Vitamin Effects in Primary Dysmenorrhea

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Primary dysmenorrhea is considered to be one of the most common gynecological complaints, affecting women's daily activities and social life. The severity of dysmenorrhea varies among women, and its management is of high importance for them. Most of them supported the anti-inflammatory, antioxidant and analgesic properties of vitamins.

Keywords: dysmenorrhea ; vitamins ; vitamin D ; vitamin E

1. Introduction

Dysmenorrhea is a common menstrual disorder prevailing among adolescent and young females [1]. The disorder actually refers to painful menstrual cramps, and it is characterized by lower abdominal pain during menstruation [2][3].

The severity of dysmenorrhea varies among women and usually improves after childbirth [4]. Approximately 10–15% of women complain about severe pain, resulting in a negative impact on their daily activities and absenteeism from school and work [5]. The overall prevalence of dysmenorrhea ranges between 50% and 90% in various populations and it is considered to be one of the major problems in women's health [6]. It is noteworthy that the World Health Organization(WHO) refers to the disorder as the main cause of chronic pelvic pain [7].

Dysmenorrhea is categorized into two types: primary and secondary. Primary dysmenorrhea occurs in the absence oforganic pelvic diseases, whereas secondary is associated with specific disorders [8]. In primary dysmenorrhea, the pain appears just before or at the beginning of menstruation and lasts for 8–72 h, approximately [9]. Additionally, some dysmenorrhea-related symptoms are fatigue, headache, nausea, vomiting and diarrhea [10]. Although its etiology is not precisely elucidated, a suggested mechanism correlates primary dysmenorrhea with an increase in endometrial prostaglandins. Many studies reveal a significant rise in the levels of prostaglandins E2α (PGE2α), F2α (PGF2α) and leukotriene during menstruation, a fact that can serve as a cause for intense uterine muscle contractions and cramps [9][11][12]. Prostaglandins derive from arachidonic acid through the enzymatic action of cyclooxygenase and lipoxygenase. An increased activity of theses enzymes has been observed in women with dysmenorrhea; thus, nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit these enzymes, are utilized as a first-line treatment [13].

NSAIDs are an effective treatment in alleviating pain in primary dysmenorrhea; however, these drugs are associated with many gastrointestinal adverse events [14]. Thus, alternative therapeutic options, such as dietary supplements, could reduce the use of NSAIDs and their side effects.

2. Effects of Vitamin D

Vitamin D (Vit D) plays a major role in the female reproductive system, as its receptors are present in ovarian and endometrial tissue, as well as in epithelial cells of the fallopian tubes, decidua and placenta [15]. Interestingly, it has been reported that Vit D deficiency correlates with severe to very severe dysmenorrhea [16]. Such a phenomenon can probably be explained by the fact that Vit D has anti-inflammatory properties via regulating prostaglandin levels [15][17][18]. In more detail, the biologically active form of Vit D suppresses cyclooxygenase 2 expression, thus reducing the prostaglandin production in the endometrium and affecting, as a result, calcium homeostasis [15][17][18]. Of note, calcium intake has a protective effect on dysmenorrhea through controlling muscle nervous activities [19].

Taking into account all of the above, it is plausible to consider that Vit D supplementation—alone or in conjunction with calcium intake and/or other dietary supplements—may contribute to the relief of primary and/or secondary dysmenorrhea. Truly, a variety of studies suggest that high doses of Vit D can reduce the prevalence and also the severity of dysmenorrhea [1][20][21][22]. For instance, in Lasco et al.'s study [20], in which 40 women with dysmenorrhea were randomized, the treatment group received a single Vit D oral dose of 300.000IU, while the control group received the placebo. Over the two-month period of the study, significant pain reduction was observed in the Vit D group compared to

the placebo [20]. In addition, in another study, by Moini et al. [21], a randomized control trial in 60 women with primary dysmenorrhea and Vit D deficiency was conducted. The treatment group received 50.000IU oral Vit D weekly for 8 weeks, while the control group received the placebo. Once again, two months after the beginning of the intervention, significant pain reduction was observed in the Vit D group compared to the placebo [21]. It is important to mention, however, that in a study conducted by Zangane et al., these beneficial effects of Vit D seemed to diminish in cases of moderate pain intensity [22].

Apart from the level of pain intensity, the time length of intervention seems to be another factor that strongly affects the benefits induced by Vit D supplementation [23]. Actually, a significant decrease in pain score between Vit D groups and placebo groups has been reported, but not before a two-month period after the beginning of the intervention [20][21][23]. According to a meta-analysis study, one month after the intervention, there seems to be no significant decrease in the pain score between the two groups (standardized mean difference −0.5, 95% CI: −1.6 to 0.6, $p = 0.36$) [23], whereas a month later (two-month period since the beginning), there is a significant decrease, as indicated by the statistics (standardized mean difference −1.02, 95% CI: −1.9 to −0.14, $p = 0.024$) [23].

In contrast to the data that recommend the use of Vit D to relieve dysmenorrhea [1][20][21][22][23], a study by Zarei et al. concluded that Vit D, combined with calcium, is incapable of decreasing pain severity [18]. Nevertheless, it is noted that the results of that study may be due to the absence of the Vit-D-alone group, as its assignment may have no further effect when calcium supplementation is sufficient [1][18].

In general, most of the available data indicate the possibility of using Vit D as a pain reliever in dysmenorrhea patients, as well as in other etiologies' chronic pain cases [24]. The potential mechanism of Vit D action, which has been previously presented [23], supports such a fact. However, it is of high importance to make clear that clinical trials including larger participant groups are needed to assess the safety of these practices, as well as clarify the optimal level of Vit D in dysmenorrhea and its associated disorders [23].

3. Effects of Vitamin B1

Vitamin B1 (Vit B1), also known as thiamin, is a water-soluble vitamin with multiple functions. Actually, Vit B1 affects the muscle tone and neuronal activity of the body, as well as hematopoiesis and metabolism of carbohydrates [25]. Its use might also have a positive effect in primary dysmenorrhea symptoms, through womb muscular contraction and carbohydrate metabolism, that can alleviate mental and physical symptoms of the syndrome [25][26].

The effect of Vit B1 in primary dysmenorrhea was investigated in two clinical trials [23]. In the first study, 152 girls with severe and moderate dysmenorrhea were randomized [27]. The first group received 100 mg of Vit B1, while the second group received 400 mg of ibuprofen for a duration of two months [27]. The study results showed no significant difference in pain reduction between the two groups during the first month ($p = 0.414$), whereas a significant reduction was reported in the second and third months of the study ($p < 0.01$). Vit B1 use was further recommended because of a better safety profile [27]. In the second study, 240 girls with dysmenorrhea were divided into four groups. The first group received 100 mg of Vit B1, the second received 500 mg of fish oil, the third received both Vit B1 and fish oil, while the fourth received the placebo every day for a duration of two months [26]. At the end of the intervention, a significant reduction in pain severity was reported for all the intervention groups examined [26]. These data, in total, indicate that Vit B1, somehow, has positive effects on dysmenorrhea.

4. Effects of Vitamin K

An acupuncture point injection of vitamin K (Vit K) has been used as an effective treatment of dysmenorrhea, providing rapid pain relief and better quality of life [28][29]. Although the role of Vit K in the coagulation process is well documented, little is known about its role (and the underlying mechanism) on menstrual pain [29]. One clinical study has been conducted to assess the pain intensity and duration in dysmenorrhea patients treated with Vit K. The study also examined whether Vit K acupuncture point injection is an optimal treatment for patients [28]. In detail, 80 patients were eligible and were randomized in three groups [28]. The first group received an acupuncture point injection of Vit K3, the second group received a saline acupuncture point injection and the third received a deep K3 muscle injection [28]. The study results showed a significant reduction in the severity of dysmenorrhea in all three groups (in Vit K3 acupuncture point injection group, pain decreased from 8.0 to 1.5, $p < 0.001$, while in the saline injection group, decreased from 7.9 to 3.0, $p < 0.001$, and in the Vit K3 muscle injection group, decreased from 8.0 to 3.3, $p < 0.001$). The authors conclude that, according to the statistics, the acupuncture point injection of Vit K3 is considered as the optimal treatment, among those tested [28].

5. Effects of Vitamin E

Vitamin E (Vit E) displays an inhibitory role in the release of arachidonic acid and its conversion to prostaglandinvia action on the enzymes phospholipase A2 and cyclooxygenase [30][31]. Due to these antioxidant properties, Vit E is considered as a potential dysmenorrhea reliever.

Truly, several studies conducted thus far confirm that Vit E supplementation is capable of alleviating dysmenorrhea and also reducing blood loss [32][33][34][35][36]. For instance, in a randomized double-blind placebo-controlled trial, 200 units of Vit E or placebo were given to the participants of the study (278 girls, aged 15–17 years old), and the severity and duration of pain, as well as the amount of menstrual blood loss, were measured at two to four months [35]. A visual analog scale was used for the pain record, whereas menstrual loss was measured via a Pictorial Blood Loss Assessment Chart (PBLAC) [35]. According to the results of the study, the Vit E group displayed lower pain severity, shorter pain duration and lower PBLAC score when compared with the placebo group, at both two and four months [35].

Another study suggests that Vit E supplementation is a good choice for dysmenorrhea patients that cannot use chemical drugs, such as ibuprofen [37]. It seems that ginger and/or Vit D serve as better choices for these patients, as they reduce the disease severity more effectively [38]. Interestingly, results from a meta-analysis study indicate that, as in the case of Vit D, Vit E's positive effects on alleviating dysmenorrhea can only be reported at a period of at least two months into the intervention [23]. Thus, it is clear that some factors, such as the length of the intervention, strongly affect the effectiveness of Vit E in dysmenorrhea management and, due to that, more studies are needed in order to bring the maximum benefits of Vit E treatmentto patients.

6. Effects of Vitamin A and Vitamin C

Data regarding the effects of other vitamins in dysmenorrhea are extremely limited. One large study in adolescent girls was conducted, and the possible relationship between serum vitamin A (Vit A) status and inflammation status in subjects with primary dysmenorrhea and/or premenstrual syndrome was examined [39]. The results of that study suggest that serum Vit A, along with high-sensitivity C-reactive protein and prooxidant antioxidant balance, are significantly associated with the presence of premenstrual syndrome and primary dysmenorrhea [39]. Of note, Vit A (also known as retinol) is vital for sustaining multiple physiological actions, such as reproduction, morphogenesis and immune responses [40].

As far as vitamin C (Vit C) is concerned, Venkata et al. reported reduced blood levels of the aforementioned vitamin in primary dysmenorrhea cases [41]. Vit C, also known as ascorbic acid, has the ability to remove oxygen-free radicals and, thus, plays a major role in the recycling of Vit E (via converting Vit Efree radical back to Vit E) to prevent fat peroxidation [42]. Interestingly, a randomized triple-blind placebo-controlled trial conducted in 2021 by Amini et al. suggested that the intake of Vit E and Vit C supplements has positive effects in women with endometriosis (whose symptoms include, among others, dysmenorrhea) [43]. In more detail, in that study, 60 reproductive women (aged 15–45 years old) were enrolled and randomized to two groups, one receiving a combination of Vit C and Vit E and the other receiving the placebo. The intervention lasted 8 weeks and, at the end of that period, a significant decrease in dysmenorrhea, pelvic pain severity and dyspareunia was reported in the treatment group, in comparison with the placebo [43]. Moreover, despite the fact that there was no significant decline in total antioxidant capacity after the treatment, the Vit E/Vit C group displayed a significant reduction in malondialdehyde and reactive oxygen species levels [43]. Taking into account these data, the authors concluded that Vit C, combined with Vit E, has an important role on the indices of oxidative stress and the severity of pain in women with endometriosis/dysmenorrhea [43].

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