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Mexican Journal of Medical Research ICSa

Biannual Publication, Vol. 12, No. 24 (2024) 30-36

ISSN: 2007-5235

The role of dietary supplements in the treatment of Primary Dysmenorrhea: Vitamin D_3 and Zinc

Papel de los suplementos alimenticios en el tratamiento de la Dismenorrea Primaria: Vitamina D_3 y Zinc

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Abstract:

Dysmenorrhea is defined as 'painful menstruation,' and two types of dysmenorrhea are known: primary, which occurs in the absence of any gynecological disease, and secondary, which is associated with underlying conditions such as endometriosis, myomatosis, among others. Primary dysmenorrhea typically occurs approximately 6 months after menarche; around 16 to 81% of women of reproductive age suffer from Primary Dysmenorrhea, of which 2 to 29% report moderate to severe intensity. The objective of this manuscript is to propose vitamin D_3 and zinc as complementary treatments to first-line analgesics to reduce the pain associated with Primary Dysmenorrhea. The treatment of Primary Dysmenorrhea focuses on pain relief; however, dietary supplements such as Vitamin D3 and Zinc should be considered. These supplements inhibit the synthesis of prostaglandins, thereby improving uterine microcirculation and reducing the intensity of uterine contractions. It is important to mention that not only pharmacological treatment should be considered, lifestyle changes should also be made that provide a maximum state of physical and emotional well-being with the aim of reducing the consumption of analgesics and controlling or remitting the underlying pathology.

Keywords:

Dysmenorrhea, Primary Dysmenorrhea, treatment, nutritional supplement, vitamin D_3, zinc, prostaglandins.

Resumen:

La dismenorrea es definida como “menstruación dolorosa”, se conocen dos tipos de dismenorrea, la primaria que se presenta en ausencia de alguna enfermedad ginecológica y la secundaria que se asocia a alguna patología subyacente como endometriosis, miomatosis, entre otras; la dismenorrea primaria se presenta aproximadamente 6 meses después de la menarca; alrededor del 16 al 81% de mujeres en edad fértil padecen Dismenorrea Primaria, de las cuales del 2 al 29% refieren intensidad moderada-severa. El objetivo de este manuscrito es proponer como tratamiento complementario a los analgésicos de primera línea a la vitamina D_3 y el zinc para reducir el dolor asociado a la Dismenorrea Primaria. El tratamiento de la Dismenorrea Primaria se centra en el alivio del dolor, sin embargo, se deben considerar suplementos alimenticios tales como la Vitamina D_3 y el Zinc, estos suplementos inhiben la síntesis de prostaglandinas, logrando así la mejora en la microcirculación uterina y por lo tanto la intensidad de las contracciones uterinas se reduce. Es importante mencionar que no sólo se debe considerar el tratamiento farmacológico, también se deben hacer cambios en el estilo de vida que provean de un estado máximo de bienestar físico y emocional con el objetivo de reducir el consumo de analgésicos y tener un control o remisión de la patología base.

Palabras Clave:

Dismenorrea, Dismenorrea Primaria, tratamiento, suplemento alimenticio, vitamina D_3, zinc, prostaglandinas.

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Received: 02/03/2024, Accepted: 25/04/2024, Postprint: 10/05/2024, Published:

DOI: https://doi.org/10.29057/mjmr.v12i24.12405

INTRODUCTION

Primary dysmenorrhea, commonly known as menstrual pain, is a condition that significantly affects the quality of life of millions of women worldwide. Although it is considered a benign condition, its impact on daily life can be debilitating, interfering with everyday activities, work performance, and emotional health.[1,2]

In recent years, there has been increasing interest in the role of nutrients and supplements in the management of Primary Dysmenorrhea. Among them, vitamin D_3 and zinc have emerged as potential agents due to their anti-inflammatory, analgesic, and hormone-regulating properties.[3]

PRIMARY DYSMENORRHEA

Definition and classification

Dysmenorrhea is defined as pain during menstruation; two types of dysmenorrhea are known: Primary Dysmenorrhea (PD) and Secondary Dysmenorrhea (SD).[1,2] The PD is the type that occurs in the absence of underlying pathology. It is considered the most common chronic cyclic pain in women aged 12 to 30 years and is known to decrease as a woman's age advances beyond the third decade of life. The duration of the condition ranges from 8 to 72 hours and is accompanied by other symptoms such as low back pain, nausea, vomiting, diarrhea, headache, and behavioral disorders, with the latter being less addressed. Additionally, symptoms such as syncope, hyperthermia, and metrorrhagia are also associated with PD and the SD is associated with the presence of underlying pathologies such as endometriosis, myomatosis, adenomyosis, and pelvic inflammatory disease, among others. Its main symptom is metrorrhagia.[4-7]

PD typically occurs approximately 6 months after the first menstruation, a time in a woman's sexual life when ovulatory menstrual cycles have been established. It is considered the most common gynecological condition in women of childbearing age.[8,9]

Epidemiology

The prevalence of menstruating women suffering from PD ranges from 16% to 91%, with 2% to 29% experiencing moderate to severe intensity pain.[6,7,10,11] It is estimated that in Mexico, around 90% of women who seek primary care report dysmenorrhea, of which 15% to 50% are women of childbearing age.[12]

Risk Factors

Risk factors for PD are varied, with the most common being early menarche. Several studies[4,11,13-17], have shown that the earlier a woman experiences menarche, the greater the risk of developing PD and the severity of symptoms, especially when menarche occurs before the age of 12. Parity and multiparity are associated with decreased intensity of PD. Age is associated with a lower severity of symptoms if the woman is over 30 years old. The amount of menstrual flow and the duration of the menstrual phase within the cycle are associated with a higher risk of severity if the woman experiences hypermenorrhea. Habits such as smoking, obesity, and sedentary lifestyle increase the risk of developing PD. The risk factors are exemplified in Table 1.

Table 1. *Risk Factors for Primary Dysmenorrhea.*[13]

Individual and Family factors	Hereditary History of 1st Grade Age <30 years old
Factors associated with menstruation	Irregularity of the menstrual cycle Early menarche Hyperpolymenorrhea Infertility
Lifestyles	Consumption of alcohol, tobacco and/or other licit or illicit drugs Sedentarism High consumption of junk food, high levels of saturated fats Obesity
Pathophysiological factors	Previous pathologies Sexual abuse Anxiety Low BMI Depression

Pathophysiology

The pathophysiology of PD involves the synthesis of Prostaglandins (PG) the Prostaglandin E_2 (PGE_2) and Prostaglandin E2 alpha ($PGE_{2\alpha}$), which cause potent vasoconstriction, ischemia, and hypoxia in the uterine muscle. They also stimulate the production of substances such as adrenaline and hormones that generate tissue damage, inflammation, and pain.[6,16] These PG are derivatives of arachidonic acid metabolism by the enzyme cyclooxygenase 1 and 2 (COX-1/2).[15-21] During the luteal phase of the menstrual cycle, the regression of the corpus luteum occurs, leading to an increase in phospholipase A2 and consequently to an increase in arachidonic acid, which in turn increases the production of PG. PG are intracellular substances that derive from long-chain polyunsaturated fatty acids. Among the 9 types of PG, PGE_2 and $PGE_{2\alpha}$ are the most implicated in PD, causing potent contraction of uterine vessels while simultaneously decreasing the pain threshold of nerve endings. It is believed that leukotriene E4 has a similar mechanism[9,13], as shown in Figure 1.

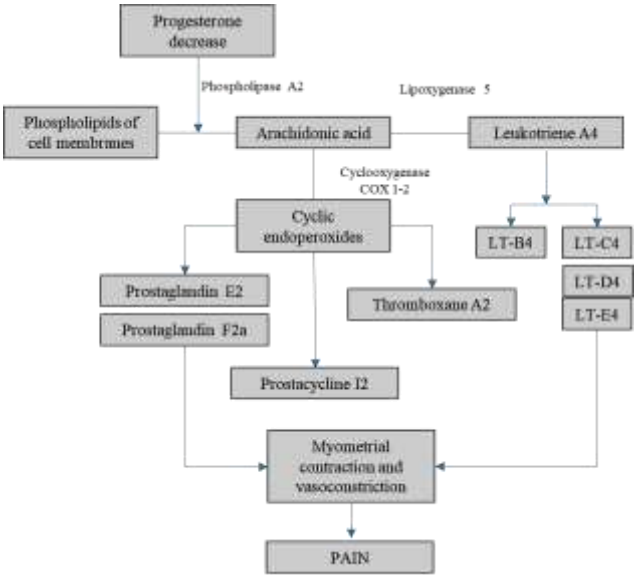

Figure 1. Pathway of Pain in Primary Dysmenorrhea.[18]

Treatment

The treatment of PD aims to provide pain relief. Treatment is divided into pharmacological, non-pharmacological, and surgical; currently, pharmacological treatment is considered the first option and mainly consists of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). According to the pathophysiology, PD is mediated by PG, which is why NSAIDs are considered the first-line treatment.[5,6,20] The first-line NSAIDs consist of non-selective ones such as naproxen, ibuprofen, mefenamic acid, flufenamic acid, acetylsalicylic acid, or the analgesic acetaminophen. For individuals at higher risk of gastrointestinal damage, the use of celecoxib, meloxicam, or nimesulide may be suggested. An alternative to pharmacological treatment could be Combined Oral Contraceptives (COC).[19,21-24]

Non-pharmacological treatment focuses on lifestyle changes (healthy eating and regular physical activity) aimed at reducing the production of arachidonic acid.[5] The placement of Transcutaneous Electrostimulators (TENS) is also considered an alternative for the treatment of PD as they provide rapid, effective, and long-lasting relief, besides being biologically safe. They are considered as an alternative capable of replacing or being combined with NSAIDs.[25]

Surgical treatment is indicated when none of the alternatives (pharmacological and non-pharmacological) has shown relief. Among the most common are laparoscopic uterosacral nerve ablation, presacral neurectomy, intrauterine manual aspiration, and hysterectomy.[5]

PHARMACOLOGICAL ALTERNATIVES: DIETARY SUPPLEMENTS.

A dietary supplement is a substance that helps meet nutritional needs in the face of a deficiency of essential vitamins or minerals. As established before, PD is a complex combination of somatic and psychological symptoms that occur from ovulation to the onset of menstrual bleeding or within the first 3 days of it. Treatment can be complemented with such supplements as vitamin D_3, zinc, magnesium, vitamin K, vitamin E, and omega-3 fatty acids, as well as supplementing the diet with fennel, dietary fiber, or olive oil.[8,26,27] The general properties of the mentioned dietary supplements are described in Table 2.

Table 2. *Dietary supplements that can complement the pharmacological treatment of PD.*[5,26-28]

VITAMINS	D_3	The vitamin D receptors located in the uterus catch the vitamin D consumed and inhibit the synthesis of prostaglandins.
	B_1	If there is a deficit of this and if it is reversed, colic is reduced, fatigue and increases tolerance to pain.
	E	Suppresses phospholipase A2 and COX activity, inhibiting prostaglandin production and promoting prostacyclin with consequent vasodilation and muscle relaxation.
	K	Shortens the duration of the menstrual cycle by its action on prothrombin.
MINERALS	Zinc	Reduces the synthesis of prostaglandins through its endogenous antioxidant catalyst and is in turn an anti-inflammatory agent which improves uterine microcirculation.
	Magnesium	The mechanism of action has not been clearly determined, but it is believed that being Ca^{+2} antagonist inhibits uterine contractility.
FATTY ACIDS	Omega 3 and 6	These fatty acids promote the formation of eicosapentaenoic and docosahexanotic acids and these in turn less inflammatory substances such as PGE_3, leukotrienes B4 and thromboxane A3, therefore menstruations are less painful.

FOOD	Fennel	Herbal therapy that relieves pain; it has been demonstrated to reduce pain compared to pharmacological therapy, and when combined with placebo, it showed a significant reduction in pain.
	Dietary fiber	The intake of dietary fiber has an inverse correlation with the menstrual pain scale
	Olive oil	It inhibits the effect of prostaglandins and therefore uterine hypercontraction. Olive oil is dose-dependent in inhibiting contractions induced with Prostaglandin $PGF_{2\alpha}$ *in vitro*.
	Turmeric	It is a bioactive polyphenol derived from the root of the plant Curcuma Longa. It has anti-inflammatory, antioxidant, neuroprotective, cardioprotective, analgesic, hypolipidemic, and antidepressant effects.

Vitamin D

Vitamin D, compared to other essential vitamins for health, is unique in its function due to the various available sources. Vitamin D_2 (ergocalciferol) is obtained from UV irradiation of ergosterol, a steroid mainly presents in fungi. Vitamin D_3 or cholecalciferol is synthesized by UV irradiation of 7-dehydrocholesterol, resulting in pre-vitamin D in the skin of animals under UVB wavelengths of 290-320nm.[29]

Vitamin D_3 is found in foods such as eggs and fatty fish, as well as in enriched and fortified foods. The daily requirement for vitamin D_3, according to age from 1 to 70 years, which includes the fertile age of women with PD (12 to 30 years old), is 15mcg (500000IU).[29,30] The amount of vitamin D in plasma is determined by exposure to sunlight radiation. It is recommended to have at least 30 minutes of exposure per day, preferably before 10 am and after 5 pm.[31,32]

The classification levels of plasma Vitamin D are as follows: deficiency: <25 mmol/L; insufficiency: 25-75 mmol/L; and normal: >75 mmol/L.[22]

Vitamin D_3 plays a very important role in calcium homeostasis. *Per se*, vitamin D_3 is biologically inert; it is metabolized through the hydroxylation of 25-hydroxyvitamin D_3 in the liver and kidney, which improves the intestinal absorption of calcium and phosphate as well as bone mineralization[31], and within the process of female reproduction, receptors for this vitamin are expressed in the endometrium, ovarian tissue, fallopian tubes, decidua, and placenta. It is known that a deficiency of this vitamin increases the risk of experiencing depressive symptoms, fibromyalgia, and uterine fibroids.[26,33]

A relationship has been identified between deficiency and insufficiency of vitamin D_3 with severe and very severe dysmenorrhea, as this vitamin reduces the production of endometrial prostaglandins, thus regulating the expression of COX 1 and 2.[31,34-36] The enzyme phospholipase A2 (PLA) releases arachidonic acid which is converted into PGE_2, this primary prostaglandin is responsible for dysmenorrhea through cooperative functions between COX-2, peroxidases (POX), and synthases. Vitamin D inhibits the expression of COX-2, therefore arachidonic acid is unable to be transformed into PGE_2, thus arachidonic acid is not released from the cell membrane, meaning that vitamins inhibit the de novo synthesis of arachidonic acid.[35] The mechanism of action of vitamin D_3 is described in Figure 2.

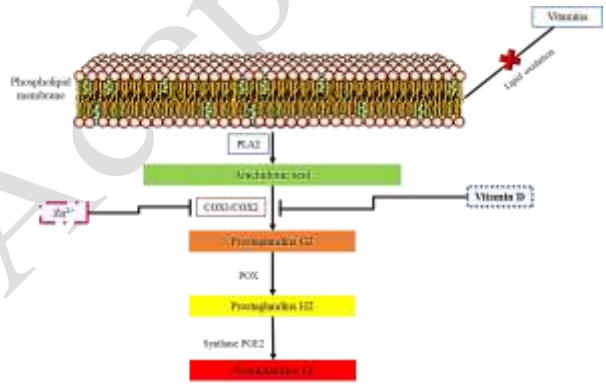

Figure 2. Mechanism of action of Vitamin D and Zinc.[35-37]

Vitamin D_3 (cholecalciferol) has been described as more efficient than vitamin D_2, the former having anti-inflammatory properties by participating in the D receptor gene (VDR) which is related to the pathogenesis of menstrual dysfunction and its consumption is associated with a 4% decrease in the risk of PD.[33,38]

The literature describes an inverse relationship between serum levels of vitamin D and PD, thus demonstrating that vitamin D deficiency is more common in patients with dysmenorrhea due to the regulatory action of calciferol on prostaglandin levels. Studies have shown that the metabolism and absorption of vitamins and minerals may play an important role in the development and treatment of menstrual disorders.[39]

This is why the intake of vitamin D3 in the form of a dietary supplement, at a dose of at least 300,000 - 500,000 IU during the luteal phase, 3 to 5 days before the menstrual phase, is recommended. This therapy should be combined with NSAIDs and complemented with Ca^{2+} supplements, and has shown effectiveness in a group of Iranian female students in the clinical trial conducted by Amzajerdi A. and colleagues in 2023.[40-42]

Vitamin D_3 deficiency is understood as levels lower than 10ng/ml in serum and is the result of decreased synthesis in the skin due to

low sun exposure, patients with celiac disease, history of bariatric surgery, consumption of anticonvulsant, antiretroviral, and glucocorticoid medications. This can lead to diseases such as osteomalacia, which is the alteration of the bone matrix with an increase in unmineralized tissue, and in children, it affects the growth cartilage causing rickets. Another pathology resulting from hypovitaminosis D_3 is vitamin D_3 myopathy, which presents as proximal muscle weakness, alterations in hip flexion-extension and abduction, difficulty in standing up, and gait abnormalities. Other less common pathologies may include ischemic cardiovascular disease, congestive heart failure, hypertension, and autoimmune diseases.[43,44]

On the opposite, hypervitaminosis D_3 causes hypercalcemia, with serum levels >14mg/dL, which treatment is symptomatic and requires strict control of serum calcium and vitamin D_3. It results from increased bone resorption, increased intestinal absorption, or decreased excretion.[45,46]

Zinc

It is the most abundant essential trace element in the human body, with its main function being its participation in biochemical processes necessary for the cell's use of oxygen, DNA and RNA reproduction by maintaining the integrity of the cell membrane, and the elimination of free radicals, as well as protein synthesis[37,47], and in the reproductive process, it actively participates at the level of ovulation, fertilization, and normal fetal development.[48]

The daily requirement of zinc is 40mg/day and it can be found in animal-derived foods, mainly lean meats from poultry, beef, and pork, as well as in seafood. Plant-based sources include nuts, seeds, and cereals.[49]

The involvement of this mineral in the treatment of PD is described by reducing prostaglandin synthesis through its endogenous antioxidant capacity and anti-inflammatory agent, as well as decreasing COX-2 activity, as it improves uterine microcirculation by preventing and inactivating oxygen-free radicals, thus preventing uterine cramps, zinc has an endogenous antioxidant effect and decreases COX-2, as well as the consequent production of prostaglandins.[37] The mechanism of action Zinc is described in Figure 2.

A published study found that women who received zinc supplementation at doses of 20-126mg/day for 3 to 6 days in at least 3 menstrual cycles reported a decrease in pain intensity assessed by the Visual Analog Scale (VAS). It was also found that zinc showed significant superiority over placebo, demonstrating an effective and sustained reduction in pain, where the pain intensity assessed by VAS decreased from 8-10 to 3.8 ± 2.85 over 3 menstrual cycles.[48,50]

Supplementation with zinc at a dose of 31mg three times a day for 3 days prior to the onset of the menstrual cycle for at least 3 menstrual cycles is recommended. Alternatively, long-term supplementation should be at least 15-30mg per day, as its bioavailability is very low.[51-53]

It is known that zinc deficiency is a result of malnutrition and, in the long term, it causes growth retardation, delayed puberty, erectile dysfunction, hypogonadism, hypochromic microcytic anemia, alterations in neurobehavioral development, skin disorders, anorexia, alterations in smell and taste, as well as impaired wound healing. Zinc overconsumption manifests as a metallic taste, abdominal cramps, vomiting, and diarrhea, while toxicity presents as immune suppression, decreased HDL cholesterol, and interferes with the absorption of quinolones, tetracyclines, penicillins, and thiazides.[54-56]

CONCLUSION

While primary dysmenorrhea (PD) has implications not only on physical but also social aspects that impact quality of life, it is our responsibility as healthcare professionals to provide the patient with the best treatment that addresses their needs. In addition to pharmacological treatment, we can complement it with a supplement based on Vitamin D_3 and/or zinc since it has been demonstrated that both inhibit the synthesis of prostaglandins, the synthesis of COX-1 and 2, and therefore the characteristic colicky pain of PD, as long as they have certification from health authorities since quality, safety and efficiency among the countless presentations that exist of these supplements are the main problems. While the efficacy of both supplements separately has been mentioned, we should not forget that the combination of these may vary in each patient, and that no studies have been conducted using combined therapy.

This article proposes a comprehensive view of PD as it emphasizes the evidence-based importance of incorporating vitamin D_3 and zinc into pharmacological treatment. This is how dietary supplements can optimize the effectiveness of said treatment. Likewise, dosages and indications of the described supplements are proposed, which facilitates healthcare professionals in offering more effective treatments for PD, a condition that has been normalized by society.

We must not overlook the importance of making lifestyle changes such as a low-fat diet, increased consumption of grains and seeds, fruits, vegetables, increased water intake, and engaging in at least 60 minutes of intense physical activity three times a week. These changes could even reduce the consumption of NSAIDs or eliminate PD.

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