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EXPLORING THE EFFECTS OF POLYUNSATURATED FATTY ACIDS ON LIPID METABOLISM AND RENAL FUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE: A NARRATIVE LITERATURE REVIEW

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Abstract: Objective: To investigate the effects of omega-3 polyunsaturated fatty acids on lipid metabolism and renal function in patients with chronic kidney disease. **Methodology**: Narrative review of experimental and observational studies, using the Pubmed database and descriptors *omega 3 fatty acids*, *chronic kidney disease*, *kidney function* and *lipid managemen*t, in the period from 2013 to 2023. A total of 70 articles were identified and, after applying the inclusion and exclusion criteria, 15 studies were selected for analysis. **Results:** Depletion of omega-3 fatty acid levels in patients with chronic renal failure has been suggested as a possible cause of an inflammatory state. Therefore, the hypothesis of n-3 PUFA supplementation emerged as a potential strategy to mitigate inflammation in individuals with CKD. Thus, polyunsaturated fatty acids have been recommended with the aim of intervening in the progression of chronic renal failure. **Final considerations:** The correlation between polyunsaturated fatty acids, particularly omega-3, and the positive impact on lipid metabolism and kidney function in patients with chronic kidney disease is well established.
Keywords: Omega 3 fatty acids; Chronic Kidney Disease; Renal Function; Lipid Management.

INTRODUCTION

Chronic kidney disease (CKD) is a global public health challenge (HU C. et al., 2018), affecting approximately 700 million people worldwide. The global prevalence is estimated to be around 1 in 11 people in the general population (ONG et al., 2023). CKD is characterized by a gradual loss of kidney function, eventually culminating in kidney damage and failure, thus reducing the patient's life expectancy and quality of life (KOCHAN et al., 2021). CKD patients suffer from chronic inflammation, oxidative stress

and various metabolic abnormalities, thus increasing the risk of cardiovascular disease (CVD), the leading cause of death in this group (KOCHAN et al., 2021; MAGLIOCCA G. et al 2022).

One of these metabolic abnormalities is dyslipidemia, which worsens as the disease progresses (KOCHAN et al., 2021). Patients with CKD have a 20-30% higher prevalence of atheromatous plaques, a prevalence that increases as CKD progresses (KOCHAN et al., 2021). From a general perspective, individuals with chronic kidney disease have a chronic and extensive inflammatory state, full of metabolic changes - such as hypertriglyceridemia - which are risk factors for cardiovascular events (ONG et al., 2023; KOSUGI et al., 2021). This inflammatory picture, even if to a small extent, was pointed out as a possible justification for the progression of renal failure.

Supplementation with omega-3 polyunsaturated fatty acids (n-3 PUFA) has been proposed as a means of reducing inflammatory markers and controlling hypertriglyceridemia in patients with CKD, despite the evidence being limited (HU C. et al., 2018; ONG et al., 2023). Some studies, however, did not find a significant reduction in the inflammatory state or the number of cardiovascular events with this supplementation (KOCHAN et al., 2021; HU J. et al., 2017). Therefore, the control of inflammation through the supplementation of long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) can bring cardiometabolic advantages and be a great ally in the clinical management of CKD progression (ONG et al., 2023; HU et al., 2017).

Given this scenario, this narrative review aims to investigate the effects of omega-3 polyunsaturated fatty acids on lipid metabolism and renal function in patients with CKD. In addition, the review seeks to elucidate the molecular and physiological mechanisms that contribute to these effects and discuss possible clinical and therapeutic implications.

METHODOLOGY

This is a narrative review of experimental and observational studies, which seeks to understand the molecular and physiological effects of omega-3 polyunsaturated fatty acids on lipid metabolism and renal function in patients with chronic kidney disease, as well as to discuss possible implications clinics and therapies. For the development of the research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "How do omega-3 polyunsaturated fatty acids affect lipid metabolism and renal function in patients with chronic kidney disease, and what are the underlying mechanisms of such affectation? The searches were performed through searches in PubMed Central (PMC) databases. Four descriptors were used: *omega 3 fatty acids, chronic kidney disease, kidney function, lipid management*, associated through boolean operators. The search strategy used was: *(omega 3 fatty acids) AND (chronic kidney disease) AND ((kidney function) OR (Lipid management))*. The inclusion criteria were: articles in the English language, published from 2013 to 2023 and that addressed the themes proposed for this research, review, observational and experimental studies, available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. After associating the descriptors used in the searched databases, a total of 70 articles were found. After applying the inclusion and exclusion criteria, 15 studies were selected to compose the collection.

RESULTS

CKD AND LIPID METABOLISM

Dyslipidemia represents one of the most significant risk factors associated with chronic kidney disease (CKD). Commonly, patients diagnosed with CKD exhibit reduced levels of high-density lipoproteins (HDL-C), increased levels of triglycerides (High-TG) and, in cases of severe proteinuria, an increase in levels of lipoproteins of low density (LDL-C). These disturbances in lipid metabolism may contribute to the increased cardiovascular risk (CVR) in this group of patients (KOSUGI T. et al., 2021). It is evident that the metabolism of lipoproteins is influenced by CKD, given that such patients have an increase in concentrations of monounsaturated fatty acids (MUFA) and a decrease in polyunsaturated fatty acids (PUFA). This depletion has been correlated with an increase in RCV (KOCHAN Z. et al., 2021).

In situations where there is a reduction in renal function, there is a consequent increase in oxidative stress, thus leading to increased oxidation of circulating lipids. This oxidative process results in oxysterols, malondialdehyde and oxidized HDL and LDL particles, which enhances the atherogenic character. Additionally, the reduction in phosphatidylcholines, sulfatides and ceramides in LDL particles, associated with an increase in N-acyltaurins, contributes to the formation of atheroma. Atherosclerosis may also be favored by the increase in Lp(a), a lipoprotein similar to LDL, which contains a single molecule of apolipoprotein B (ApoB). Lp(a) tends to increase in the early stages of CKD due to its reduced clearance, being able to competitively inhibit fibrinolysis, which would predispose to thrombosis and atherosclerosis (FERRO C. J. et. al. 2018).

Changes in the mechanisms of hepatic lipases, which degrade lipoproteins, also interfere with cholesterol metabolism. In particular, triglyceride lipase dysfunction can lead to the accumulation of triglyceride-rich lipoproteins in the body of individuals in advanced stages of chronic renal failure. Thus, patients in less advanced stages of the disease are less likely to have dyslipidemia and hypertriglyceridemia (ISEKI K., 2014).

Although there is a clear association between CKD and dyslipidemia, it is recognized that several factors such as age, inflammatory status and nutritional status of the individual are also involved. The heterogeneous relationship of these variants manifests itself in a complex way in the pathophysiology of patients with CKD. From this analysis, it is understood that the intervention must be multifactorial with the objective of reducing morbidity and mortality associated with the disease (NAKANO T. et al., 2021).

OMEGA-3 FATTY ACIDS AND INFLAMMATION IN SDB

Chronic kidney disease (CKD) is characterized by the gradual loss of kidney function, which can occur over months to years. Its main causes include diabetes, nephroangiosclerosis, infectious processes, reduced renal blood flow and urinary tract obstruction. The classification of CKD is based on stages of evolution, with stage 1 being the lightest and stage 5 being the most severe (TUROLO S. et al., 2017). This pathology presents a wide heterogeneity in its manifestations, being associated with an inflammatory and oxidative process, resulting in elevated levels of CRP, IL-6 and elevated TNF-alpha (FAZELIAN S. et al., 2021; VALLE FLORES J. et al, 2020). During the disease, there is a change in the levels of polyunsaturated fatty acids, especially omega-3 fatty acids, which play anti-inflammatory and antioxidant functions in

the body, in addition to playing an important role in renal hemodynamic regulation and glomerular filtration (SAGLIMBENE V. M. et al., 2020).

Omega-3 fatty acids are made up of long-chain polyunsaturated fatty acids, including α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These acids can be obtained through food, with ALA present in vegetable oils such as linseed, canola, olive oil and nuts, while EPA and DHA are found in greater quantities in marine oils and fish, such as tuna, salmon and trout (HU C et al., 2018).

Such compounds play a significant role in reducing the inflammatory process. EPA and DHA inhibit the formation of prostaglandins and leukotrienes derived from arachidonic acid, in addition to producing pro-resolution mediators, such as resolverins, protectins, and maresins, which play a significant role in controlling inflammation (YOUNG K. et al., 2019; MAGLIOCCA G. et al 2022). Active metabolites of DHA, such as resolverins, facilitate the termination of inflammation in the early stages. In addition, omega-3 acid regulates the immune and inflammatory response, decreasing the synthesis of pro-inflammatory cytokines, such as Interleukin-1 (IL-1), Interleukin-6 (IL-6) and TNF-alpha (HU C et al., 2018).

Supplementation of omega-3 fatty acids has been associated with positive effects on the course of chronic kidney disease. Such compounds act directly as antioxidants, combating the production of reactive oxygen species (ROS) that are increased in chronic diseases. In addition, they exert an indirect action by modulating the intestinal microbiota, which influences the body's inflammatory process (FERRO C. J. et al., 2018). Several studies have shown the benefits of omega-3 fatty acids in controlling the inflammatory process in patients with chronic renal failure. One of these studies analyzed the effects of oral omega-3 fatty acid supplementation at a dose of 1.3 g/day for 3 months and demonstrated a reduction in CRP concentrations. Another study used a dose of 1,800 mg/day for 4 months and observed a significant reduction in CRP and IL-8 levels (VALLE FLORES J. et al., 2020).

These compounds are considered useful in individuals at high risk of inflammatory diseases, due to their ability to control the inflammatory process and reduce oxidative stress (VALLE FLORES J. et al., 2020, YOUNG K. et al., 2019). A prospective, randomized, double-blind study carried out in patients with CKD on hemodialysis demonstrated that oral ingestion of omega-3 fatty acids contributed to the reduction of inflammatory mediators. Participants were divided into two groups, with group A receiving 4 capsules of 2.4 g of omega-3 fatty acids daily for 12 weeks, while group B received paraffin oil capsules as a control. During the study, general aspects of the patients, nutritional indicators, inflammatory markers and markers of kidney disease were evaluated. The results showed reductions in serum levels of C-reactive protein, Interleukin-6 and tumor necrosis factor alpha in group A, in addition to a decrease in the interleukin 10/ interleukin 6 ratio after 12 weeks. In group B, no significant changes were observed in inflammatory markers (VALLE FLORES J. et al., 2020). Accordingly, several randomized clinical trials have shown that omega-3 fatty acid supplementation improves the lipid profile, controls heart rate and reduces systemic inflammation (SAGLIMBENE V. M. et al., 2020). Such supplementation is also associated with a lower risk of progression to end-stage renal failure (HU J. et al., 2017).

Linoleic acid (ALA), an essential fatty acid, can be converted by enzymes into longer-chain omega-3 fatty acids such as EPA and DHA,

but this conversion occurs at a slow rate. In addition, ALA has a higher rate of oxidation compared to other fatty acids. Therefore, eating seafood as a source of omega-3 fatty acids may be more beneficial for kidney health than just using plant-derived oils (FAZELIAN S. et al., 2021).

Adding oral supplements containing omega-3 fatty acids to the diet has also been shown to have positive effects on factors related to cardiovascular disease. Controlled randomized studies have shown a reduction in blood pressure, an important risk factor in the development of chronic kidney disease, and also a slowdown of CKD progression in already affected patients (ONG K.L. et al., 2023).

An analysis of 19 cohorts of more than 25,000 patients showed that higher levels of omega-3 fatty acids found in seafood are associated with an 8% lower risk of CKD incidence and a slower decline in kidney function (FAZELIAN S et al., 2021).

FINAL CONSIDERATIONS

Polyunsaturated fatty acids, particularly omega-3, have a beneficial effect on lipid metabolism and kidney function in patients with chronic kidney disease. This fruitful relationship was evidenced during the investigation of the underlying mechanisms of chronic kidney disease, identifying a strong correlation of this with chronic inflammation, oxidative stress and metabolic abnormalities that progressively exacerbate cardiovascular risk as the pathology progresses. Inserted in this scenario, several studies reveal that polyunsaturated fatty acids are capable of reducing inflammatory markers, in addition to playing a fundamental role in renal hemodynamic regulation and glomerular filtration. As a result, there is a decrease in the progression of chronic kidney disease, as well as an improvement in the lipid profile, culminating in a reduction in cardiovascular risk and, consequently, in an increase in the life expectancy of individuals with chronic kidney disease.

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