shows a similar deficiency rate (85.2%). Interestingly, despite the high deficiency rates in both studies, the vitamin D levels in our adolescent group were slightly higher (13.63 ± 5.67 ng/L) compared to the adult women in the Turkish study.

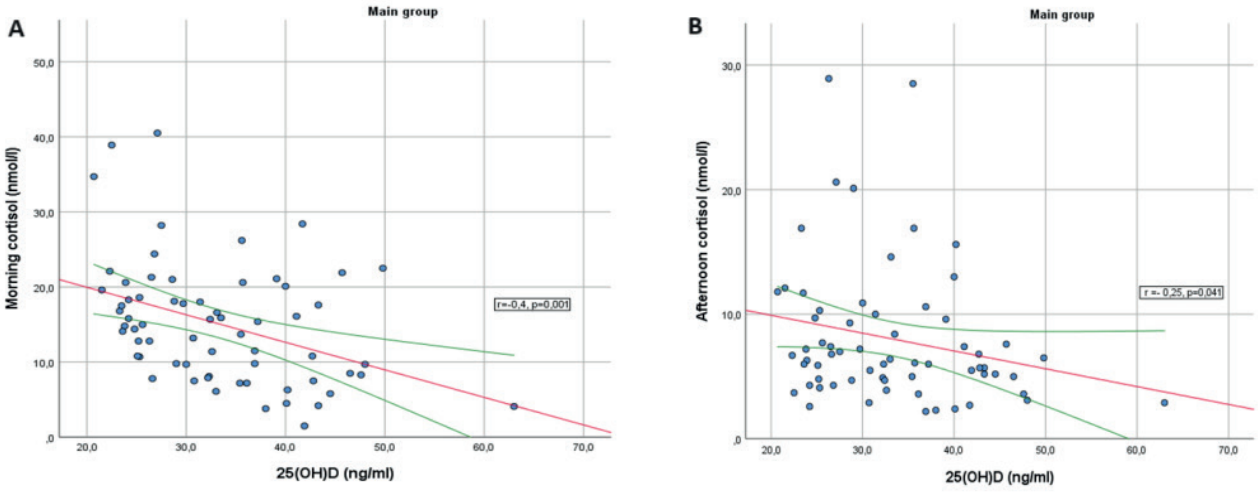

Figure 6. Correlations between vitamin D and cortisol levels: A – morning cortisol; B – afternoon cortisol.

An investigation from Indonesia involving participants with and without chronic primary dysmenorrhea showed elevated cortisol levels in the dysmenorrhea group (72.3 ± 7.2 g/dL) compared to the control group (60.4 ± 6.0 g/dL) [19]. However, both groups fell within the normal range, and the difference wasn't statistically significant. Our findings align with this observation.

A Russian study found high cortisol levels in saliva (15.6 ± 1.5 ng/mL) before treatment in girls with dysmenorrhea, with only 21% having normal levels [12]. After treatment, cortisol levels decreased slightly (13.35 ± 1.55 ng/mL), but the percentage with normal levels only rose to 38%. Interestingly, our results show the opposite trend. We found mostly normal cortisol levels (79%) before the intervention, and a slight decrease afterwards. Notably, after taking vitamin D (main group) or placebo (control group), the percentage of girls with normal cortisol levels increased significantly (87.4% and 95%, respectively). This suggests a potential difference in how vitamin D and the treatment process in our study might have impacted cortisol levels compared to the Russian study. The authors of the Russian study suggest that high cortisol levels, linked to the body's stress response system, might contribute to pain and other symptoms during menstruation in girls with dysmenorrhea.

An analysis by Abu-Samak et al. found a weak positive link between vitamin D deficiency and morning cortisol levels in young adults and older people[20]. However, our study in adolescent girls with dysmenorrhea showed a negative association, meaning higher vitamin D levels were linked with lower cortisol levels, both in the morning and afternoon. This contradicts some existing research and highlights the need for further investigation. Notably, Abu-Samak et al.'s study is the first to explore vitamin D and cortisol deficiency as stress hormones in a broader population, although the results differ from ours.

A study by Rolf et al. investigated how vitamin D supplements compared to a placebo might affect the body's stress response system (hypothalamic-pituitary-adrenal axis)[21]. They found no significant changes in cortisol levels throughout the day in either group. In contrast, our study showed a decrease in cortisol levels in both the vitamin D and placebo groups, with a significant difference only seen in the placebo group.

Iranian researchers investigated whether supplements with zinc, vitamin D, or both could impact cortisol levels (a stress hormone) in the blood [22]. They found no significant changes (p-value = 0.974). Interestingly, our study showed a decrease in cortisol levels in saliva after vitamin D intake, although this decrease wasn't statistically significant compared to the initial levels.

In a double-blind randomized controlled trial, Ramezani Ahmadi A. et al. found a significant decrease in serum cortisol levels in patients with vitamin D deficiency in the group receiving vitamin D (2000 IU/day) for 12 weeks (p = 0.042) [15]. In our study with teenage girls, however, the vitamin D group only showed a slight decrease in salivary cortisol (p = 0.845), while the placebo group had a significant decrease (p = 0.001).

These contrasting results might be due to the difference in subjects - adult men in their study versus teenage girls in ours.

According to the data of scientists from Poland, taking vitamin D supplements led to significant increasing its concentration in the body, regardless of the type of diet, which also coincides with our results. Cortisol levels decreased in both groups, the change was statistically significant only in the high-carbohydrate diet group and amounted to -3.5% (in this group, fasting cortisol levels decreased from 14.17 ± 3.35 to 13.93 ± 2.63 μg/g (p=0.03), whereas our study found a decrease in cortisol levels in both the vitamin D and placebo groups. However, this decrease was only statistically significant in the placebo group[23].

A study by Mahmoud et al. found a slight tendency for vitamin D deficiency to be linked with higher blood cortisol levels (stress hormone)[24]. In contrast, our study showed an opposite trend. After correcting for vitamin D levels, we observed a negative association, meaning higher vitamin D levels were associated with lower cortisol levels in saliva.

Several other randomized controlled trials involving salivary cortisol levels before and after treatment have shown positive placebo effects. This means the placebo group sometimes experiences similar changes to the group receiving the actual intervention. For example, a Croatian study found a decrease in cortisol levels in both the laser therapy and placebo groups for treating burning mouth syndrome [25]. Similarly, a US study observed reduced tension, anxiety, and cortisol increase in response to stress in both the placebo and intoxicated groups compared to the sober group[26]. In our study, a similar positive placebo effect was observed. Adolescent girls with primary dysmenorrhea in the placebo group taking a placebo for three months experienced a significant decrease in salivary cortisol levels compared to the vitamin D group, which also showed a slight decrease.

CONCLUSION

Our study suggests a promising link between vitamin D supplementation and stress reduction in teenage girls with primary dysmenorrhea. After three months, those taking vitamin D showed a connection between higher vitamin D levels and lower cortisol levels in their saliva, both in the mornings and, to a lesser extent, in the afternoons. Cortisol is a key stress hormone, so this finding suggests that vitamin D supplementation may help manage stress levels in these girls.

ACKNOWLEDGMENTS

Conflict of interest: No conflicts related to this research.

Consent to participate

Written informed consent was obtained from all participants following a comprehensive explanation of the study's objectives and procedures. Throughout this study, no adverse effects or unintended consequences were reported.

Data availability

Further data is available from the corresponding author on reasonable request.

Authorship

DK, AA and AD contributed to conceptualizing, methodology, writing the original draft, and editing the manuscript. AB, YS, AA and BK contributed to data collection, curation, and analysis.

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