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Omega-3 Supplementation in Children with Chronic Kidney Disease

Seham Fathy Abd El-Hameed[1], Asmaa Mohammed Hosny[2], Mohammed Attia Naguib[1], Sabry Abdel Rahman Tolba[1]

[1] Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt

[2] Clinical Pathology, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Mohammed Attia Naguib

Email: attiahh8899@gmail.com

Abstract:

Chronic kidney disease (CKD) affects around 10–15% of community-dwelling children and increases their risk of cardiovascular death by 2–3 times compared with the general population. The accelerated onset of cardiovascular risk may be caused by inflammation, oxidative stress, and altered metabolism, leading to vascular calcification. Dietary and supplemental omega-3 have shown vascular benefits for the general population, but effects among people with chronic kidney disease (CKD) are largely uncertain.

Keywords: Omega 3, Fish oil, CKD, ESKD, Dialysis.

Introduction:

Omega-3 fatty acids, also written as ω-3 fatty acids, constitute a series of essential unsaturated fatty acids that have a final carbon-carbon double bond in the n-3 position (also known as the ω position), that is, the third bond from the methyl end of the fatty acid. As such, omega-3 fatty acids are commonly referred to as n-3 fatty acids (**1**).

Nutritionally important omega-3 fatty acids include the plant-derived αlinolenic acid (ALA) and the marine animal-derived eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), all of which are polyunsaturated (**2**).

The three main forms of omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Lovaza is a mixture of esters of EPA and DHA, whereas Vascepa is an ester of EPA. Different from Lovaza and Vascepa, Epanova is a mixture of free EPA and DHA (**3**).

Chemistry of Omega-3 Fatty Acids:

Omega-3 fatty acids, called *n*-3 fatty acids or ω−3 fatty acids (*n*-3 FAs), are a heterogeneous group of fatty acids with a double bond between the third and fourth carbon atoms from the methyl end (from the ω−1 carbon atom). In general, we distinguish among them monounsaturated fatty acids (MUFAs; one double bond in carbon chain) and polyunsaturated fatty acids (PUFAs; more than one double bond in carbon chain). Conjugated fatty acids (CFAs) are a subset of PUFAs with at least one pair of conjugated double bonds, i.e., the double bonds are not separated by methylene bridges, but one single bond. We also mention some examples of modified omega-3 fatty acids like hydroxy fatty acids (HFAs), oxo fatty acids (keto fatty acids) and hydroperoxy fatty acid. Among the hydroxy fatty acids, we distinguish saturated or unsaturated fatty acids, consisting of a long unbranched carbon chain with a carboxyl group at one end and one or more hydroxy groups. Oxo or keto fatty acids are fatty acids having both a carboxy group and a ketonic or aldehydic group in the molecule. Hydroperoxy fatty acids, in turn, carry at least one hydroperoxy group (-OOH) in the molecule.

Some authors find the terms long-chain (LC) *n*-3 PUFAs and omega-3 fatty acids identical in meaning (**4**), which can be misleading because ―omega-3 fatty acids‖ is a broader term.

We assumed all fatty acids with a double bond at the ω−3 carbon atom to be omega-3 fatty acids. Omega-3 fatty acids show *cis-trans* isomerism with its extension to *E-Z* configuration (**5**).

We can speak of geometrical isomerism in the case of omega-3 fatty acids because two carbon atoms with sp2 hybridization connected by a double bond are linked to a hydrogen atom and group of atoms each. In order to determine the type of geometrical isomerism, at the beginning we choose the two most important substituents—one on the left, the second on the right of the double bond. In fatty acids, we have only one group (of atoms) on each side, because the two remaining binding sites occupies a hydrogen atom. In the *cis*isomer these two groups are located on the same side of the reference plane (the plane passing through the atoms connected by a double bond and perpendicular to the plane in which these atoms and atoms directly associated with them are situated); in the *trans*-isomer they are in contrary positions (**6**).

The *E-Z* system is a bit more detailed. The mutual placement of the substituents is described by the Cahn-Ingold-Prelog (CIP) rule. The most important is the substituent whose atom directly connecting to the rest of the molecule (directly with the atom forming the double bond) has a higher atomic number (in the case of isotopes, a higher atomic mass). If in this position, in the substituents (on the right or left side of the double bond), there are identical atoms, then (to choose a substituent of greater importance) we take into account subsequent atoms, always choosing atoms with the highest atomic number. If a given atom is connected by multiple bonds, the bond should be replaced by the number of single bonds appropriate for its multiplicity—each atom present at a multiple binding must after transformation have a corresponding number of single bonds (C=C = 2 × C-C). The ―*E*‖ configuration (from entgegen, German for ―opposite‖) means that two groups of higher CIP priority (one on the left, the second on the right from the double bond) are on opposite sides of the double bond (in the synperiplanar position). If those groups are on the same side of the double bond (in antyperiplanar position), configuration is defined as ―*Z*‖ (from zusammen, German for ―together‖) (**6**).

For simplicity, according to many authors, we used the terms ―*cis*‖ and ―*Z"* as well as ―*trans*‖ and ―*E"* interchangeably. The *cis-trans* isomerism of fatty acids seems to play a particularly important role in shaping their chemical and biological activity, a good example of which are the various properties of conjugated fatty acid isomers (**7**).

Naturally occurring fatty acids usually have from four to 28 carbon atoms. However, many of them, especially those found in the brain, retina and spermatozoa, have a longer carbon chain (**6**). Fatty acids can be divided, depending on the length of the carbon chain, into four basic groups:

i. Short-chain fatty acids (SCFAs), sometimes called volatile fatty acids (VFAs), contain from one to six carbon atoms (C1–6), formed as a result of the fermentation of carbohydrates by the gut microbiota in the digestive tract of mammals (**8**).

ii. Medium-chain fatty acids (MCFAs) have from seven to 12 carbon atoms (C7–12); according to other sources eight to 14 carbon atoms (**9**).

iii. Long-chain fatty acids (LCFAs) have from 14 to 18 carbon atoms (C14– 18) and constitute the majority of fatty acids taken with food (diet) (**10**).

iv. Very long-chain fatty acids (VLCFAs) have backbones containing more than 20 carbon atoms (C > 20), or according to other authors no fewer than 20 carbon atoms (C ≥ 20) or even more than 22 carbon atoms (C > 22) (**11**).

There can also be distinguished fatty acid subgroups, such as dietary long-chain saturated fatty acids (C ≥ 16) and long-chain polyunsaturated fatty acids (LCPUFAs/LC PUFAs; C ≥ 18). While dietary long-chain

saturated fatty acids do not directly concern the subject of this article, they deserve to be distinguished in the general chemical classification due to the ease of incorporation into the adipose tissue, and therefore, *nomen omen*, special dietary significance (**12**).

Fatty acids with nine or fewer carbon atoms are in a liquid state at room temperature. The most important, but small, group of fatty acids for humans are essential fatty acids (EFAs), which are necessary to maintain homeostasis, cannot be synthesized, or rather cannot be synthesized sufficiently by the organism, and must be supplied with food (**13**).

The significance of fatty acids in the animal diet was discussed by Osborne and Mendel in 1920. In 1929 Burr and Burr proved in their experiments on rats the essential‘ nature of some fatty acids. Some authors consider all PUFAs to be essential fatty acids and determine linoleic acid (LA) and *alpha*-linolenic acid (ALA) as the most important, calling them parent essential fatty acids‖ (**14**).

Others considered only arachidonic and linoleic acids as essential fatty acids because of their importance for the body‘s growth and for maintaining the integrity of the skin (**15**).

The mammalian literature indicates 23 acids as essential, while the aquatic literature quotes only two EFAs EPA and DHA. Considering the importance of ARA, we can take ARA, DHA and EPA as the most important long-chain PUFAs in mammals and fish. Some animals can synthesize them using LA and ALA as precursors. However, those precursors must be available in sufficient quantities (**16**).

Considering that there is insufficient data showing that any individual PUFA is absolutely necessary during life, Cunnane divided essential fatty acids into conditionally indispensable‘ and conditionally dispensable‘ (**17**).

Basic Biology:

Findings from various experimental models including animals and cultured cells show that omega-3 fatty acids are anti-inflammatory molecules. In animal models, omega-3 fatty acids protect against various forms of cardiovascular injury including myocardial ischemia-reperfusion injury and doxorubicin-induced cardiotoxicity. Evidence also suggests an antioxidant property for omega-3 fatty acid likely via activating Nrf2 signaling, an essential mechanism of upregulation of antioxidative gene expression (**18**).

Notably, Nrf2 also is an anti-inflammatory regulator. Hence, it is not surprising that Nrf2-activating antioxidative molecules are usually anti-inflammatory. In addition to Nrf2 signaling, the G proteincoupled receptor 120 (GPR120) has been shown to function as an omega-3 fatty acid receptor/sensor to mediate the anti-inflammatory and insulinsensitizing effects of omega-3 fatty acids (**19**).

Human genetic and animal gene-knockout studies suggest a crucial role for GPR120 in regulating insulin sensitivity and metabolism and in antiinflammation. Activation of this receptor by omega-3 fatty acids has been demonstrated to mediate the insulin-sensitizing (e.g., increased glucose uptake) and anti-inflammatory effects of these dietary fatty acids in experimental models (**3**).

Bioavailability:

Bioavailability is a relative term, which can refer to both the speed of absorption and the quantity of the substance absorbed. The speed can be understood as the rate at which the substance is absorbed from the gastrointestinal tract and reaches the portal system. Absorption of the substance occurs in the gastrointestinal tract only to a certain extent, depending on many factors. The extent of absorption and the speed of substance transport to the portal circulation describe the bioavailability in the narrower sense. Traditionally, bioavailability can also be considered in a broader context, taking into account the amount of substance that reaches the systemic circulation or the place of physiological destiny (activity). This broader approach is particularly important when considering the effect of metabolic processes and excretion on the transport of substances from

the portal circulation. Not all of the absorbed substance reaches the systemic circulation or tissue compartment consistent with the physiological destination. This difference in amount is very important from the point of view of pharmacokinetics and dietary planning. Fatty acids may be present in the body as free fatty acids, bound to glycerol, to form triacylglycerol (TG), diacylglycerol (DAG) or monoacylglycerol (MAG), or to form a composition of membrane phospholipids. In naturally occurring TG molecules, LC PUFA occupies the second position (**20**).

In the phospholipids of cell membranes the latter position is competed by EPA and DHA with arachidonic acid, and if necessary, they are released by the enzyme phospholipase A2 and are used to synthesise eicosanoids (**21**). Otherwise, in the human brain, VLCFAs (C34–38) are attached to the skeleton of glycerol (glycerol moiety), which in phospholipids are located in the *sn*-1 position (**22**).

In fish and fish oils, LC omega-3 PUFAs are mainly found as triacylglycerides and free fatty acids (**23**).

In Krill oil phospholipids are also an important fraction of these fatty acids (30–65% of EPA and DHA), mainly phosphatidylcholine (**24**).

EPA and DHA represent approximately 18% and 12%, respectively, of the content of naturally occurring fish oils (**20**).

However, due to the transesterification process, oil blends often contain much more of both EPA and DHA. This process is related to the substitution of the removed glycerol backbone with ethanol, resulting in the formation of ethylesters (EE), which can then be converted to re-esterified TG (rTG)ethanol is enzymatically removed, resulting in free fatty acids being released, then attached by enzymes back to the glycerol backbone. An example of a drug in which the content of EPA (DHA) is increased as a result of transesterification is Lovaza. Another method to increase the content of EPA and DHA has been used in Epanova. Glycerol is removed and replaced with a hydrogen atom, which, in combination with the released fatty acid, forms a carboxylic acid. Ethylesters (of which Lovaza is composed) require the hydrolysis of the ester bond by pancreatic lipase before they release the free fatty acids that can be absorbed in the small intestine. This step is not required by the carboxylic acids. Interestingly, EPA and DHA-EE are also absorbed unchanged. However, this form accounts for < 1% of the total pool of EPA and DHA in circulation after ingestion of omega-3 acids EE (**23**).

In rTG, LC PUFAs take up not mainly the *sn*-2 position (which takes place in natural TG), but can also (simultaneously) be bound in the position of *sn*-1 or *sn*-3 with equal paradigmicity. rTG particles frequently contain two LC PUFAs—then the probability of binding EPA and DHA in the *sn*-1 or *sn*-3 position is higher than in the *sn*-2 position. According to **Schuchardt and Hahn, (20**) binding of LC omega-3 PUFA to glycerol in the *sn*-1/3 position facilitates the lipase hydrolysis of the bond, thus increasing bioavailability. **(20**)

According to **Dyerberg et al., (25**) the presence of MAG and DAG in rTG mixtures increases the absorption of LC PUFAs in the intestine due to the easier formation of micelles.

Bandarra et al., (26), in turn, based on the results of his research on hamsters, proves that the location of DHA in the *sn*-2 position increases the absorption of this acid in the intestine and its incorporation into tissues.

However, a certain limitation of Bandarra‘s study is that the author used a commercially available fish oil, which is known only to be rich in DHA with an unspecified binding site with the glycerol backbone—we do not know what part of DHA is associated in positions other than *sn*-2.

Methods of Measuring the Bioavailability of Omega-3 Fatty Acids:

We can measure omega-3 FAs concentration in plasma, serum, blood cells and lymph. The content of FAs in the plasma reflects the short to medium-long supply of fatty acids in the diet, while the concentration of fatty acids in the blood cells is usually a good indicator of long-term bioavailability (**27**).

As far as the long-chain omega-3 fatty acids are concerned, it is possible to measure many markers that indicate the presence of DHA in a specific form, but only one (the level of phospholipid EPA in plasma) that is useful for determining the level of EPA. Admittedly, erythrocyte EPA is a weak dosedependent indicator of LC omega-3 PUFAs substitution at normal dietary levels, however (sum of), erythrocyte EPA and DHA concentration seems to be, as will be mentioned below, a relatively good indicator of long-term bioavailability and also reflects the content of LC omega-3 PUFAs in nonblood tissues (**20**).

In Browning‘s study, (**28**) EPA + DHA-PC (in the case of sudden changes in intake) and platelet/mononuclear cells EPA + DHA (in the case of long-term consumption assessment) were considered biomarkers that best represent the intake of fish with high fat content in a typical UK population (1–4 servings a week).

Brain Transport:

Omega-3 acids are incorporated into the cell membrane of many organs and tissues, above all the heart, nervous tissue and retina (**20**).

Oral supplementation with omega-3 PUFAs increases the content of these acids in the cerebrospinal fluid. Efficient passage of the blood-brain barrier, however, requires carrier particles in the case of DHA, it is 1-lyso, 2-docosahexaenoyl glycerophosphocholine (LysoPC-DHA), which increases intracerebral DHA transport up to 10-fold. It is a brain-specific particle and does not facilitate the transport of DHA to the heart, liver or kidney, although detailed studies are required in humans. Carriers (transporting DHA to the brain) with potentially better properties are synthesized, an example of which is obtaining of AceDoPC (1-acetyl,2-docosahexaenoyl-glycerophosphocholine) (**29**).

Parenteral Administration:

Most of the studies, especially those based on humans, which serve to determine the bioavailability of omega-3 acids, apply to their oral administration. It is difficult to fully validate the parenteral administration of omega-3 fatty acids in relation to the healthy population, because this method of supply is reserved mainly for patients undergoing intensive therapy, both adults and preterm infants (**30**).

In addition, it is worth noting that parenteral administration of mixtures based on fish oil may lead to biochemical liver damage and even the progression of fibrosis in this organ (**31**).

Al-Taan et al., (32) conducted a study on 20 patients awaiting the surgical removal of colorectal metastases from liver cancer. These individuals had normal liver function tests and plasma lipid levels within the reference range. The aim of the study was to assess the content of fatty acids in plasma phosphatidylcholine and erythrocytes during and after intravenous infusion of oil emulsion. Phosphatidylcholine (PC) is the main phospholipid that can be found in the circulation (blood) and erythrocyte (membrane) during and shortly after intravenous infusion of the oil emulsion. Parenteral administration of DHA and EPA lipid emulsion allowed a rapid and significant increase in their blood levels (EPA/DHA in plasma PC and EPA in erythrocytes). However, EPA levels returned to their initial values five–12 days after the end of the infusion. Not only Al-Taan, but also **Browning et al., (28**), suggested a quicker turnover of EPA than DHA in cells, and thus this effect occurs with both oral and intravenous supply, with a different time of administration. The fact of a relatively short infusion of oil emulsion is also significant.

Clinical Use:

Besides the anti-inflammatory and antioxidative properties of omega-3 fatty acids, reduction of triglycerides in individuals with severe hypertriglyceridemia by large dosages of these fatty acids is well established. Indeed, the US FDA has approved three pharmaceutical preparations of large dosages of omega-3 fatty acids, namely, Lovaza, Vascepa, and Epanova, for treating severe hypertriglyceridemia (≥ 500 mg/dl). At the recommended dosage of 4 g daily, these omega-3 fatty acid-based drugscanreduce blood triglyceride levels by ~20–50%. The mechanisms by which omega-3 fatty acids at high dosages reduce triglycerides remain elusive. It has been suggested that the triglyceride-lowering effect of omega-3 fatty acids may result from the inhibition of acyl-CoA: 1,2-diacylglycerol acyltransferase (DGAT, an important enzyme in triglyceride biosynthesis) and activation of lipoprotein lipase (an important enzyme in triglyceride hydrolysis), as well as increased oxidation of fatty acids (fatty acids as building blocks for triglyceride synthesis). Whether GPR120 is involved in the triglyceride-lowering effect, however, remains unknown. (**3**)

Effect of Omega-3 Supplementation on Lipid Profile and Inflammatory Markers in Children with Chronic Kidney Disease:

Omega-3 fatty acids have shown promise in modifying a host of disease processes involving the inflammatory pathways, arteriosclerosis and CVD, cardiac dysrhythmias, and lipid regulation (**33**).

El-Shinnawy et al., (34) reported that omega-3 resulted in a significant decrease in serum TG levels, TC levels, and LDL levels and an increase in HDL levels in their prospective case–control study conducted on 80 chronic hemodialysis adult patients selected from the El-Maadi Liver and Kidney Transplantation Hospital in Egypt (range: 40–60 years). The experimental group received four capsules of omega-3 per day (each capsule contain 1000 mg omega-3) for 6 months.

Also **Movahedian et al., (35**) reported a significant reduction in the levels of TG and very LDL with a marked elevation of HDL levels in their interventional study on 42 hyperlipidemic men with ESRD on regular hemodialysis, with ages from 35 to 70 years who were daily treated with 2000 mg of omega-3 for 3 months.

Also, **Zhu et al., (36**) in their systematic review and meta-analysis of RCTs on the effects of fish oil on serum lipid profile in dialysis patients as they reported that fish oil supplements reduced serum TG levels and TC levels and increased HDL levels among dialysis patients. Also **Chi et al., (37**) in their systematic literature search to identify the relevant RCTs that investigated the effects of omega-3 supplementation on dialysis patients (a total of 678 patients from 14 trials were subjected to meta-analysis) and reported that omega-3 supplementation could significantly decrease the levels of serum TG and LDL.

On the other hand, **Omrani et al. (38**) in their randomized clinical trial study on 60 chronic hemodialysis patients (mean age: 55 years) reported that a dose of 1 g/day of omega-3 capsules for 10 weeks received by hemodialysis patients only showed significant decrease in serum TC level, but not other lipids.

Elshafie et al. (39) in their clinical trial on 23 children with ESRD undergoing hemodialysis, these patients received 1 g omega-3 per day for 3 months, as they reported that there were statistically highly significant differences between the level of TGs before and after supplementation with omega-3 fatty acid although there were nonstatistically significant difference in LDL, HDL, and TC levels.

Using a low dose of omega-3 (1 g/day) in **Elshafie et al. (39**) studies may be a possible explanation for the difference in the effect of omega-3 on lipid profile between their studies.

Tayyebi-Khosroshahi et al. (40) reported that 3 g of Omega 3 per day for three months in chronic HD patients showed a reduction of inflammatory markers (CRP and IL-6).

Furthermore, **Dashti et al. (41**) reported in their study that 1800mg of Omega-3 fatty acids per day for 4 months relatively improved highsensitivity CRP and IL-6 of chronic HD patients.

Furthermore, **Daud et al. (42**) reported that in chronic HD patients, 2.4 g Omega 3 after their routine dialysis session for six months had beneficial effects on CRP levels.

Fiedler et al. (43) reported that using of only high doses of Omega 3 for a longer time could decrease inflammatory marker levels of CKD patients on regular HD.

Svensson et al. (44) studied 206 hemodialysis adult patients in 11 hospitals in Denmark in a double-blinded clinical trial. They showed that daily intake of two 1.7 g capsules of omega 3 for 6 months led to a significant reduction in serum triglyceride levels without any clear effect on total cholesterol levels, HDL-c, and LDL-c.

Madsen et al. (45), who carried out a randomized, double-blind, placebo-controlled study. They found a trend toward a reduction in hs-CRP in the n-3 PUFA group, but there was no significant difference in hs-CRP levels when both groups were compared.

Bowden et al. (46) reported that consumption of 960 mg/day of EPA and 600 mg/day of DHA led to lower CRP levels. However, low-dose omega-3 fatty acids had no effect on the plasma hs-CRP levels.

Rasic-Milutinovic et al. (47) studied the effects of omega-3 fatty acid (2.4 g/day) administered for 8 weeks in 35 patients with CRF on maintenance HD. There was a significant decrease in the levels of hs-CRP ($P = 0.01$).

Svensson et al. (44) showed that levels of Hb, ferritin, PTH, total LDL-c, and HDL-c before and after supplementation with omega-3 fatty acid did not show significant differences.

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