Polyunsaturated fatty acids and metabolic health: novel insights

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Abstract

Purpose of review: This review aims to discuss the potential roles of omega-3 (ω-3) and omega-6 (ω-6) polyunsaturated fatty acids (PUFAs) in the prevention and treatment of metabolic diseases, to provide the latest evidence from epidemiological and clinical studies, and to highlight novel insights into this field.

Recent findings: Higher dietary or circulating ω-3 PUFA levels are related to a lower risk of metabolic syndrome. Novel findings in obesity indicate higher proportions of ω-6 and ω-3 PUFAs, a modulated oxylipin profile and an altered transcriptome in subcutaneous white adipose tissue, that seem resistant to the effects of ω-3 PUFAs compared with what occurs in normal weight individuals. ω-3 PUFAs may improve the blood lipid profile and glycemic outcomes in patients with type 2 diabetes mellitus and reduce liver fat in non-alcoholic fatty liver disease; the findings of several recent meta-analyses support these effects. Genetic background affects inter-individual variability in the insulin sensitivity response to ω-3 PUFA supplementation. ω-3 PUFAs have prebiotic effects, altering the gut microbiota.

Summary: Although evidence for health benefits of ω-3 PUFAs is strong, recent findings suggest a more personalized approach to ω-3 PUFA intake for individuals at high risk for metabolic diseases.

Key words: Metabolic diseases, Risk factors, Omega-3, Omega-6, Diabetes

Introduction

Metabolic syndrome (MetS) is a multifactorial disease that includes various health issues such as abdominal obesity, dyslipidemia, insulin resistance (IR) and hypertension [1*]. Altered lipid metabolism and glycemic control appear to be major risk factors in developing non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) [2, 3]. Furthermore, oxidative stress, systemic inflammation, gut dysbiosis, cytokines, adipokines, hepatokines and genetics make a large contribution to complex metabolic disturbances [4]. Together with promoting a healthy lifestyle and a more personalized medication approach, there is growing interest in the use of nutraceuticals and dietary supplements in the treatment or co-treatment of cardiometabolic disease and related features such as dyslipidemia [5*]. The 2019 European Society of Cardiology/European Atherosclerosis Society Guidelines list several nutraceuticals and nutritional supplements including phytosterols (i.e., sterols and stanols), red yeast rice extract, dietary fibers, and omega-3 (ω-3) fatty acids to be considered for the management of dyslipidemias [6]. However, the most relevant and recent American and European guidelines do not encourage any nutraceutical or food supplement approach concerning obesity due to insufficient safety and efficacy data (see [5*] for references). Although several nutraceuticals have been suggested for glycaemic control, alone or as an adjunct to standard medical care (e.g., berberine, *Morus alba* extract) [7, 8], the updated Standards of Medical Care in Diabetes has not supported the implementation of any nutraceutical or supplement products in the management of type 2 diabetes mellitus (T2DM) [9]. This is similar to a consensus report published in 2018 by the American Diabetes Association and the European Association for the Study of Diabetes [10]. Despite a lack of consensus on the recommendation for patients at high cardiometabolic risk, ω-3 and omega-6 (ω-6) polyunsaturated fatty acids (PUFAs) have been recognized to offer multiple mechanisms of action to counteract a cluster of metabolic

disorders. The aim of this article is to discuss the role of PUFAs in the prevention and treatment of metabolic diseases, reviewing the latest evidence and highlighting novel insights in this field.

Epidemiology of polyunsaturated fatty acids and metabolic health

Much evidence has accumulated from prospective and case-control studies indicating that a higher intake of long-chain PUFAs, especially ω-3 PUFAs, is related to an improved profile of risk factors of MetS. These studies have been summarized in systematic reviews and meta-analyses and are discussed in detail elsewhere recently [11*]. For example, early epidemiological data showed that Greenland Inuit had a much lower prevalence of cardiometabolic disease, including diabetes mellitus and atherosclerosis, considered to be the result of the high ω-3 PUFA content and more optimal ω-6/ω-3 PUFA ratio of their traditional diet. However, over the last half-century, due to lifestyle changes (e.g., replacing traditional with imported foods, being sedentary) and possibly gene-lifestyle interactions, the Inuit in Greenland have experienced a significant rise in incidence and prevalence of obesity and metabolic disorders [12]. A recent meta-analysis of data from cross-sectional and case-control trials identified that higher blood levels of ω-3 PUFAs are associated with a lower risk of MetS [13]. Another meta-analysis pooled results from prospective cohort studies and confirmed that higher dietary or circulating ω-3 PUFA levels were associated with 26% lower MetS risk than lower dietary or circulating levels (odds ratio (OR)/relative risk (RR) 0.74; 95% confidence interval (CI) 0.62, 0.89) [14*]. Interestingly, docosahexaenoic acid (DHA) appeared to have greater effectiveness (OR/RR 0.66; 95% CI 0.49, 0.88) than other ω-3 PUFAs (i.e., alpha-linolenic acid (ALA), docosapentaenoic acid (DPA) and eicosapentaenoic acid (EPA)), which did not show significant effects. Also, null results were observed concerning the association between circulating or dietary ω-6 PUFAs and MetS. However, a recent meta-analysis of cohort studies evaluated the association between intake of PUFAs and incidence of T2DM, and found

that DHA increased risk while the ω-6 linoleic acid (LA) decreased risk of T2DM (RR 1.164; 95% CI 1.048 to 1.294 and RR 0.956; 95% CI 0.930 to 0.983, respectively) [15*]. A de novo pooled analysis of 17 prospective cohort studies with 42,466 individuals reported the association between a lower risk for death from cardiovascular disease in patients with the highest versus the lowest quintile of circulating long-chain ω-3 PUFAs [16*].

Biological actions of PUFAs

Blood triglyceride (TG) levels, blood pressure, fasting blood glucose (FBG), high-density lipoprotein (HDL) cholesterol, and insulin resistance are all improved by ω-3 PUFAs, probably explaining their protective effects on MetS and cardiovascular disease [11*]. Similarly, ω-6 PUFAs, instead of saturated fat, can positively impact blood lipid management (especially low-density lipoprotein (LDL) cholesterol) and insulin resistance [11*]. As a structural component of cell membranes, bioactive PUFAs act through various mechanisms influencing the function of membrane proteins, intracellular signalling pathways and gene expression, and altering the production of lipid mediators (i.e., eicosanoids and docosanoids) [17]. Oxylipins are bioactive metabolites generated from PUFAs, including EPA and DHA and the ω-6 PUFA arachidonic acid (AA), through enzymatic and non-enzymatic oxidation [18, 19*, 20, 21*]. Enzymatic oxidation of ω-3 and ω-6 PUFAs shares the same enzymes, i.e., lipooxygenases (LOXs), cyclooxygenases (COXs), and cytochromes P450 (CYP-450) [18, 19*, 20, 21*]. These enzymes are expressed in various cells and tissues. Oxylipins may act as both pro- and anti-inflammatory molecules [20, 21*]. Although oxylipins are triggered in response to inflammatory stimuli, a recent study reported that these same stimuli also programme their removal, for example by upregulation of mitochondrial β-oxidation [22*]. In general, an increased presence of ω-3 PUFAs in cell membranes leads to an increased generation of less-inflammatory and pro-resolving mediators as a result of LOX and COX action on ω-3 rather

than ω-6 PUFAs [20, 23, 24]. Uncontrolled (unresolved) inflammation and continuous release of pro-inflammatory mediators can cause metabolic changes, tissue damage, and loss of function, and oxylipins produced from EPA and DHA are able to both prevent and reverse these effects [25*]. For example, pro-inflammatory activities of AA-derived oxylipins lead to altered lipid metabolism and remodelling and expansion of adipose tissue (see [26*] for references). On the other hand, reduced inflammatory actions and pro-resolving activities of oxylipins derived from EPA and DHA, so-called specialized pro-resolving mediators (SPMs), better regulate the expression of inflammatory cytokines [25*, 27*]. SPMs have been described in human blood and other fluids including breast milk and in human tissues [28*]. The production of SPMs is favoured by the higher EPA and DHA status brought about by increased oral intake of these fatty acids [28*]. SPMs may be responsible for many of the biological actions ascribed to EPA and DHA [28*]. DPA is also a substrate for synthesis of SPMs [29]. Recent findings suggest that genetic/pharmacological targeting of carnitine palmitoyl transferase 1, enhances oxylipin removal via mitochondrial β-oxidation independently of oxidative phosphorylation and energy production [22*]. Upregulation of many genes is observed in a regulatory metabolic checkpoint for oxylipins during inflammation [22*]. Thus, lipidomic profiling targeting oxylipins may contribute to deeper understanding the role of these bioactive metabolites in the development and progression of human diseases. In addition to biological activities, ω-3 PUFAs appear to affect the gut microbiome [30*]. This seems to result in three related effects: altered diversity and abundance of the gut microbial community, modulated levels of pro-inflammatory molecules such as intereleukin-17 and lipopolysaccharides, and altered concentrations of short-chain fatty acids and their salts [30*, 31]. Firmicutes (F) and bacteroidetes (B) are the two major bacterial phyla representing about 90% of the human gut microbiota, and an increase in the F/B ratio due to an inappropriate diet including a high ratio of ω-6 to ω-3 PUFAs may lead to overweight, obesity, non-alcoholic fatty liver disease and CVD [32-35].

Latest clinical trials and meta-analysis of trials related to PUFA supplementation and metabolic disease

A recently published double-blind randomised controlled trial has reported novel insights into fatty acid composition, oxylipin profile and transcriptome in human subcutaneous white adipose tissue (scWAT) in obese individuals [26*]. Fifty healthy normal weight individuals and 50 individuals living with obesity were randomly assigned to receive a supplement providing 1.1 g EPA + 0.8 g DHA or corn oil (as the comparator oil) and were followed up for 12 weeks. Significantly higher proportions of ω-6 and ω-3 PUFAs in scWAT were observed in individuals with obesity compared to normal weight individuals at study entry. The proportion of EPA in scWAT was positively correlated with adipose-IR (ρ 0.248, P = 0.043) and the proportion of DPA with homeostatic model assessment of insulin resistance (HOMA2-IR) and adipose-IR (ρ 0.258, P = 0.038, and ρ 0.342, P = 0.005 respectively). Regarding the oxylipin profile of the whole scWAT, 33 fatty acid metabolites of 111 identified were significantly modified in individuals living with obesity compared to normal weight subjects; typically scWAT from indivduals with obesity has lower levels of hydroxy-DHAs and some SPMs. Proportions of several oxylipins were inversely correlated with HOMA2-IR, indicating a link between lower levels of oxylipins with increased insulin resistance [26]. The expression of the genes encoding CYP1B1, ALOX5 (which encodes 5-LOX), and PTGS1 (which encodes COX-1) was upregulated in scWAT from obese individuals. Transcriptional changes, including 622 upregulated and 174 downregulated genes in scWAT in individuals living with obesity, indicated upregulation of inflammatory and immune responses in scWAT in obesity. In addition to dysregulated expression of inflammatory and immune response related genes, nearly 20% of these genes were associated with lipid and carbohydrate metabolism and signalling which may contribute to an upregulation in the T2DM signalling pathway and interruption of whole tissue

160 homeostasis occurring in these early stages of obesity. Following 12 weeks of ω-3 PUFA
161 intervention, an altered response was noticed in individuals with obesity compared with those
162 of normal weight. Although a decrease of AA metabolites in scWAT was observed, modulation
163 of ω-3 PUFA derived oxylipins was impaired in those with obesity compared with what was
164 seen in normal weight individuals suggesting a lack of response in SPM formation and reduced
165 ability to self-resolve inflammation, even when additional ω-3 PUFAs are provided. Despite
166 the incorporation of EPA and DHA resulting in similar levels in scWAT in both groups, this
167 was not sufficient to change ω-6 and ω-3 proportions enough to promote the generation of ω-3
168 PUFA derived oxylipins or have a greater effect on gene expression in obese individuals
169 compared to normal weight individuals. In response to ω-3 PUFA supplementation, 51 and 21
170 genes were differentially expressed in scWAT in normal weight and obese individuals,
171 respectively. The modulation of these genes was linked with the overall downregulation of
172 inflammatory and immune responses as well as upregulation of glucose homeostasis in normal
173 weight individuals, with the absence of these effects in individuals living with obesity.
174 Decreased levels of SPMs and increased expression of genes associated with immune and
175 inflammatory signalling in scWAT, appear to affect whole-body homeostasis.

176 Another study reported the importance of genetic background in interindividual
177 variability in the insulin sensitivity response to ω-3 PUFA supplementation using a genetic
178 score approach [36]. Treatment was with 1.9-2.2 g EPA + 1.1 g DHA per day for six weeks.
179 HOMA-IR was used to classify participants as high or low risk depending on their HOMA-IR
180 change following the ω-3 PUFA supplementation compared to pre-treatment values (some
181 individuals (23.2%) had increased HOMA-IR after ω-3 PUFAs). Of the 210 participants,
182 genome-wide genotyping data were obtained for 138 subjects: eight gene loci had frequency
183 differences between high-risk and low risk participants and a genetic risk score (for increased
184 HOMA-IR with supplemental ω-3 PUFAs) was created. This had a predictive accuracy of 0.85

and explained 40% of the variation in HOMA-IR change. These results suggest that genetic background has a role in determining the interindividual variability observed in the insulin sensitivity response following ω-3 PUFA supplementation. The authors suggested that people at risk of insulin sensitivity lowering following ω-3 PUFA supplementation may be able to be identified using genetic-based approaches.

In a double-blind clinical trial, the effects of marine-based and plant-based ω-3 PUFAs on glucose and lipids profiles in 150 patients with T2DM were investigated [37]. Patients were randomized in three groups to receive fish oil containing 143 mg EPA and 172 mg DHA/capsule, perilla oil providing 322 mg ALA/capsule, or linseed and fish oil providing 105 mg EPA, 60 mg DHA and 140 mg ALA/capsule. All patients were supplemented with 6 capsules (3 g of oil) each day for six months. Treatment with perilla oil significantly lowered FBG while fish oil prompted a favorable reduction of serum TG levels compared to baseline values. Additionally, supplementation with ω-3 PUFAs significantly decreased serum total cholesterol, apolipoprotein A1, insulin, C-peptide and IL-6 levels in all the treatment groups compared to initial values. Hence, marine-derived and plant-derived ω-3 PUFAs showed different but overlapping effects on glucose and lipid metabolism.

The potential prebiotic effects of ω-3 fatty acids were investigated in 69 participants who were randomised to take ω-3 capsules containing 165 mg EPA and 110 mg DHA daily or 20 g of inulin fiber for a period of 6 weeks [38*]. ω-3 PUFA supplementation resulted in marked increases in Bacteroides spp and Coprococcus spp and significant decreases in the fatty-liver related Collinsella spp. On the other hand, similar to the inulin fiber arm which resulted in significant increases in butyrate, iso-butyrate and iso-valerate, ω-3 PUFA supplementation showed favorable increases in iso-butyrate and isovalerate and an almost significant increase in butyrate. Coprococcus, which was significantly higher after the treatment with ω-3 PUFAs, was found to be positively correlated with isobutyric acid and negatively correlated with serum

lipids such as VLDL-TG after adjusting for confounders. Thus, ω-3 PUFA supplementation altered gut microbiota composition and some microbiota-mediated metabolic effects, indicating that ω-3 PUFAs may be a helpful prebiotic nutrient.

Ten RCTs were summarized in a meta-analysis to evaluate the effects of supplemental ω-3 PUFAs on proteinuria, estimated glomerular filtration rate (eGFR) and metabolic biomarkers among patients with T2DM and type 1 diabetes mellitus (T1DM) [39]. Although ω-3 PUFAs reduced the rate of proteinuria among diabetic patients, this was significant only in patients with T2DM (SMD = -0.29; 95% CI: -0.54, -0.03; p = 0.03). Additionally, patients who were supplemented for at least 2 years with EPA or EPA+DHA showed significant lower proteinuria compared to controls (SMD = -0.30; 95% CI: -0.58, -0.02; p = 0.04). Regarding eGFR, there was an increasing trend in the ω-3 PUFA group, but the effect was not statistically significant (WMD = 1.56 mL/min/1.73 m^2; 95% CI:-1.53, 4.65; p = 0.32). A pilot RCT included 27 subjects with T1DM who were assigned to receive 3.3 g/day of encapsulated ω-3 PUFAs (i.e., 2.8 EPA + 0.8 DHA g/day) or encapsulated corn oil placebo for 6 months [40]. No significant differences were found between ω-3 PUFA and placebo groups in metabolic, glycemic or vascular outcomes. It is important to note the low sample size of this trial.

A meta-analysis of 30 RCTs published in 2021 reported the effects of ω-3 PUFA supplementation on metabolic and inflammatory biomarkers, weight, and body mass index (BMI) in patients with T2DM [41*]. Glycemic factors including FBG, glycated hemoglobulin (HbA1c), and HOMA-IR were significantly reduced in ω-3 PUFA supplemented groups [-0.36 (-0.71 to -0.01), -0.74 (-1.13 to -0.35), -0.58 (-1.13 to -0.03), respectively]. ω-3 PUFAs were associated with statistically significant reductions in concentrations of total cholesterol (-0.60 (-0.88 to -0.32)), LDL cholesterol (-0.54 (-0.85 to -0.23)), HDL cholesterol (0.60 (0.23 to 0.96)) and TG (-0.27 (-0.37 to -0.18)). Inflammatory biomarkers such as tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) were not significantly decreased. Furthermore, there was

no significant reduction in weight and BMI. Sub-group analysis of supplemental ω-3 PUFAs according to prior defined doses (i.e., <1, 1 to 2, and >2 g/d) and duration ≤8 week/>8 week showed that supplementation with 1 to 2 g/d for more than 8 weeks significantly affected FBG level and HOMA-IR, while a significant reduction was found for HbA1c at all the 3 dose sub-groups and both ≤8 week/>8 weeks. All 3 dose sub-groups significantly lowered TG and total-cholesterol levels during both ≤8 week/>8 weeks. The findings revealed that ω-3 PUFA doses >1 g/d significantly changed LDL and HDL levels. However, the statistically significant reduction in LDL concentration occurred only when ω-3 PUFAs were consumed for more than 8 weeks, while improvement in HDL level was noticed during all analyzed periods (41*). A previous meta-analysis of 45 RCTs, involving 2647 patients with T2DM, showed an association between ω-3 PUFA supplementation and favorable improvement in lipid profile, inflammatory markers and HbA1c level [42].

Lee et al. [43*] included 22 RCTs with 1366 participants in a meta-analysis of the effect of ω-3 PUFAs in treating NAFLD. The dosage of ω-3 PUFAs used in the included trials was in range of 0.25 to 5 g/day and duration was 3 to 18 months. Treatment with ω-3 PUFA supplements significantly reduced liver fat compared to placebo (pooled RR 1.52; 95% CI: 1.09, 2.13). ω-3 PUFA supplementation also improved the levels of TG, total cholesterol and HDL cholesterol, and BMI, with a pooled mean difference and 95% CI being -28.57 (-40.81 to -16.33), -7.82 (-14.86 to -0.79), 3.55 (1.38 to 5.73), and -0.46 (-0.84 to -0.08), respectively. These effects were obtained mainly with the treatment course of at least six months. Liver enzymes, LDL cholesterol, HOMA-IR, or FBG did not show a remarkable improvement in NAFLD patients taking supplemental ω3 PUFAs.

Summary, discussion & conclusion

Current epidemiological studies and intervention trials suggest that higher ω-3 PUFA intake may effectively lower the prevalence of metabolic diseases and mechanistic studies suggest that this is through multiple actions of bioactive fatty acids (EPA and DHA) and their bioactive metabolites. DHA has attracted more attention with its greater effectiveness in reducing MetS risk and incidence of T2DM than other ω-3 PUFAs. The main biological activities of ω-3 PUFAs are improvement in blood lipids, fasting blood glucose and insulin resistance, and promoting anti-inflammatory and pro-resolving actions. Additionally, prebiotic activities of ω-3 PUFAs have recently been recognized: these fatty acids appear to modulate gut microbiota composition with promising effects on metabolic disease risk.

Over the last years, there has been increasing evidence from clinical trials suggesting that dysregulated expression of inflammatory and immune response-related genes and processes in obesity may be a reason for the lack of response to ω-3 PUFA interventions in obese individuals [26*, 44]. Altered adipose tissue fatty acid composition, modified oxylipin profile, and dysregulation of endocannabinoid concentrations and gene expression profiles in the early stages of obesity seem to be closely related. On the other hand, the genetic background affects inter-individual variability in the insulin sensitivity response to ω-3 PUFA supplementation [36]. Several studies and meta-analyses confirmed favorable improvement in lipid profile and glycemic outcomes in patients with T2DM taking supplemental ω-3 PUFAs. However, similar findings were not observed in patients with T1DM. Evidence from metabolomic studies implicates that a sub-optimal fatty acid profile in early life may signal the risk of pancreatic islet autoimmunity [45-47]. The possible effect of ω-3 PUFAs regarding the prevention of T1DM is unclear. A meta-analysis of patients with NAFLD revealed that ω-3 PUFA supplementation considerably improved liver fat and blood lipids except for LDL cholesterol, while liver enzymes and glycemic parameters remained unchanged [43*].

283 The evidence base for the relationship between ω-3 PUFA (i.e. EPA and DHA) intakes
284 and blood levels on one hand and "health", including biomarkers, risk factors and clinical
285 outcomes, on the other hand includes both observational studies and intervention studies. It is
286 important to consider the intakes and blood levels that these different study types might reflect,
287 particularly in the context of intake recommendations. Different organisations make different
288 recommendations for the combined intake of EPA and DHA that is thought necessary to support
289 good health. For example, the Food and Agricultural Organisation of the United Nations
290 recommends a minimum of 250 mg EPA+DHA per day for adult males and non-pregnant or
291 non-lactating adult females [48] and the European Food Safety Authority states the adequate
292 intake as 250 mg/day for adult males and non-pregnant adult females [49]. The French Agency
293 for Food, Environmental and Occupational Health Safety sets a target of 400 to 500 mg/day for
294 adults in the general population [50], while the United Kingdom recommendation based upon
295 fish consumption is a minimum of 450 mg/day [51]. The Australian National Health and
296 Medical Research Council recommends a target of 430 to 610 mg EPA+DHA per day for adults
297 in the general population [52]. In comparison to these recommendations most adults consume
298 less than 200 mg EPA+DHA per day [53,54]. Higher intakes can be achieved by eating fatty
299 fish regularly or by using supplements that contain EPA and DHA. A standard one g fish oil
300 capsule will provide about 300 mg EPA+DHA [55]. Observational studies that associate ω-3
301 PUFA intakes to health-related outcomes report intakes of EPA and DHA across the range of
302 tens to hundreds of mg/day. Intervention studies using ω-3 PUFA supplements typically
303 provide EPA and DHA intakes in excess of recommendations, often over 1000 mg/day, as
304 described earlier. Blood levels of EPA and DHA strongly relate to intakes of these fatty acids;
305 this is clearly demonstrated in intervention studies that report linear associations between intake
306 and levels of EPA and DHA in blood lipids and blood cells [56-59]. Most intervention studies
307 with ω-3 PUFAs have a duration of 4 weeks to 3 months, although there are studies of longer

duration. With increased daily intake of ω-3 PUFAs from supplements, net incorporation of the fatty acids into blood lipids and some blood cells becomes detectable within a few days [60], although a new steady state is not reached for blood lipids until after a few weeks [56-59]. Incorporation into blood cells is slower, because cells turn over at a slower rate than blood lipids; incorporation into erythrocytes is slower than into platelets and leukocytes because erythrocytes turn over more slowly. Platelets and leukocytes reach a new steady state after about one to two months and for erythrocytes this is not reached until about six months [56,59].

Recent evidence from epidemiological and intervention trials summarized here supports a role for ω-3 PUFAs (EPA and DHA) in prevention of cardiometabolic disease and in control of several recognized risk factors. However, even though ω-3 PUFAs are recommended as effective therapeutic agents in managing dyslipidemias [61], further investigations are needed to clarify the dose-dependent effects of EPA and DHA, separately and together, on metabolic disease risk factors and related clinical outcomes.

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Conflicts of interest

ID has no conflict of interest to declare. PCC acts as an advisor/consultant to DSM, BASF AS, Cargill, Smartfish, Fresenius-Kabi, Bayer Consumer Care and GSK Consumer Healthcare.

Key points

- Higher dietary and circulating ω-3 PUFAs may decrease the prevalence of metabolic diseases through multiple biological actions
- DHA has a higher potential to reduce metabolic disease risks than other ω-3 PUFAs
- ω-3 PUFAs modulate gut microbiota and may act as a prebiotic agents
- Dysregulated expression of inflammatory and immune response-related genes in obesity may be a reason for the lack of response to ω-3 PUFA interventions in obese individuals
- ω-3 PUFAs improve lipid profile and glycemic outcomes in patients with type 2 diabetes mellitus and decrease liver fat in patients with non-alcoholic fatty liver disease

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