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The Impact of Polyunsaturated Fatty Acid Supplementation on Inflammatory Markers in Preterm Infants – A Literature Review

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Abstract

Introduction

Inflammation in fetuses and newborns, particularly in the population of preterm infants, is associated with increased mortality and adverse health outcomes. It has been shown that the placental transfer of polyunsaturated fatty acids (PUFAs) is limited in very preterm infants. Studies have demonstrated that low levels of PUFAs correlate with the severity of inflammation in infants' bodies. They are also associated with an increased incidence of diseases, including bronchopulmonary dysplasia and retinopathy of prematurity. One of the beneficial effects of PUFA supplementation is its inhibitory action on inflammatory processes in the body.

Aim of the study

Supplements containing fatty acids are among the most popular complementary health interventions introduced in children. Considering this potential benefit, we would like to present research studies that describe the relationship between the supplementation of polyunsaturated fatty acids and the levels of inflammatory markers in preterm infants.

Materials and Methods

A review of randomized clinical trials (RCTs) published in 2020-2024 regarding the

relationship between the supplementation of polyunsaturated fatty acids and the levels of inflammatory markers in preterm infants. Three studies meeting specific selection criteria were identified.
Results
All the studies discussed in our work demonstrate that supplementation with polyunsaturated fatty acids in preterm infants reduces the levels of inflammatory markers. Research consistently shows that PUFA supplementation lowers IL-6 levels, a cytokine considered a risk factor for sepsis in preterm infants.
Conclusion
Supplementation with polyunsaturated fatty acids holds potential for modulating inflammatory processes in preterm infants, with efficacy likely influenced by factors such as the specific type of fatty acid used, timing and form of administration, and individual variations in response.
Key words
polyunsaturated fatty acids, inflammatory markers, preterm infants

1.Introduction

Inflammation in fetuses and newborns, particularly in the population of preterm infants, is associated with increased mortality and adverse health outcomes. It has been shown that the placental transfer of polyunsaturated fatty acids (PUFAs) is limited in very preterm infants. Studies have demonstrated that low levels of PUFAs correlate with the severity of inflammation in infants' bodies. They are also associated with an increased incidence of diseases, including bronchopulmonary dysplasia and retinopathy of prematurity. One of the beneficial effects of PUFA supplementation is its inhibitory action on inflammatory processes in the body.
Cytokines are key molecules regulating the inflammatory response in the body. When a "cytokine storm" occurs, the excessive concentration of cytokines can lead to severe complications, such as the formation of blood clots or organ damage [1]. Specialized pro-resolving mediators (SPMs) are responsible for resolving inflammation by neutralizing pro-inflammatory cytokines and clearing inflammatory debris, allowing tissues to heal and restore balance [2]. SPMs are derived from omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Both omega-3 and omega-6 fatty acids are classified as polyunsaturated fatty acids. Scientific studies have shown that omega-6 fatty acids tend to exhibit pro-inflammatory effects [3]. In contrast, omega-3 fatty acids demonstrate anti-inflammatory properties by increasing the levels of eicosanoids and resolvins [4,5,6]. Additionally, omega-3 fatty acids reduce the concentrations of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) [7].

Several studies have suggested that omega-3 supplementation might lower the risk of infections and influence the progression of certain diseases [8,9]. However, clinical trials explicitly confirming these hypotheses are limited. Notably, fatty acid supplements are among the most utilized health interventions in pediatric populations.

Given the potential benefits, this review aims to summarize the scientific research investigating the relationship between polyunsaturated fatty acid supplementation and inflammatory marker levels in preterm infants.

2. Study Objective

The objective of this study is to review current scientific reports and summarize the state of knowledge regarding the impact of polyunsaturated fatty acid (PUFA) supplementation on inflammatory markers in preterm infants. The analysis evaluates whether regular intake of these fatty acids can effectively reduce inflammation associated with chronic diseases and infections in early childhood.

3. Review Methods

The literature review was conducted in December 2024 using the PubMed database. Articles were identified using the keywords "polyunsaturated fatty acids,", "inflammatory markers" and "preterm infants". The analysis was restricted to publications from 2020 to 2024. Search results were further narrowed to clinical studies focusing on pediatric populations.

An initial screening identified 35 randomized controlled trials (RCTs). The following inclusion criteria were applied: (1) study design: RCTs, (2) intervention: PUFA supplementation, (3) population: preterm infants, (4) publication quality: studies published in peer-reviewed journals. Exclusion criteria included: (1) non-RCT studies, (2) participants older than one month.

3. Results

The final analysis included three studies published between 2020 and 2024. The characteristics of the included studies, organized chronologically, are presented in Table 1.

First author, month, year of publication	Number of participants, age	Duration of study	Inclusion criteria	Intervention group	Control group
Klevebro S, 05.2024	183; <1 month of age	40 weeks	Infants born before 28+0 weeks of gestation at one of three research centers in Gothenburg, Stockholm, or Lund.	Enteral daily dose of 50 mg/kg DHA and 100 mg/kg AA, starting three days after birth and continuing until 40 weeks of age.	Did not receive placebo.
Papandreou P, 11.2020	92; <1 month of age	15 days	<32 weeks of gestation and birth weight	Intravenous fat emulsion enriched with MCT/ω-3	Placebo.

			<1500 g, admitted to the neonatal intensive care unit within 12 hours of birth.	PUFA.	
Wendel K, 03.2023	120; <1 month of age	36 weeks	Infants with a gestational age (GA) below 29 weeks.	Enteral supplementation (Formulaid™, DSM Nutritional Products Inc.) containing 100 mg/kg ARA and 50 mg/kg DHA.	Medium-chain triglycerides (MCT-oil™, Nutricia).

Table 1.

The Klevebro team [10] analyzed the impact of polyunsaturated fatty acid supplementation on inflammatory markers in preterm infants born at less than 28 weeks of gestation. Patients included in the study were divided into two groups. The intervention group received arachidonic acid (AA) and docosahexaenoic acid (DHA) from the third day of life until 40 weeks of age, while the control group did not receive a placebo. Feeding practices were consistent across both groups. Blood samples were initially collected every three days and then biweekly after two weeks. In addition to measuring inflammatory markers, the levels of AA and DHA in the blood samples were analyzed.

Infants in the intervention group showed increased serum levels of both AA and DHA. Supplementation did not affect the concentrations of other fatty acids. The study found that the levels of several inflammation-related proteins correlated with the levels of both fatty acids. AA levels declined rapidly during the first week of life and then gradually stabilized. AA was associated with inflammatory proteins in both a positive manner (enhancing their activity) and a negative one (dampening activity), but its impact on inflammation appeared less pronounced than that of DHA. DHA levels initially dropped but then steadily increased over time.

The study concluded that DHA exhibited a stronger and more consistent association with inflammation-related proteins compared to AA. Additionally, the research demonstrated that both fatty acids influenced numerous proteins involved in inflammation, with most proteins responding similarly to both acids. In summary, DHA appeared to have a stabilizing effect on the immune system by regulating inflammatory proteins more effectively than AA. The combination of AA and DHA may act synergistically in modulating inflammatory processes, potentially mitigating them at specific times.

Papandreou and colleagues [11] analyzed the effects of intravenous supplementation with a fat emulsion enriched with polyunsaturated fatty acids (PUFAs) on the anti-inflammatory

fatty acid profile in preterm neonates. The study included neonates born at a gestational age of <32 weeks, with a birth weight <1500 g, admitted to the neonatal intensive care unit (NICU) within 12 hours after birth. Exclusion criteria included anticipated parenteral nutrition (PN) needs accounting for >70% of total daily energy for <10 days, intrauterine infection, perinatal asphyxia, or congenital abnormalities.

Ultimately, 92 preterm infants participated in the study and were divided into an intervention group and a control group. The intervention group received an intravenous fat emulsion (IVFE) enriched with medium-chain triglycerides (MCT) and ω-3 PUFAs. The control group received a placebo in the form of a soybean oil-based IVFE.

The primary outcome was to detect clinically significant differences in plasma levels of ω-3 PUFAs, ω-6 PUFAs, and EPA (eicosapentaenoic acid) between the MCT/ω-3 PUFA IVFE group and the control group. Secondary outcomes included significant changes in serum IL-6 levels, the plasma ω-6/ω-3 PUFA ratio, and levels of linoleic acid (LA), DHA, and oleic acid.

The study demonstrated that after 15 days of intervention, parenteral supplementation with MCT/ω-3 PUFA IVFE significantly increased total plasma levels of ω-3 PUFAs, EPA, and oleic acid compared to the control group. Additionally, the ω-6/ω-3 PUFA ratio and ω-6 PUFAs were significantly lower in the intervention group than in the control group. The control group exhibited higher increases in LA and alpha-linolenic acid (ALA) levels. The type of fat emulsion administered did not significantly influence changes in serum IL-6 levels.

In summary, the alteration of the plasma fatty acid profile, particularly the increase in ω-3 PUFAs, appeared to improve inflammatory markers in preterm neonates, especially in the intervention group. This suggests a beneficial effect of these fatty acids in reducing inflammation.

Wendel and colleagues [12] conducted a study analyzing the effects of arachidonic acid (ARA) and docosahexaenoic acid (DHA) supplementation on early inflammation in preterm infants, aiming to identify inflammatory factors involved in early inflammatory states. The study included 120 preterm infants born before 29 weeks of gestation. Exclusion criteria were congenital developmental abnormalities, chromosomal anomalies, or critical illness with a short life expectancy.

Infants in the intervention group received an enteral supplement (Formulaid™, DSM Nutritional Products Inc.) containing 100 mg/kg ARA and 50 mg/kg DHA, while the control group was given medium-chain triglycerides (MCT-oil™, Nutricia). Fatty acid supplementation was administered as a daily bolus via feeding tube starting from the second day of life until 36 weeks postmenstrual age. The nutritional approach did not differ between the groups.

The analysis revealed significantly lower blood IL-6 levels in the intervention group compared to the control group. Additionally, on days 3 and 5 of supplementation, TNF-α levels were significantly lower in the intervention group. By day 14, IL-1β concentrations were also significantly reduced in the intervention group compared to the control. However, the study did not find a statistically significant association between ARA blood levels and IL-6, IL-8, IL-1β, or TNF-α levels from birth to day 28 of life.

In conclusion, the study demonstrated that daily ARA and DHA supplementation in preterm infants led to a significant reduction in IL-6 levels from day 3 to day 28 compared to the placebo group.

Discussion

All the studies discussed above demonstrate that supplementation with polyunsaturated fatty acids (PUFAs) in preterm infants reduces inflammatory markers. Research has consistently shown that PUFA supplementation lowers IL-6 levels [13], a cytokine considered a risk factor for sepsis in preterm infantsenomenon has also been confirmed in in vitro studies, where PUFAs were shown to decrease IL-6 expression in macrophages activated by polysaccharides [14]. Similaoliakou and colleagues [15] showed that administering medium-chain triglycerides (MCT) and ω-3 PUFAs to preterm infants results in cytokine and fatty acid profiles consistent with attenuated inflammatory responses.

Furthermore, Ramiro-Cortijo et al. [16] demonstrated that PUFA supplementation reduces oxidative stress, highlighting another beneficial effect of these fatty acids in neonatal care . These findings offer a non for managing preterm infants, who are more susceptible to inflammation due to their physiological immaturity and the high prevalence of health complications in this population.

Recent guidelines by the *European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN*) [17] recommend high daily enteral intake of both arachidonic acid (AA) and docosahexaenoic acid (DHA) for infants born with a birth weight below 1800 g . This recommendation aligns with egesting that PUFA supplementation plays a critical role in modulating inflammatory responses in preterm neonates.

Hellström and colleagues [18] provided further insights by showing a significant association between DHA serum levels and inflammatory responses in preterm infants during the first days of life. Their study examined DHA and AA levels, whi-chain PUFAs (LCPUFAs), in relation to inflammatory markers. They found that preterm infants with lower DHA and AA levels had elevated IL-6 levels, a pro-inflammatory cytokine crucial for initiating and regulating inflammatory processes.

IL-6 is a marker of inflammation, and its elevated levels indicate heightened inflammatory responses. This is especially significant for preterm infants, whose immune systems are underdeveloped. The findings suggest that low DHA and AA levels may disrupt the balance between pro-inflammatory and anti-inflammatory responses, potentially leading to adverse health outcomes, including a higher risk of inflammation-related complications during the neonatal period.

In summary, supplementation with PUFAs, particularly DHA and AA, is a promising strategy for reducing systemic inflammation and improving outcomes in preterm infants. These findings reinforce the importance of including these fatty acids in neonatal nutrition, particularly for those at the highest risk of inflammatory complications.

Long-chain polyunsaturated fatty acids of the omega-6 and omega-3 series play a critical role in modulating the immune system through diverse biological mechanisms. It has been demonstrated that they possess the capacity to alter the activity of signaling proteins within immune cells, such as kinases and receptors, which regulate inflammatory processes, lymphocyte differentiation, and immune responses. Additionally, certain fatty acids, such as docosahexaenoic acid (DHA) and arachidonic acid (AA), are integral components of phospholipids that form the structural framework of cellular membranes. This structural role enables them to influence the functionality of receptors, transporters, and protein complexes responsible for intercellular signal transduction [19, 20, 21].

These multifaceted actions render LC-PUFAs pivotal not only for maintaining immune homeostasis but also for the prevention and management of diseases associated with chronic inflammation, including autoimmune, metabolic, and cardiovascular disorders.

Future research should focus on the long-term effects of fatty acid supplementation on the development of preterm infants, particularly concerning their immune system and the risk of chronic inflammatory diseases. Studies aimed at determining the optimal dosages and combinations of fatty acids to provide the most effective protection against inflammation in preterm infants will also be of paramount importance.

In summary, supplementation with polyunsaturated fatty acids holds potential for modulating inflammatory processes in preterm infants, with efficacy likely influenced by factors such as the specific type of fatty acid used, timing and form of administration, and individual variations in response. However, further research is required to fully elucidate the mechanisms underlying these supplements and their long-term impact on the health of preterm infants.

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The author declares no conflict of interest.

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