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N-3 polyunsaturated fatty acids (PUFAs) and physical exercise have the potential to reduce pain intensity in women with primary dysmenorrhea: Systematic Review

Los ácidos grasos poliinsaturados n-3 (PUFA) y el ejercicio físico tienen el potencial de reducir la intensidad del dolor en mujeres con dismenorrea primaria: Systematic Review

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Abstract. This review aims to highlight the potential of n-3 PUFAs and physical exercise in reducing pain intensity in women with primary dysmenorrhea. This type of research is a systematic review using comprehensive strategies such as searching for articles in research journal databases. The databases used are Pubmed/MEDLINE, Scopus, Web of Science, and Embase. The populations analyzed in this paper are: the potential of n-3 PUFAs and physical exercise to reduce primary dysmenorrhea. The inclusion criteria in this study were journals that discussed n-3 PUFAs, exercise, primary dysmenorrhea, and menstrual pain. The exclusion criteria in this study were disreputable international journals. For standard operationalization, This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This review explains that N-3 PUFAs given at the right dose, around 1000 mg/day have the potential to reduce pain intensity by suppressing the production of pro-inflammatory cytokines and eicosanoids. In addition, N-3 PUFAs have the potential to prevent and reduce pain intensity by inhibiting prostaglandin synthesis. Progesterone is very important in women with primary dysmenorrhea in order to control prostaglandin secretion. This review explains that regular exercise with low to moderate intensity (30-75% of maximum ability) performed 3 times in 1 week can increase progesterone concentrations. Physical exercises that can be done to reduce pain intensity due to primary dysmenorrhea include stretching exercises, jogging, and yoga exercises.
Keywords: N-3 PUFAs, Physical Exercise; Dismenore Primer; Menstrual Pain.

Resumen. Esta revisión tiene como objetivo resaltar el potencial de los n-3 PUFAs y el ejercicio físico para reducir la intensidad del dolor en mujeres con dismenorrea primaria. Este tipo de investigación es una systematic review que utiliza estrategias integrales, como la búsqueda de artículos en bases de datos de revistas de investigación. Las bases de datos utilizadas son Pubmed/MEDLINE, Scopus, Web of Science y Embase. Las poblaciones analizadas en este trabajo son: el potencial de los n-3 PUFAs y el ejercicio físico para reducir la dismenorrea primaria. Los criterios de inclusión en este estudio fueron revistas que hablaran sobre los n-3 PUFAs, el ejercicio, la dismenorrea primaria y el dolor menstrual. Los criterios de exclusión en este estudio fueron revistas internacionales de mala reputación. Para la operatividad estándar, este estudio sigue los elementos de informe preferidos para revisiones sistemáticas y metanálisis (PRISMA). Esta revisión explica que los n-3 PUFAs administrados en la dosis correcta, alrededor de 1000 mg/día, tienen el potencial de reducir la intensidad del dolor al suprimir la producción de citoquinas proinflamatorias y eicosanoides. Además, los n-3 PUFAs tienen el potencial de prevenir y reducir la intensidad del dolor al inhibir la síntesis de prostaglandinas. La progesterona es muy importante en mujeres con dismenorrea primaria para controlar la secreción de prostaglandinas. Esta revisión explica que el ejercicio regular de intensidad baja a moderada (30-75% de la capacidad máxima) realizado 3 veces en 1 semana puede aumentar las concentraciones de progesterona. Los ejercicios físicos que se pueden hacer para reducir la intensidad del dolor debido a la dismenorrea primaria incluyen ejercicios de estiramiento, trote y ejercicios de yoga.
Palabras clave: N-3- PUFAs; Ejercicio físico; Dismenorrea primaria; Dolor menstrual.

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Introduction

Primary dysmenorrhea is caused by uterine contractility and hypersecretion of prostaglandins, especially F2 Alpha (PGF2-a) when women are menstruating (Barcikowska et al. 2022; Romero-Morales et al. 2020; Hong et al. 2022). Primary dysmenorrhea is menstrual pain that arises and is felt in the absence of organic disease (Bernardi et al. 2017; Abreu-Sánchez et al. 2020). In general, pain in women with primary dysmenorrhea reaches its peak on the first and second day of the menstrual cycle (Itani et al. 2022). Prostaglandin secretion is controlled by progesterone (Willis, Bridges, and Fortune 2017). When progesterone decreases, there will be an increase in the secretion of prostaglandin levels due to negative feedback (Kannan et al. 2019). In addition, a decrease in progesterone will trigger an increase in pro-inflammatory cytokines during the menstrual cycle (Barcikowska et al. 2020; Kırıcı and Tanrıverdi 2021).

Based on world data, the incidence of primary dysmenorrhea reaches an incidence of 45% in fertile women and the highest incidence occurs in women aged 13-17 years (Bernardi et al. 2017). The phenomenon so far is the management of pain due to primary dysmenorrhea using non-steroidal anti-inflammatory drugs (NSAIDs) (Oladosu, Tu, and Hellman 2018; Nie et al. 2020). If the use of NSAIDs is always applied, it will certainly have an impact on health.

Alternative solutions need to be found to overcome these problems. One of the natural ingredients contained in fish oil is n-3 polyunsaturated fatty acids (PUFA). N-3 PUFAs are well known for their anti-inflammatory prop-

erties (Oppedisano et al. 2020; Stupin et al. 2019; Y. Park 2022). Our previous study reported that omega 3 was able to reduce pain intensity by decreasing levels of Tumor Necrosis Factor Alpha (TNF-a) in the blood after weight training (Novadri Ayubi et al. 2022). In the medical world, N-3 PUFAs have been widely used to accelerate wound healing (Meng et al. 2021; Zaloga 2021; Komprda et al. 2020). In addition, the physical activity carried out by women has the potential to increase the hormone progesterone (Jaleel et al. 2022). In this regard, it is necessary to know the potential of n-3 PUFAs and physical exercise in reducing pain intensity in women with primary dysmenorrhea. These issues provide us with an opportunity to discuss them in depth through a systematic review.

This review aims to highlight the potential of n-3 PUFAs and physical exercise in reducing pain intensity in women with primary dysmenorrhea.

Methods

This type of research is a systematic review using comprehensive strategies such as searching for articles in research journal databases. The databases used are Pubmed/MEDLINE, Scopus, Web of Science, and Embase. The populations analyzed in this paper are: the potential of n-3 PUFAs and physical exercise to reduce primary dysmenorrhea. The inclusion criteria in this study were journals that discussed n-3 PUFAs, exercise, primary dysmenorrhea, and menstrual pain. The exclusion criteria in this study were disreputable international journals. Notes were compiled, titles and abstracts were screened, and full-text articles were verified using reference management software (Mendeley). A total of 3990 articles from the Pubmed/MEDLINE, Scopus, Web of Science, and Embase databases were identified. A further 8 articles that met all inclusion requirements or at least some of them were selected for this systematic review. For standard operationalization, this study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

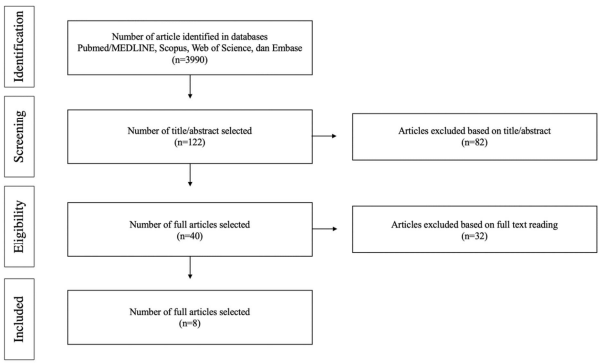

Figure 1. PRISMA flowchart of the article selection process.

Results

The results of the research used in this systematic review areas follows (table 1).

Table 1.
Research on the effect of n-3 PUFAs and physical exercise on menstrual pain intensity in women with primary dysmenorrhea

Author	Sample Characteristics	Study Design	Intervention	Results
(Mehrpooya et al. 2017)	40 women aged 18 to 45 years with moderate to severe symptoms of primary dysmenorrhea participated in this study. Subjects were divided into two groups, namely the group receiving calcium and the group receiving N-3 PUFAs.	Randomized double-blinded clinical trial	Intervention of calcium and N-3 PUFAs is given every day in the first cycle before 2 days until the end of the menstrual cycle.	N-3 PUFAs are effective in reducing pain intensity and pathological symptoms of primary dysmenorrhea.
(Sadeghi et al. 2018)	100 women with primary dysmenorrhea were divided into four groups, namely the n-3 PUFAs group (n=25), the vitamin E group (n-25), the n-3 PUFAs + vitamin E group (n=25), and the control group (n =25).	Experimental	N-3 PUFAs (180 mg EPA and 120 mg DHA) and 200 international units of vitamin E administered daily during the menstrual cycle.	N-3 PUFAs and vitamin E are very helpful in reducing the pain intensity of primary dysmenorrhea.
(Duman, Yıldırım, and Vural 2022)	180 students with primary dysmenorrhea agreed to take part in the study.	Cross-sectional	Mind-body techniques, applying heat to the stomach, taking hot baths, consuming n-3 PUFAs, consuming ginger.	Risk factors for primary dysmenorrhea are family history, smoking, emotional problems, and consuming caffeine regularly. Applying heat to the stomach, taking a hot bath, consuming PUFAs, and consuming ginger are alternative solutions to reduce primary dysmenorrhea.
(Yokoyama et al. 2022)	2060 women with an average age of 31 years who had symptoms of primary dysmenorrhea participated in this study.	Cross-sectional	N-3 PUFAs given to group <1 time/week, 2-3 times/week, >4 times/week.	There is a significant negative relationship between the frequency of intake of n-3 PUFAs and primary dysmenorrhea. Thus, n-3 PUFAs are suggested to be consumed to prevent and reduce primary dysmenorrhea by inhibiting the synthesis of PGF2-a.
(Demirturk et al. 2002)	44 women aged 15-19 years who experienced dysmenorrhea participated in this study.	Experimental	n-3 PUFA at a dose (1500 mg) given for 2 months during menstrual cycle.	N-3 PUFAs can significantly reduce primary dysmenorrhea.
(Motahari-Tabari, Shirvani, and Alipour 2017)	122 female students who experienced primary dysmenorrhea participated in this study. Subjects were divided into 2 groups, namely the exercise group and the mefenamic acid group.	Randomized double-blinded clinical tria	Abdominal stretching exercise for 15 minutes 3 times/week. The mefenamic acid group received 250 mg capsules every 8 hours from the start of menstruation.	Abdominal stretching exercise is as effective as mefenamic acid in reducing pain intensity.
(Fernández-Martínez, Onieva-Zafra, and Parra-Fernández 2019)	305 women with an average age of 20 years with primary dysmenorrhea participated in this study.	Cross-sectional	Subjects completed surveys regarding sociodemographics, gynecology, and lifestyle	Women who do not suffer from primary dysmenorrhea generally do aerobic exercises such as pilates and jogging regularly.
(Kim 2019)	203 women with primary dysmenorrhea were included in a meta-analysis to compare the effect of practicing yoga (n=129) and not practicing yoga (n=101) on menstrual pain.	A meta-analysis of randomized controlled trials	Meta-analyst Yoga practice and not Yoga practice	Yoga practice is an effective alternative to reduce pain intensity in women with primary dysmenorrhea.

Discussion

The main aim of this systematic review was to evaluate the effect of n-3 PUFAs and physical exercise on reducing pain intensity in women with primary dysmenorrhea. The occurrence of menstruation is associated with a decrease in progesterone (Barcikowska et al. 2020; Écochard et al. 2022). The decrease in progesterone causes the release of acid phosphatase and lytic enzymes in the lysosomes to the cytoplasm (Azeez et al. 2021). These enzymes digest the cells causing the secretion of prostaglandins (Barcikowska et al. 2020). In addition, the decrease in progesterone contributes to the inflammatory response that leads to sloughing and menstrual bleeding (Romero-Parra et al. 2020). Activated macrophages will trigger an increase in cytokines. pro-inflammatory cytokines such as TNF-a, IL-1, and IL-6 (N Ayubi et al. 2022). Several studies have reported that pro-inflammatory cytokines stimulate the synthesis and release of prostaglandins (Mahesh, Anil Kumar, and Reddanna 2021; Leimert et al. 2019; Kannan, Cheung, and Lau 2019).

Primary dysmenorrhea is believed to occur due to increased secretion of prostaglandins, especially F2 Alpha (PGF2-a) during endometrial sloughing or the menstrual cycle (Itani et al. 2022). Prostaglandins are closely related to increased myometrial contractions and vasoconstriction which causes anaerobic metabolic production and uterine ischemia causing excessive pain berlebih (Sachs et al. 2018; Rasmussen et al. 2020).

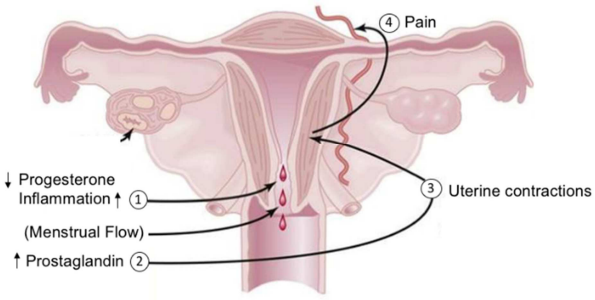

Figure 2. Pathophysiology of Primary Dysmenorrhea

Potential of N-3 PUFAs in Reducing Pain Intensity in Women with Primary Dysmenorrhea

N-3 PUFAs consists of several ingredients such as alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Visioli and Agostoni 2022; Nursyifa Fadiyah, Megawati, and Erlangga Luftimas 2022), as shown in Figure 3-5.

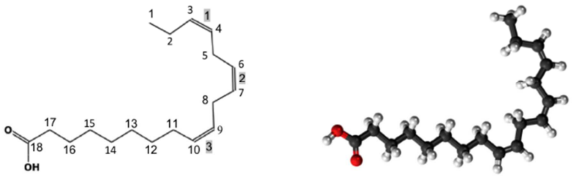

Figure 3. Molecular structure of alpha-linolenic acid (ALA, 18:3n-3)

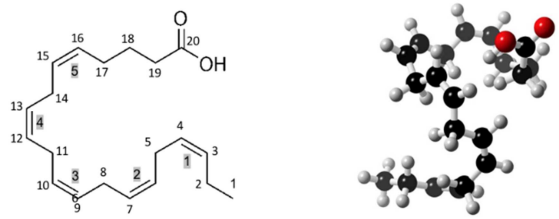

Figure 4. Molecular structure of eicosapentaenoic acid (EPA, 20:5n-3)

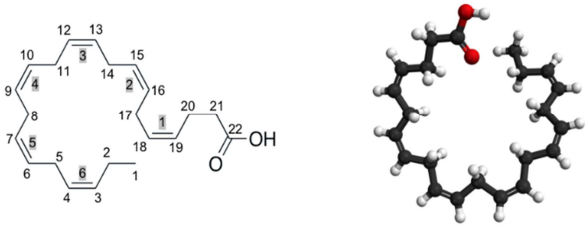

Figure 5. Molecular structure of eicosapentaenoic acid (DHA, 22:6n-3)

Menstruation is associated with an inflammatory response that leads to fusion and bleeding in the uterus (Vena and Paschou 2022; Granda, Szmidt, and Kaluza 2021; Sima et al. 2022; Santos, Price, and Bueno 2020). Various studies have reported that N-3 PUFAs are molecules that have the potential to reduce inflammation, so they can protect against various forms of degenerative disorders (Simonetto et al. 2019; Wu et al. 2019). TNF-a and IL-6 are believed to be pro-inflammatory cytokines that trigger pain during inflammation (Novadri Ayubi et al. 2022; Li, Xu, and Yang 2017). An experimental study conducted on women aged 18-45 years with primary dysmenorrhea reported that administration of N-3 PUFAs at a dose of 1000 mg for 3 months in the menstrual cycle can reduce pain intensity (Mehrpooya et al. 2017). In addition, a study conducted on women aged 18-25 years with primary dysmenorrhea reported that the combination of N-3 PUFAs (dose of 180 EPA and 120 mg DHA) with vitamin E given in the first 5 days of menstruation was able to significantly reduce pain intensity (Sadeghi et al. 2018). Another study supports the results of previous research which reported that N-3 PUFA is an alternative that can reduce pain in women with primary dysmenorrhea. (Duman, Yıldırım, and Vural 2022).

Besides being able to reduce the inflammatory response during, N-3 PUFA can also reduce the prostaglandin which is the main cause of primary dysmenorrhea. A recent study reported that women with primary dysmenorrhea who regularly consume N-3 PUFAs can prevent and reduce pain intensity by inhibiting PGF2-a synthesis (Yokoyama et al. 2022). The lack of research on this matter, previous studies are supported by a previous study conducted on adolescents. 15-19 years old with primary dysmenorrhea reported that giving N-3 PUFA for 2 months could reduce pain intensity during menstruation (Demirturk et al. 2002).

Potential of Physical Exercise in Reducing Pain Intensity in Women with Primary Dysmenorrhea

Progesterone has an anti-inflammatory effect by regu-

lating the synthesis of prostaglandins and leukotrienes (Maybin and Critchley 2011; Molla et al. 2022). The important role of progesterone in women with primary dysmenorrhea is to control prostaglandin secretion (Cui et al. 2022). The concentration of progesterone can increase with exercise, but the concentration also depends on the intensity of the exercise (Rocha-Rodrigues et al. 2021).

Researchers have reported that exercise performed for 20-30 minutes per training session, exercise performed 3 times in 1 week with an intensity of 30%-75% of maximum ability can increase progesterone concentrations (Jaleel et al. 2022). Prostaglandin hypersecretion has been believed to be the main cause of menstrual pain and primary dysmenorrhea (J. Park et al. 2022). In this regard, an experimental study conducted on 21-year-old female students with primary dysmenorrhea reported that 15-minute stretching exercises performed 3 times in 1 week were effective in the treatment of primary dysmenorrhea. The results of this study indicate that stretching exercises significantly reduce the intensity of menstrual pain (Motahari-Tabari, Shirvani, and Alipour 2017). In addition, a study conducted on 305 female students to complete a self-report survey on primary dysmenorrhea reported that female students who did not suffer from primary dysmenorrhea generally did aerobic exercise such as Pilates and jogging regularly (Fernández-Martínez, Onieva-Zafra, and Parra-Fernández 2019). In addition to pilates and jogging, a meta-analysis study reported that a yoga exercise program was effective in reducing pain intensity in women with primary dysmenorrhea (Kim 2019).

Conclusions

Prostaglandin hypersecretion is the main cause of primary dysmenorrhea in women. This review explains that N-3 PUFAs given at the right dose, around 1000 mg/day have the potential to reduce pain intensity by suppressing the production of pro-inflammatory cytokines and eicosanoids. In addition, N-3 PUFAs have the potential to prevent and reduce pain intensity by inhibiting prostaglandin synthesis.

Progesterone is very important in women with primary dysmenorrhea in order to control prostaglandin secretion. This review explains that regular exercise with low to moderate intensity (30-75% of maximum ability) performed 3 times in 1 week can increase progesterone concentrations. Physical exercises that can be done to reduce pain intensity due to primary dysmenorrhea include stretching exercises, jogging, and yoga exercises.

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Conflicts of Interest

The authors declare no conflict of interest

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