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# The role of omega-3 on type 2 diabetes (T2DM)

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# The role of omega-3 on type 2 diabetes (T2DM)

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**Abstract:**

unsaturated fatty acids are of particular interest in the nutritional therapy for diabetes, given their potential role in several pathophysiological processes related to cardiovascular disease. Both omega-3 beneficial for improving lipid profiles in healthy individuals and among type 2 diabetic patients: Supplementation with omega-3 fatty acids lowers triglycerides and VLDL-cholesterol. However, they might also increase LDL-cholesterol. Omega-3 fatty acids are, from the latest evidence, not related to mortality and cardiovascular disease. Similarly, glucose control and hypertension, as well as risk of microvascular complications, seem unaffected by omega-3 supplementation. Most studies involved mainly patients with type 2 diabetes, and future research needs to focus on the type 1 diabetic patient. Also, the role of omega-3 fatty acids remains largely unknown.

**Keywords: Type 2 diabetes. Omega-3 fatty acids, oxidative stress,**

**Abbreviations:**

PUFA: Polyunsaturated Fatty Acid

HDL: High Density Lipoprotein

LDL: Low Density Lipoprotein

ALA: Alpha-linolenic Acid

EPA: Eicosatetraenoic Acid

DHA: Docosahexaenoic acid

## 1- Introduction

Diabetes type 2 is a diverse illness. The illness must have both hereditary and environmental components in order to manifest clinically. Its genesis is hypothesized to be the consequence of the evolution of a frugal genotype that was advantageous for survival in the past but is harmful in the present setting. Another notion that contradicts this one is that it's an adult metabolic reaction to fetal malnourishment. In type 2 diabetes, either an absolute or relative insulin insufficiency is the cause of hyperglycaemia. Relative insulin shortage is typically caused by a failure to sufficiently compensate for insulin resistance. Numerous genetic or metabolic variables can result in insulin resistance. Central adiposity is the most frequent etiological cause for insulin resistance. Insulin resistance is linked to several metabolic.(Lebovitz, 1999) Interest in omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) has escalated in recent years because of their various roles in health promotion and disease risk reduction. ω-3 PUFAs include α-linolenic acid (ALA; 18:3 ω-3), sardonic acid (SDA; 18:4 ω-3), eicosatetraenoic acid (EPA; 20:5 ω-3), docosapentaenoic acid (DPA; 22:5 ω-3), and docosahexaenoic acid (DHA; 22:6 ω-3). Oils containing these fatty acids (FAs), or some of these fatty acids, originate primarily from certain plant sources or are modified in plants, as well as marine, algal, and single-cell sources. Long-chain (LC) ω-3 FAs such as EPA and DHA occur in the body lipids of fatty fish, the liver of white lean fish, and the blubber of marine mammals. Fish oils are sold as ω-3 PUFA supplements or in a concentrated form as ethyl esters (EEs) or acylglycerols, whereas algal, fungal, and single-cell oils have recently become popular as novel and renewable sources of LC ω-3 FA. In addition, krill oil containing both triacylglycerol (TAG) and phospholipid (PL) forms containing EPA and DHA has been successfully marketed. Researchers have also incorporated ω-3 PUFAs into different oils such as borage oil and evening primrose oil to provide a better balance of PUFA components(Shahidi & Ambigaipalan, 2018) insulin resistance can be related to genetic abnormalities in a few individuals, but in most it appears to be related to obesity and in particular to central or visceral obesity (Lemieux et al., 1996)After hyperglycemia is present an additional com- ponent of insulin resistance occurs that is caused by the effects of hyperglycemia itself (glucose toxicity or desen- sitization) (Lemieux et al., 1996)Insulin resistance as defined by the euglycemic insulin

clamp, the Bergman minimal model, the fasting plasma insulin, or the Homeostasis Model Assessment model is an impairment of that function of insulin that causes the normal glucose uptake by muscle and/or restraint in glucose production by the liver. The degrees to which other actions of insulin are normal or resistant in type 2 diabetes are not clear. Insulin effects on ovarian androgen production and lipogenesis among others appear not to be resistant (Goudas & Dumesic, 1997)

PUFA polyunsaturated fatty acids T1D type 1 diabetes T2DM type 2 diabetes CVD cardiovascular disease MI Myocardial infarction CHD coronary heart disease TIA transient ischemic attack DN Diabetic nephropathy GFR glomerular filtration rate LDL low density lipoprotein VLDL very low-density lipoprotein HDL high density lipoprotein IMT Carotid intima-media thickness ESRD End-stage renal disease UPE urinary protein excretion

Introduction(Rao Kondapally Seshasai et al., 2011)

The prevalence of type 2 diabetes (T2DM) is increasing worldwide Diabetes increases the risk of cardiovascular morbidity and mortality through various abnormalities in glucose, lipid, and lipoprotein metabolism, increased plate- let aggregation, endothelial dysfunction, and increased risk of cardiac arrhythmia. Diet can play a role in the prevention of T2DM and is also a central component of therapy. Polyunsaturated fatty acids (PUFAs) are of particular inter- est, given their potential role in several pathophysiological processes related to cardiovascular disease (CVD). Omega- 3 fatty acids (FAs) have received substantial attention, initi- ated by the first studies done by Bang and Dyerberg in Greenland. The two Danish researchers observed that the Inuit diet was high in omega-3 FAs caused by a high intake of traditional marine food (Shah & Garg, 2015)

**2-Type 2 diabetes**

Type 2 diabetes affects how your body uses sugar (glucose) for energy. It stops the body from using insulin properly, which can lead to high levels of blood sugar if not treated.

Over time, type 2 diabetes can cause serious damage to the body, especially nerves and blood vessels.

Type 2 diabetes is often preventable. Factors that contribute to developing type 2 diabetes include being overweight, not getting enough exercise, and genetics.

Early diagnosis is important to prevent the worst effects of type 2 diabetes. The best way to detect diabetes early is to get regular check-ups and blood tests with a healthcare provider.

Symptoms of type 2 diabetes can be mild. They may take several years to be noticed. Symptoms may be similar to those of type 1 diabetes but are often less marked. As a result, the disease may be diagnosed several years after onset, after complications have already arisen.

More than 95% of people with diabetes have type 2 diabetes. Type 2 diabetes was formerly called non-insulin dependent, or adult onset. Until recently, this type of diabetes was seen only in adults but it is now also occurring increasingly frequently in children.

**3- Role of diet in type 2 DM**

Apart from the heightened genetic susceptibility of ethnic groups, environmental and behavioral factors are also very important in the development of T2D. Globalization results in altered dietary and lifestyle habits such as taking more high-fat or high-carbohydrate foods and sedentary lifestyles with low energy expenditure

Frontiers Diets induce multiple metabolic processes and modify the metabolism homeostasis of the organism Therefore, unhealthy dietary habits such as Western diet have been one of the most important drivers of glucose metabolism disorder that leads to diabetes finally (Rico-Campa The increase in the prevalence of T2D is associated with
a concomitant rise in the incidence of metabolic disorders. Long-term high glucose levels will trigger chronic metabolic syndrome and include obesity Diet alone or with hypoglycemic agents is the way to control
blood glucose levels in the treatment ofT2D (Zimmet et al., 2001)

Different diets with varied nutrient composition result in changes of metabolites and gut microbiome that are responsible for the glucose metabolism of the whole-body example, different amino acid content diets can lead to alterations of plasma branched-chain amino acid (BCAA) concentrations, which are linked to the risk of T2D Fiber- and protein-enriched diet changed the abundance of Akarnania municipia, decreasing fasting glucose levels of participants. However, the interactions between dietary and glucose metabolism need further study to understand the importance of its actions for glucose management.(Garcia-Perez et al., 2017)

**4- Omga3 unsaturated fatty acid**

The human body can make most of the types of fats it needs from other fats or carbohydrates. That isn’t the case for omega-3 polyunsaturated fatty acids (also called omega-3 fats and n-3 fats). These are essential fats—the body can’t make them from scratch but must get them from food. Foods high in omega-3 include certain fish and seafood, some vegetable oils, nuts (especially walnuts), flax seeds, and leafy vegetables.

What makes omega-3 fats special? They are needed to build cell membranes throughout the body and affect the function of the cell receptors in these membranes. They also provide the starting point for making hormones that regulate blood clotting, contraction and relaxation of artery walls, and inflammation. In addition, they can bind to receptors in cells that regulate genetic function. Due to these effects, omega-3 fats can help prevent heart disease and stroke, may help control lupus, eczema, and rheumatoid arthritis, and may play protective roles in cancer and other conditions

**4.1 Omega 3 fatty acids and over view**

Fatty acids are hydrocarbon chains with a carboxyl group at one end and a methyl group at the other. The carboxyl group is reactive and readily forms ester links with alcohol groups, for example those on glycerol or cholesterol, in turn forming acylglycerols (eg, triacylglycerols, phospholipids) and cholesteryl esters. Fatty acids containing double bonds in the hydrocarbon chain are referred to as unsaturated fatty acids; a fatty acid containing 2 double bonds is called a polyunsaturated fatty acid (PUFA). Fatty acids have common names and systematic names. They are also referred to by a shorthand nomenclature that denotes the number of carbon atoms in the chain, the number of double bonds, and the position of the fi rst double bond relative to the methyl (ω; sometimes called n) carbon. Omega-3 fatty acids are so called because the first double bond is on carbon number 3, counting the methyl carbon as carbon number 1.(Yaqoob, 2009)

**4.2 Types of Omega-3s**

There are two main types of omega-3 fats that have essential roles in human health:

EPA and DHA: Eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) come mainly from cold-water fish, so they are sometimes called marine omega-3s. Salmon, mackerel, tuna, herring, and sardines contain high amounts of EPA/DHA. EPA and DHA can be made from another omega-3 fat called alpha-linoleic acid (ALA), so they are more accurately termed “conditionally essential” fats. But because the conversion from ALA to EPA/DHA may not be sufficiently efficient, EPA/DHA are best obtained directly from food sources.

ALA: Alpha-linolenic acid (ALA), the most common omega-3 fatty acid in most Western diets, is found in plant oils (especially canola, soybean, flax), nuts (especially walnuts), chia and flax seeds, leafy vegetables, and some animal fats, especially from grass-fed animals. ALA is a true essential fat because it cannot be made by the body, and is needed for normal human growth and development. It can be converted into EPA and DHA, but the conversion rate is limited so

we are still uncertain whether ALA alone can provide optimal intakes of omega-3 fatty acids. (Swanson et al., 2012)

The simplest omega-3 fatty acid is alpha-linolenic acid (ALA) (18:3ω-3). Alpha-linolenic acid is synthesized from linoleic acid (18:2ω-6) by desaturation, catalyzed by delta-15 desaturase (confusingly, the desaturase enzymes are named according the first carbon carrying the newly inserted double bond, counting the carboxyl carbon as carbon number 1). Animals, including humans, do not possess the delta-15 desaturase enzyme and thus cannot synthesize ALA. Plants possess delta-15 desaturase and so are able to synthesize ALA. Although animals cannot synthesize ALA, they can metabolize it by further desaturation and elongation; desaturation occurs at carbon atoms below carbon number 9 (counting from the carboxyl carbon) and mainly occurs in the liver. Alpha-linolenic acid can be converted to sardonic acid (18:4ω-3) by delta-6 desaturase and then sardonic acid can be elongated to 20:4ω-3 (Figure 1). This fatty acid can be further desaturated by delta-5 desaturase to yield eicosatetraenoic acid (EPA) (20:5ω-3) (Figure 1). A path- way for further conversion of EPA to docosahexaenoic acid (DHA) (22:6ω-3) exists; this pathway involves addition of 2 carbons to form docosapentaenoic acid (DPA) (22:5ω-3), addition of 2 further carbons to produce 24:5ω-3 desaturation to form 24:6ω-3(Yaqoob, 2009)

here are three main types of omega-3 fatty acids:

- **EPA (eicosatetraenoic acid)**. EPA is a “marine omega-3” because it’s found in fish.
- **DHA (docosahexaenoic acid)**. DHA is also a marine omega-3 found in fish.
- **ALA (alpha-linolenic acid)**. ALA is the form of omega-3 found in plants.

**Figure** 1. Pathway of alpha-linolic acid conversion to longer chain, more unsaturated omega-3 fatty acids.

**5- Dietary Sources and Typical Intakes of Omega-3 Fatty Acids**

Green leaves contain a significant proportion (typically 50%) of their fatty acids as ALA, however green leaves are not rich sources of fat. Several seeds and seed oils and some nuts contain significant amounts of ALA. Linseeds (flaxseeds) and their oil typically contain 45% to 55% of fatty acids as ALA, while soybean oil typically contains 5% to 10% of fatty acids as ALA. Rapeseed oil and walnuts also contain ALA. Corn oil, sunflower oil, and safflower oil are rich in linoleic acid but contain very little ALA. Typical intakes of ALA among Western adults are 0.5 to 2 g/d.2,3 The main PUFA in most Western diets is the omega-6 fatty acid LA (18:2ω-6), which is typically consumed in 5- to 20-fold greater amounts than ALA.2,3 Seafood is a source of the longer chain, more unsaturated omega-3 PUFAs. Fish can be classified into

lean fish that store lipid in the liver (eg, cod) or "fatty" ("oily") fish that store lipid in the flesh (eg, mackerel, herring, salmon, tuna, and sardines). Compared with other foodstuffs, fish and other seafood are good sources of the very long-chain omega-3 fatty acids EPA, DPA, and DHA. However, different types of fish contain different amounts of these fatty acids and different ratios of EPA to DHA.(Yaqoob, 2009)

**6- Health benefits of Omega-3 fatty acids**

Omega-3 fatty acids help all the cells in your body function as they should. They're a vital part of your cell membranes, helping to provide structure and supporting interactions between cells. While they're important to all your cells, omega-3s are concentrated in high levels in cells in your eyes and brain.

In addition, omega-3s provide your body with energy (calories) and support the health of many body systems. These include your cardiovascular system and endocrine system. Omega-3 fatty acids have many potential benefits for your cardiovascular health. One key benefit is that they help lower your triglyceride levels. Too many triglycerides in your blood (hypertriglyceridemia) raises your risk of atherosclerosis, and through this, can increase your risk of heart disease and stroke. So, it's important to keep triglyceride levels under control. In addition, omega-3s may help you by raising your HDL (good) cholesterol and lowering your blood pressure.(Yaqoob, 2009)

Some studies show omega-3s may lower your risk for:

- Cardiovascular disease (CVD).
- Death, if you have CVD.
- Sudden death caused by an abnormal heart rhythm (arrhythmia).
- Blood clots.

Beyond heart health, omega-3s may help lower your risk of developing:

Some forms of cancer, including breast cancer.

- Alzheimer's disease and dementia.
- Age-related macular degeneration (AMD).

**7- Mechanism of action of omega 3 fatty acid in type 2 DM**

The potential mechanisms by which dietary omega-3 PUFA alters ER stress and mitochondrial metabolic activities to stop the progression of IR are explained in this article. The electronic archiving resources used for the literature search included Google Scholar, Science Direct, PubMed, and ResearchGate. To find more literature, the references list of related works was checked. Keywords include insulin resistance, polyunsaturated fatty acids, PUFA, omega-fatty acids, omega-3 fatty acids, diabetes mellitus, cardiovascular diseases,

endoplasmic reticulum stress, mitochondrial dysfunction, reactive oxygen species (ROS), oxidative stress, fish oil, randomized control trial, and inflammatory pathways. Papers authored in languages other than English and published before 2000 were excluded. The suitability of the articles was carefully assessed before they were added to the research. Duplicate articles were eliminated. Following the independent assessment and insertion of the suggested works of literature, a follow-up conversation was held to clarify any ambiguities, problems, mistakes, or biases pertaining to the specific articles.(Zhu et al., 2020).

**8- Insulin sensitivity and glucose regulation**

Insulin resistance is identified as the impaired biologic response of target tissues to insulin stimulation. All tissues with insulin receptors can become insulin resistant, but the tissues that primarily drive insulin resistance are the liver, skeletal muscle, and adipose tissue. Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia. Recent studies have debated whether hyperinsulinemia precedes insulin resistance, as hyperinsulinemia itself is a driver of insulin resistance. This concept may be clinically valuable, suggesting that hyperinsulinemia associated with excess caloric intake may drive the metabolic dysfunction associated with insulin resistance. The metabolic consequences of insulin resistance include hyperglycaemia, hypertension, dyslipidaemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state. Progression of insulin resistance can lead to metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), and type 2 diabetes.(Seong et al., 2019)

**9- Inflammation and oxidative stress**

Inflammation is a “host defense” mechanism against pathogens which involves an enhanced or exaggerated ROS generation by activated inflammatory and immune cells. ROS that is produced as part of the inflammatory response facilitates clearance of tissue invasive bacteria, but when produced for prolonged periods can promote oxidative stress and chronic inflammation associated disorders. Additionally, although inflammation induces oxidant injury, the reverse sequence of events is also true. Thus, inflammation and oxidative stress are inextricably interrelated. While most of these modifications lead to irreparable damage, some modifications are more subtle and fully reversible. The reversible modifications can initiate signaling cascades known as “redox signaling.” This chapter reviews the role of oxidative stress and inflammation in the onset of signaling that underlies the pathology of several diseases. (oxidative stress induced inflammation), and the intersection of these are also

reviewed. Finally, the antioxidant regulatory mechanisms that modulate the balance between host defense, inflammation, and oxidative stress are discussed.(Chatterjee, 2016)

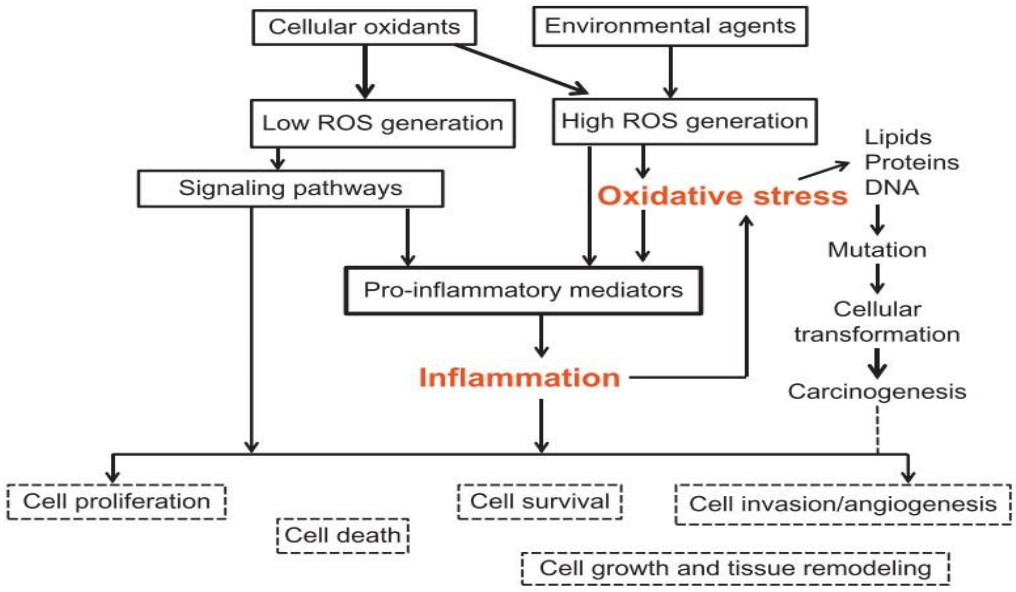



**Figure (1) Interrelationship between ROS, oxidative stress, inflammation, and cellular physiology and pathology.**

Oxidative stress is a term coined to denote the state of imbalance between the generation of oxidants (ie, free radicals and ions collectively called reactive oxygen species (ROS) and the availability of endogenous antioxidants to scavenge this ROS resulting in an excess production of oxidants. As this ROS produced in biological systems can readily react with lipids, proteins, and DNA, an excessive production of ROS can be detrimental. Indeed, studies have shown that ROS either through direct damage to biomolecules or modifications in proteins and genes are pivotal in triggering signaling cascades that lead to the onset of numerous pathologies and ultimately cell injury and death.(Lushchak, 2014)

### 3.3 Omega-3 fatty acids coordinate glucose and lipid metabolism in diabetic patients

The potential different effects of diverse sources of n-3 PUFA (e.g. fish vs vegetable on glycolipid metabolism have not been fully investigated. A known difference between vegetable and marine n-3 PUFA is the cholesterol lowering effect vs triglyceride lowering effect, respectively; nevertheless, whether vegetable n-3 PUFA may have an effect on blood glucose has not been established .In an elegant double-blind clinical trial, Liu and colleagues evaluated the different effects of marine-derived and plant-derived omega-3 PUFA on the fatty acids of erythrocytes and glycolipid metabolism in patients with diabetes .(Imamura et al., 2016).

The study was conducted on 150 patients with a diagnosis of T2DM, of which 52 were randomly assigned to the fish oil group, 50 to the perilla oil group, and 48 to the linseed and fish oil group. All patients were followed up for six months. Intriguingly, while the

supplementation with perilla oil (a vegetable oil rich in alpha-linolenic acid significantly decreased fasting blood glucose compared to baseline, fish oil supplementation prompted a marked reduction of serum triglycerides (TG) levels. (Gaundal et al., 2021)Therefore, marine-based and plant-based n-3 PUFAs exhibited different effects on the regulation of glycolipid metabolism Intriguingly, the administration of all types of n-3 PUFA significantly reduced insulin and C-peptide concentrations compared to baseline. Similarly, serum total cholesterol, apolipoprotein A1, and IL-6 levels significantly decreased in all the treatment groups compared to baseline values (Fig. 1)

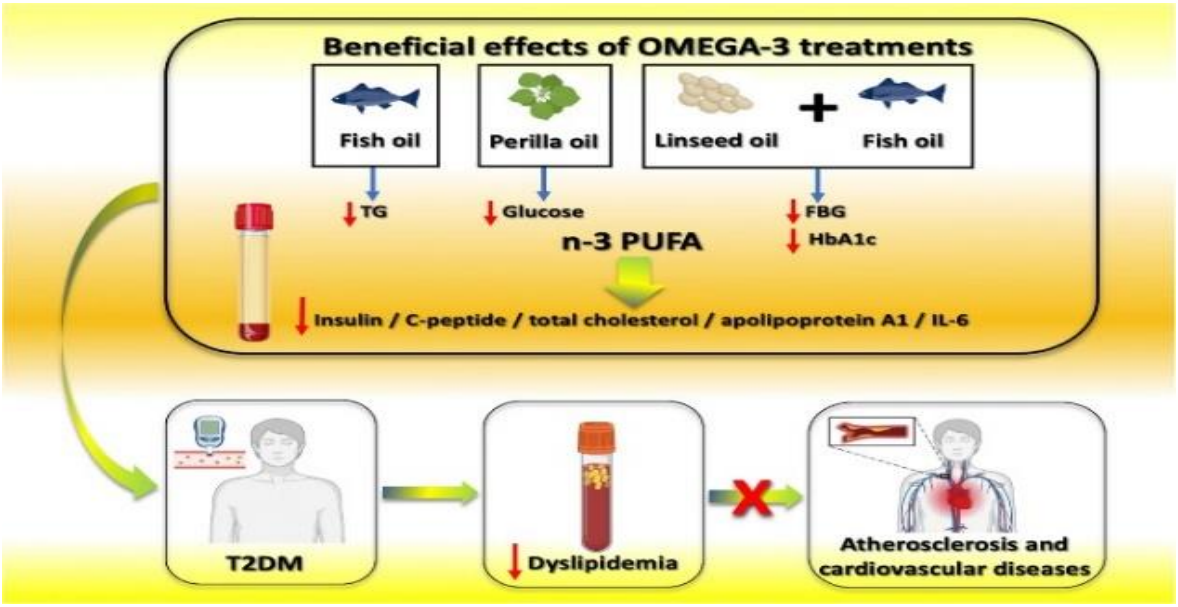



**Figure (2)** Different effects of marine-derived and plant-derived n-3 PUFA on lipid and glucose metabolism in people with T2DM. (Kaze et al., 2021)

**10- clinical studies and evidence**

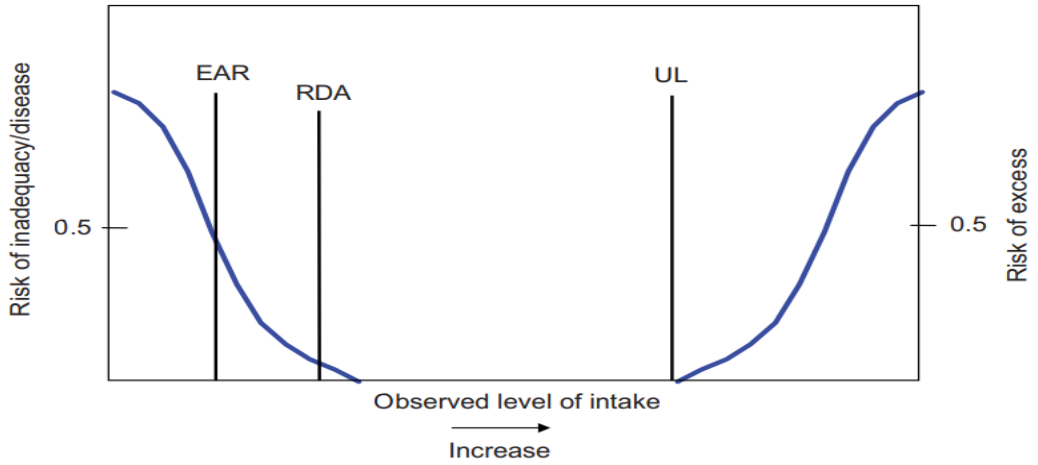
While omega-3 fatty acid supplements might reduce the risk of HF risk factors and HF hospitalization in general, it is less clear whether patients with T2D may benefit more that non-diabetic patients from omega-3 fatty acid supplements. Furthermore, the paucity of trial data among Blacks is an important gap to address. In this study, we found that supplementation with omega-3 fatty acids reduced the incidence of HF hospitalization, especially among patients with T2D and Blacks. If confirmed by future trials, these findings could help clinicians improve management and prevention of HF in subgroups of high-risk patients.

**10.1 reviews meta-analysis and system**

The relationship between omega-3 polyunsaturated fatty acids (n-3 PUFA) from seafood sources (eicosatetraenoic acid, EPA; docosahexaenoic acid, DHA) or plant sources (alpha-linolenic acid, ALA) and risk of type 2 diabetes mellitus (DM) remains unclear. We systematically searched multiple literature databases through June 2011 to identify prospective studies examining relations of dietary n-3 PUFA, dietary fish and/or seafood, and circulating n-3 PUFA biomarkers with incidence of DM. Data were independently extracted in duplicate by 2 investigators, including multivariate-adjusted relative risk (RR) estimates and corresponding 95 % CI. Generalized least-squares trend estimation was used to assess dose–response relationships, with pooled summary estimates calculated by both fixed-effect and random-effect models. From 288 identified abstracts, 16 studies met inclusion criteria, including 18 separate cohorts comprising 540 184 individuals and 25 670 cases of incident DM**.**(Wu et al., 2012) The overall pooled findings do not support either major harms or benefits of fish/seafood or EPAþDHA on development of DM, and suggest that ALA may be associated with modestly lower risk. Reasons for potential heterogeneity of effects, which could include true biologic heterogeneity, publication bias, or chance, deserve further investigation.

**10.2 Dietary EPA and DHA**

Various organizations worldwide have made dietary recommendations for eicosatetraenoic acid (EPA), docosahexaenoic acid (DHA), and fish intake that are primarily for coronary disease risk reduction and triglyceride (TG) lowering. Recommendations also have been made for DHA intake for pregnant women, infants, and vegetarians/vegans. A Dietary Reference Intake (DRI), specifically, an Adequate Intake (AI), has been set for a-linolenic acid (ALA) by the Institute of Medicine (IOM) of The National Academies. This amount is based on an intake that supports normal growth and neural development and results in no nutrient deficiency. Although there is no DRI for EPA and DHA, the National Academies have recommended that approximately 10% of the Acceptable Macronutrient Distribution Range (AMDR) for ALA can be consumed as EPA and/or DHA. l recommendations for long-chain omega-3 fatty acids underscore the pressing need to establish DRIs for DHA and EPA because DRIs are recognized as the ‘‘official’’ standard by which federal agencies issue dietary guidance or policy directives for the health and wellbeing of individuals in the United States and Canada. Because of the many health benefits of DHA and EPA, it is important and timely that the National Academies establish DRIs for the individual long-chain (20 carbons or greater) omega-3 fatty acids.(Kris-Etherton etal., 2009)

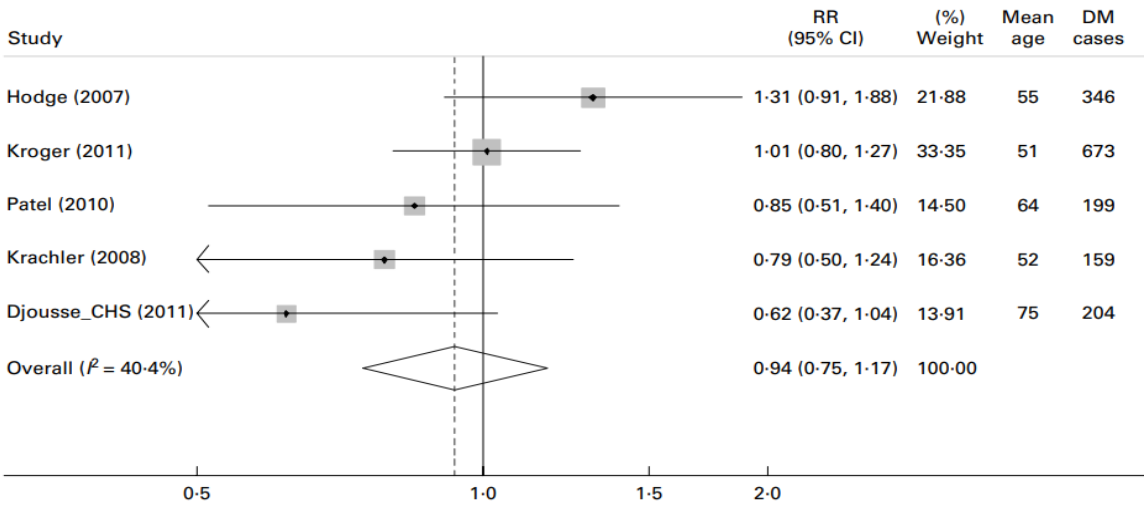



**Figer(3) Dietary reference intakes: risk relationships-nutrient adequacy and disease indicators.(Kris-Etherton et al., 2009)**

### 10.3 Observation studies

The overall findings from this systematic review and metanalysis suggest that dietary EPAþDHA and fish/seafood consumption do not have either major harmful or beneficial associations with the development of DM. However, we identified substantial heterogeneity in findings across studies. Our findings also suggest that plant-derived ALA could be protective, though this result was of borderline statistical significance. We found little evidence that fish or seafood, dietary EPAþDHA, or circulating EPAþDHA biomarkers were associated with risk of DM overall. These studies typically comprised moderately overweight but otherwise generally healthy participants at baseline. Prior short-term randomized controlled trials have found very little effect of n-3 PUFA supplementation on glucose metabolism or indices of insulin resistance in healthy subjects. (Griffin et al., 2006)). Therefore, our overall findings are consistent with these prior metabolic trials and suggest that, at typical dietary levels of consumption in generally healthy subjects, fish, seafood, or dietary EPAþDHA may have minimal effects on development of DM.

**Meta-analysis of n-3 fatty acids and incident diabetes**




**Figer (5)**. Relative risk of type 2 diabetes associated with EPAþDHA biomarker concentrations (as % of total fatty acids) in 5 prospective cohorts including 10 382 individuals and 1581 incident diabetes cases. Within-study relative risks and 95 % CI's were quantified using generalized least squares trend estimation, and study-specific results were pooled using random effect meta-analysis.(Wu et al., 2012)

## 11 Literature Review

**Charlotte Jeppesen, Katja Schiller & Matthias B. Schulze** in 17 January 2013 they did research about Omega-3 and Omega-6 Fatty Acids and Type 2 Diabetes in which they indicated that Polyunsaturated fatty acids are of particular in terest in the nutritional therapy for diabetes, given their potential role in several pathophysiological processes re late to cardiovascular disease. Both omega-3 and omega 6 fatty acids are beneficial for improving lipid profiles in healthy individuals and among type 2 diabetic patients: Supplementation with omega-3 fatty acids lowers trigly Carides and VLDL-cholesterol. However, they might also increase LDL-cholesterol. Omega-3 fatty acids are, from the latest evidence, not related to mortality and cardiovascular disease. Similarly, glucose control and hypertension, as well as risk of microvascular complications, seem unaffected by omega-3 supplementation. Most studies involved mainly patients with type 2 diabetes.

**Chao Gao1 and his coworker** in 2020 did research about Effects of fish oil supplementation on glucose control and lipid levels among patients with type 2 diabetes mellitus: a Meta-analysis of randomized controlled trials that they mentioned Previous studies have yielded inconsistent findings on the role of fish oil in type 2 diabetes mellitus (T2DM). We systematically summarized the available evidence from randomized controlled trials (RCT) and aimed to investigate the effects of fish oil supplementation on glucose control and lipid

levels among patients with T2DM. A comprehensive literature search was performed in electronic databases (PubMed, ProQuest, Cochrane Library, CNKI, VIP, and Wanfang) to identify all relevant RCTs which were published up to May 31st, 2019. We used Modified Jadad Score system to evaluate the quality of each included RCT. The pooled effects were estimated using random-effects model and presented as standardized mean differences with 95% confidence intervals. A total of 12 RCTs were included in this meta-analysis. There was no significant difference in glucose control outcomes comparing fish oil supplementation to placebo. The effect size of fasting plasma glucose (FPG) was 0.13 (95% CI: −0.03 to 0.28, p>0.05). No marked change was observed in fasting insulin (FINS), glycosylated hemoglobin (HbA1c), and HOMA of insulin resistance (HOMA-IR) levels. Fish oil supplementation was associated with a decrease of triglyceride (TG) level by − 0.40 (95%CI: − 0.53 to − 0.28, p < 0.05), and an increase of high-density lipoprotein (HDL) cholesterol level by 0.21 (95%CI: 0.05 to 0.37, p < 0.05). In subgroup analysis, HDL cholesterol level was higher among Asian and low-dose This meta-analysis shows that among patients with T2DM, fish oil supplementation leads to a favorable blood lipids profile but does not improve glucose control

**12- Conclusions**

The relationship between omega-3 polyunsaturated fatty acids (*n*-3 PUFA) from seafood sources (eicosatetraenoic acid, EPA; docosahexaenoic acid, DHA) or plant sources (alpha-linolenic acid, ALA) and risk of type 2 diabetes mellitus (DM) remains unclear. We systematically searched multiple literature databases through June 2011 to identify prospective studies examining relations of dietary *n*-3 PUFA, dietary fish and/or seafood, and circulating *n*-3 PUFA biomarkers with incidence of DM. Data were independently extracted in duplicate by 2 investigators, including multivariate-adjusted relative risk (RR) estimates and corresponding 95 % CI. Generalized least-squares trend estimation was used to assess dose–response relationships, with pooled summary estimates calculated by both fixed-effect and random-effect models. From 288 identified abstracts, 16 studies met inclusion criteria, including 18 separate cohorts comprising 540 184 individuals and 25 670 cases of incident DM.

Omega-3 polyunsaturated fatty acids (n-3 PUFA) include eicosapentaenoic acid (EPA, 20: 5n-3) and docosahexaenoic acid (DHA, 22: 6n-3) from seafood, and alpha-linolenic acid (ALA, 18: 3n-3) from plant sources. Based on animal experimental studies, n-3 PUFA improve several metabolic abnormalities underlying the development of DM. Such effects include insulin-sensitizing effects via increased production and secretion of adipocytokines such as adiponectin

and leptin (and potential prevention of insulin resistance via anti-inflammatory effects mediated directly or through conversion to specialized pro-resolution mediators such as resolves and protections). Through modulation of transcription factors (e.g. sterol regulatory element binding protein-1c), n-3 PUFA could also enhance fatty acid oxidation and reduce de novo lipogenesis, effects which could reduce hepatic fat accumulation and preserve hepatic insulin sensitivity.

Despite metabolic benefits in animal experiments, the impact of n-3 PUFA consumption on risk of DM in humans remain uncertain. In meta-analyses of controlled supplementation trials, n-3 PUFA supplementation does not produce major changes in biomarkers of glucose-insulin homeostasis in subjects with DM similar trials in healthy subjects have reported conflicting findings. In addition to these short-term trials, which generally tested high supplemental doses of n-3 PUFA, several long-term prospective studies have assessed how habitual dietary consumption of n-3 PUFA or seafood, or circulating biomarkers of consumption, relate to incidence of DM, but with mixed findings. Therefore, whether n-3 PUFA influence risk of incident DM and, if so, the direction and magnitude of effect remain unknown. To address these important scientific and public health questions, we carried out a systematic review and meta-analysis of prospective studies that assessed the relation of dietary n-3 PUFA, fish and/or seafood consumption, and biomarker levels of n-3 PUFA with the incidence of DM.

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