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Minireview

Role of Omega-3 Polyunsaturated Fatty Acid Supplementation in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background and Aim The advantages of omega-3 fatty acid, which is one of the polyunsaturated fatty acids (PUFA), for health are the subjects of an increasing number of studies. Omega-3 may help prevent or treat obesity and related metabolic illnesses, according to studies conducted both on mice and people. This study aims to survey the benefits of omega-3 in type 2 diabetes mellitus.
Methods Online databases PubMed, Google Scholar, and Science Direct were searched for articles discussing omega-3 fatty acid and diabetic patients in the recent five years (2017-2023).
Results Recent research has shown the value of omega-3 fatty acid supplements, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), in the treatment of several disorders. Omega-3 fatty acids have beneficial effects on glycemic control and insulin resistance in patients with type 2 diabetes mellitus.
Conclusions Clinical studies have demonstrated that omega-3 fatty acids may assist in controlling type 2 diabetes mellitus and reducing obesity and related metabolic diseases.

Keywords: Omega-3, Type 2 diabetes mellitus, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), metabolic diseases.

1. INTRODUCTION

Diabetes refers to a group of metabolic diseases which is characterized by hyperglycemia over a long period. In this condition, the patient's ability to produce insulin is impaired or the body becomes resistant to insulin, thus, insulin becomes disabled to perform its normal function.[1] Chronic inflammation, oxidative stress and impaired mitochondrial function in skeletal muscle, adipose tissue or monocytes/macrophages are closely related to the pathogenesis of insulin resistance and T2DM. Therefore, the suppression of oxidative stress/inflammation and preservation of mitochondrial function should be therapeutic targets for insulin resistance and T2DM.[2]

A sedentary lifestyle is a serious risk factor for type 2 diabetic patients. Clinical trials have suggested that physical activity interventions have a beneficial effect on glucose tolerance improvement and reduction of the risk of T2DM.[3] Type 2 diabetes (T2D) is the most prevalent form of diabetes, accounting for up to 90–95% of diagnosed cases of diabetes, and is on the rise.[4] The International Diabetes Foundation (IDF) reported that in the age range of 20–79 years, approximately 537 million adults suffer from diabetes,

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a number which is expected to rise to approximately 643 million in the year 2030 and 783 million in the year 2045.[5]

In this condition, at least early in the course of the disease, the body becomes resistant to insulin with a "relative" deficiency of insulin. However, in the later stages of the disease, some subjects are not able to produce enough insulin to compensate for the hyperglycemic stress. This reflects the underlying dysfunction of the pancreatic β cell. Obesity is considered a major risk factor for the development of type 2 diabetes.[6]

The fundamental problem in the prevention and treatment of type 2 diabetes (T2D) is the maintenance and restoration of insulin sensitivity in target tissues, which is disturbed already in prediabetic subjects. Optimal strategies in the prevention of obesity and T2D are always based on a healthy lifestyle, including increased physical activity and proper nutrition. These manipulations were sufficient to lower the incidence of T2D in patients with impaired glucose tolerance (IGT) by 60 %.[7]

Dietary supplementation with omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), is a prevailing habit and has been recognized with several health benefits for the cardiovascular system due to their anti-inflammatory activities and irisin secretion.[8]

Polyunsaturated fatty acids (PUFAs) are fatty acids with 18–24 carbon atoms and two or more double bonds. Omega-6 fatty acids account for the majority of polyunsaturated fatty acids in the food supply. They are the predominant PUFA in all diets, especially Western diets. Omega-3 fatty acids namely docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA) are not produced by the human body.[1] They act as natural hypolipidemic and anti-inflammatory agents and ameliorate various aspects of the metabolic syndrome.[7] Recent data supports the beneficial effects of omega-3 fatty acids intake on metabolic issues in patients with T2DM, obesity, atherosclerosis, and chronic inflammation.[9]

Some studies have revealed that circulating levels of omega-3- fatty acid had a negative association with the risk of T2DM. Many studies have revealed that omega-3 fatty acids improve insulin sensitivity in overweight women with an inflammatory phenotype.[10] Some studies have reported that omega-3 fatty acids in healthy people have no effect on insulin sensitivity.[11] Others observed that omega-3 fatty acids in pregnant women with gestational diabetes mellitus (GDM) have a favorable effect on inflammation and oxidative stress.[12] These variations may be due to differences in study populations, dosages of omega-3 fatty acids, and treatment durations. Also, omega-3's effects may depend on disease progression, age of subjects, and other variables. We aimed to monitor the beneficial role of omega-3 fatty acids in type 2 diabetic patients in the past five years in a narrative review.

This research aimed to explain the effect of omega-3 fatty acids on glucose homeostasis, inflammatory markers, insulin sensitivity, and the cardiovascular risk of type 2 diabetes mellitus.

2. MATERIALS AND METHODS

Online databases PubMed, Google Scholar, and Science Direct were searched for articles discussing omega-3 fatty acid and diabetic patients. To find more literature, the references list of similar works was searched. We included primary articles when possible. We eliminated duplicate articles. For the search of the articles, the following descriptors while searching online databases were used: "omega-3 fatty acids, Human" and "Diabetes Mellitus". Included studies conducted on participants who were at least 30 years of age, type 2 diabetics, or obese patients treated with omega-3 fatty acids. The strategy of sample selection was made through 3 steps: electronic research on the database, selection, and identification of the eligible articles by applying the inclusion criteria. Original articles on the English language, full texts available online, and studies that work with adults on its sample were adopted as eligibility criteria. We excluded papers written in languages other than English and published papers before 2017. Research that did not approach the proposed theme, reviews, and those related to type 1 and gestational diabetes were also excluded.

3. RESULTS

3.1. Mechanisms of action of (n-3) fatty acids

Omega-3 fatty acids are biologically active fatty acids. The fatty acid α-linolenic acid can be converted to the omega-3 fatty acids EPA and DHA by a series of desaturation and elongation reactions. Omega 3 fatty acids have different mechanisms to affect cell and tissue behavior. Omega-3 fatty acids might have an impact on metabolite and hormone concentration or could affect the oxidation of LDL. They seem to have an action via receptors or sensors to regulate gene expression. Omega-3 fatty acids could change the composition of the fatty acid cell membrane which in turn affects intracellular signaling processes, gene expression, and the production of lipid mediators.[13]

3.2. Effects of omega-3 on the liver

Peroxisome proliferator-activated receptors (PPAR) are transcription factors that regulate gene expression, so they can affect cell and tissue behavior. The well-understood PPARs are Peroxisome proliferator-activated receptor α (PPARα) and peroxisome proliferator-activated receptor γ (PPARγ).[13] Omega-3 fatty acids activate PPARα that is expressed mainly in the liver resulting in increased fatty acid oxidation in peroxisomes and mitochondria. They could suppress lipogenic gene expression resulting in decreased

formation of fatty acids. Omega-3 fatty acids could activate AMPK in the liver through an adiponectin-mediated mechanism and higher production of lipid mediators (resolvins E1 and D1 and protectin D1) that protect hepatocytes during liver injury.[7] The primary mechanisms regulating the liver's lipid state include fatty acid oxidation, de novo lipogenesis, lipid uptake from the bloodstream and its conversion into lipids, and the assembly and release of very low-density lipoprotein (VLDL). All these activities are at least partially impacted by omega-3 PUFA due to their effects on their function and/or significant transcriptional factors that affect the expression of the genes encoding the proteins involved in these processes .[13]

3.3. Effects of omega-3 on adipose tissue

PPARγ is expressed in adipose tissue, where it promotes insulin sensitivity through its impact on gene expression modulation involved in the differentiation of fat cells and regulation of the metabolic responses of adipocytes.[7,13] Omega-3 fatty acids stimulate mitochondrial formation in fat cells in abdominal white adipose tissue (WAT) thus stimulating the entry of fatty acid into mitochondria. Omega-3 fatty acids induced β-oxidation of mitochondria in WAT. Increasing fatty acid oxidation in adipocytes may contribute to the hypolipidemic and anti-obesity effects of EPA and DHA. The anti-obesity effect of omega-3 in combination with caloric restriction, stimulates lipid catabolism in WAT. PPARγ is also expressed in inflammatory cells and exerts an anti-inflammatory action through its impact on the production of inflammatory mediators.[7]

Omega-3 fatty acids can affect metabolic processes and differentiation of adipocyte and cell inflammation through the induction of peroxisome proliferator-activated receptors (PPAR) and inhibition of nuclear factor-κB (NFκB).[13] PPAR are ligand-activated transcription factors that regulate genes responsible for cell differentiation and many metabolic processes, like lipid and glucose homeostasis.[14] This mechanism might explain how omega-3 fatty acids can improve insulin sensitivity and decrease inflammation.[13]

3.4. Effects of omega-3 on diabetic patients

The clinical trials relating to omega-3 fatty acids and diabetes mellitus published in the recent 5 years (2017-2023)[15-26] are shown in Table 1.

3.5. Omega-3 fatty acids and Irisin

Irisin is a recently recognized myokine produced directly into the blood circulation during exercise and is secreted in response to peroxisome ɣ and its coactivator-1α (PGC-1α) activation; this hormone induces the browning of white fat cells. This brown fat reduces body weight, increases total body energy expenditure, and increases insulin sensitivity.[27] Some studies have found that omega-3 supplementation could significantly increase serum irisin levels in Type 2 Diabetic patients.[1] Irisin facilitates glucose uptake by skeletal muscles, improves hepatic glucose and lipid metabolism that have a positive effect on hyperlipidemia and hyperglycemia caused by obesity and metabolic syndrome, and therefore acts as an insulin-sensitizing hormone.[28] Furthermore, irisin improves insulin sensitivity by increasing glycogenesis and decreasing gluconeogenesis, so irisin may be useful in the prevention and treatment of diabetes and obesity.[29] The advantages of omega-3 PUFAs for health are the subject of an increasing number of studies. Omega-3 PUFA may help prevent or treat obesity and related metabolic illnesses, according to studies conducted both on mice and humans. higher energy expenditure, decreased fat formation, and higher fat oxidation are some of these effects.[9]

Finally, antidiabetic medicines with a favorable influence on renal and cardiovascular outcomes will play a crucial role in altering the way diabetes complications are handled given the bidirectional association between kidney and cardiovascular events in diabetes patients.[30,31] According to the findings of a recent systematic review, omega-3 polyunsaturated fatty acids (n-3 PUFAs) can reduce cardiovascular risk factors in people with type 2 diabetes.[32]

Table 1. Summary of the randomized clinical trials (n=12 study).

Study	Details	Results	Conclusion
[15]	• Randomized, controlled trial (RCT). • Humans. • Placebo (1 g capsules containing olive oil) or 1 g capsules containing omega-3 fatty acids were taken daily for 4.4 years.	In the fatty acid group, 689 patients (8.9%) experienced a major vascular incident, while 712 (9.2%) in the placebo group.	There was no statistically significant difference in the risk of major vascular events between those who received n-3 fatty acid supplementation and those who received a placebo.
[16]	• A randomized, double-blind, parallel-group design. • Human subjects. • Placebo (gelatin capsules 500 mg) or n-3 PUFA (capsules containing 180 mg of eicosatetraenoic acid and 120 mg of docosahexaenoic acid) three capsules a day for 8 weeks.	Only the n-3 PUFA supplementation group showed a reduction in triglyceride levels after the supplementation period. TRAP levels after exercise are reduced by Supplementation.	Omega-3 fatty acids reduced triglycerides and TRAP levels after exercise, No significant effect on inflammatory and oxidative stress markers.

[17]	• RCT. • Humans • For 12 weeks, subjects were given one of these diets: a low-protein with low omega-3 PUFA diet (control), a low-carbohydrate high-protein (LCHP) diet, omega – 3 diet or a low-carbohydrate – high-protein (LCHP) with omega-3 diet	Glycated hemoglobin (HbA1c) and fasting glucose were reduced greatly in all the other three diet groups compared to the control diet group.	LCHP with omega-3 diet showed greater effects on fasting glucose and HbA1c than LCHP diet group and omega-3 diet group.
[18]	• RCT. • Humans • Three groups received either 1 g of omega-3 fatty acids from flaxseed oil, 1g of omega-3 fatty acids from fish oil, or a placebo for a period of 12 weeks (twice a day).	Flaxseed and fish oil supplementation significantly reduced insulin levels compared to the placebo. Also, C-reactive protein decreased significantly after flaxseed oil supplementation compared with the placebo. Total nitrite increased significantly after flaxseed oil and fish oil intake compared with placebo.	The study reveals that the effect of flaxseed oil and fish oil in reducing insulin and increasing total nitrite and total antioxidant capacity (TAC), is the same.
[19]	• Randomized, double-blinded, placebo-controlled trial. • Human subjects • For a period of 12 weeks, participants were allocated to either double placebo (PL) or curcumin plus placebo matching for LCn-3PUFA (CC), or LCn-3PUFA plus placebo matching for curcumin (FO), or curcumin plus LCn-3PUFA (CC-FO)	No change in HbA1c and fasting glucose in all groups. Insulin sensitivity was improved significantly in the CC supplemented group compared to PL.	The study suggests that curcumin and LCn-3PUFA reduced insulin resistance and triglycerides, so it could be an encouraging strategy for lowering the risk of developing T2D.
[20]	• RCT • Diabetic humans with vitamin D deficiency • 50,000 IU vitamin D every 2 weeks + 2000 mg/day omega-3 fatty acids	Both, the mean and maximum levels of left carotid intima-media thickness (CIMT) and the mean and maximum levels of right CIMT are decreased significantly with co-supplementation of vitamin D and omega-3 fatty acids compared to the placebo.	Supplementation of vitamin D with omega-3 fatty acids improved cardio-metabolic risk markers.
[21]	• RCT. • Human subjects • The control group (received corn oil), fish oil group (eicosatetraenoic acid, EPA: docosahexaenoic acid, DHA = 3:2, total 2.0 g/day), and the fish oil + high intensity interval training group (HIIT).	Compared to fish oil supplementation, High intensity interval training (HIIT) shows an additive effect on glycemic control, insulin resistance and cardiovascular risk.	The combination of fish oil and HIIT shows better results than fish oil intervention because of the greater effects on glycemic control, insulin resistance and cardiovascular risk.
[22]	• RCT • Humans • Test group (TG)1 received 3g fish oil plus 100mg aspirin (ASA) daily for 2 months), or test group (TG)2 received 3 g fish oil plus 100 mg aspirin daily for 2 months prior to periodontal exfoliation	Deep and medium pockets have demonstrated clinical attachment gain for TG1. For both test groups, IFN-γ and IL-8 levels are decreased over time. HbA1c levels decreased for TG1.	The study reveals that supplementation with omega-3 fatty acids and ASA adjunct to periodontal debridement provides clinical and immunological advantages for patients with type 2 diabetes

[23]	• RCT • Type 2 diabetes and NAFLD were randomly assigned 1:1:1:1 to four treatments. • Each group received oral doses of one of the following: 10 mg dapagliflozin (n = 21), 4 g OM-3CA (n = 20), a combination of both (n = 22) or placebo (n = 21).	Combination treatment reduced liver proton density fat fraction (PDFF) (p = 0.046) and total liver fat volume (relative change, -24%, p = 0.037) in comparison with placebo. Dapagliflozin alone and in combination with OM-3CA improved glucose control and reduced body weight and abdominal fat volumes.	The study shows that Dapagliflozin and OM-3CA therapy in combination dramatically decreased the amount of liver fat. All assessed hepatocyte damage biomarkers were decreased, as well as FGF21, by dapagliflozin monotherapy, suggesting a disease-modifying impact in NAFLD.
[24]	• Double-blind, randomized, parallel-arm placebo-controlled. • Obese humans • For a period of 12 weeks, participants received either 2g/day of corn oil or 2g/day of fish oil.	Compared to corn oil, fish oil decreased fasting insulin levels and HOMA-IR.	The study reveals that fish oil supplementation adjunct to dietary and lifestyle advice has a beneficial effect for overweight and obese men and women.
[25]	• RCT • Type 2 diabetic humans • The participants were randomly allocated to two intervention groups receiving either n-3 PUFAs (2,700 mg/day) (n= 30) or placebo soft gels containing 900 mg of edible paraffin (n= 30).	In n-3 PUFA-supplemented subjects, NRF2 gene expression was significantly increased, compared with the placebo group. Plasma total antioxidant status was also significantly augmented in n-3 PUFA-supplemented subjects.	N-3 PUFA supplementation increased NRF2 gene expression and elevated overall antioxidant capacity, which may be helpful in reducing oxidative stress and preventing problems from T2DM.
[26]	• RCT • Humans • From 2011 to 2017, participants received 1 g/day of fish omega-3 fatty acids and 2000 IU/day of vitamin D3 (cholecalciferol).	The HR for the first HF hospitalization was 0.69 (95% CI: 0.50–0.95) in patients with prevalent T2D and 1.09 (95% CI: 0.88–1.34) in participants without T2D when omega-3 supplements were compared to placebo.	The study reveals that, in patients with T2D, supplementation with omega-3 fatty acid had a beneficial effect on incidence of HF hospitalization, but not in people without T2D, and such benefit seemed to be more noticeable in Black patients with T2D.

LCn-3PUFA: long-chain omega-3 polyunsaturated fatty acids; LCHP: low-carbohydrate high-protein; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; IFN-γ: Interferon gama; IL-8: Interleukin 8; TRAP: total reactive antioxidant potential; HR: Hazard Ratio; HF: Heart Failure; CI: Confident Interval; OM-3CA: omega-3 (n-3) carboxylic acids; NFLD: non-alcoholic fatty liver disease; NRF2; transcription factor that induces the expression of several proteins with antioxidant properties; T2D: Type 2 Diabetes Mellitus.

4. CONCLUSION

Clinical studies have demonstrated that omega-3 fatty acids have beneficial effects on glycemic control and insulin resistance, so they might help to reduce obesity and associated metabolic diseases. These results include increased fat oxidation, decreased fat accumulation, and increased energy expenditure. Additional studies including other biomarkers such as Irisin or others, are required to better assess this response and to comprehend the effect of

different types of omega-3 fatty acids such as fish oil, flaxseed oils, and EPA and DHA supplements in T2DM.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no conflict of interest.

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