Maturitas 74 (2013) 303–308

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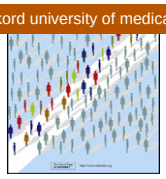

Review

Role of dietary n-3 polyunsaturated fatty acids in type 2 diabetes: A review of epidemiological and clinical studies

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ARTICLE INFO

Article history:
Received 15 October 2012
Received in revised form 8 January 2013
Accepted 9 January 2013

Keywords:
Type 2 diabetes mellitus
n-3 PUFAs
Epidemiological studies
Clinical studies

ABSTRACT

The worldwide increasing prevalence of type 2 diabetes mellitus (T2DM) poses an immense public health hazard leading to a variety of complications such as cardiovascular diseases, nephropathy and neuropathy. Diet, as a key component of a healthy human lifestyle, plays an important role in the prevention and management of T2DM and its complications. The dietary n-3 polyunsaturated fatty acids (PUFAs) have been associated with various favourable functions such as anti-inflammatory effects, improving endothelial function, controlling the blood pressure, and reducing hypertriglyceridemia and insulin insensitivity. According to some epidemiological studies, a lower prevalence of T2DM was found in populations consuming large amounts of seafood products, which are rich in n-3 PUFAs. However, the evidence on the relation between fish intake, dietary n-3 PUFAs, and risk of T2DM is controversial. Therefore, this paper aimed to review the epidemiological and clinical studies on the role of dietary n-3 PUFAs in T2DM. Also, the limitations of these studies and the need for potential further research on the subject are discussed.
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1. Introduction

Diabetes has become a worldwide problem leading to blindness, renal failure and lower limb amputation. Moreover it is a significant risk factor for coronary heart disease and stroke [1,2]. The number of adults with diabetes in the world is thought to increase from 285 million (6.4%) in 2010 to 439 million (7.7%) in 2030 [3]. Insulin resistance is a major problem in type 2 diabetes mellitus (T2DM) and is determined by normal amounts of insulin failing to maintain normal blood glucose because of decreased responsiveness of muscle (glucose uptake), liver (inhibition of gluconeogenesis) and fat cells (inhibition of lipolysis) [4–6]. There are several factors contributing to the development of insulin resistance and T2DM such as genetic predisposing factors, diet, activity of antibodies against insulin and its receptors, stress and inflammation [6,7].

n-3 polyunsaturated fatty acids (PUFAs) are long-chain fatty acids found in seafood products such as fish and shellfish, and plant products such as nuts, soybean, flaxseed, linseed, canola and mustard. Unlike saturated fatty acids (SFAs), long-chain n-3 PUFAs have an important impact in human nutrition, disease prevention and health promotion [6]. Most of the *in vivo* studies declare anti-inflammatory effects of n-3 PUFAs, however it is controversial in clinical trials [8–10]. Therefore, they may be useful to prevent or at least reduce insulin resistance and diabetes [5]. The most important long-chain n-3 PUFAs are eicosapentaenoic acid (EPA),

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0378-5122/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.maturitas.2013.01.008

docosahexaenoic acid (DHA), and α-linolenic acid (ALA). Moreover, ALA is the precursor of DHA and EPA [9,11]. It can be converted to DHA and EPA by δ-6 desaturase/elongase and δ-5 desaturase/elongase, respectively. However, the conversion efficiency is very limited [9,11,12]. Seafood products are the main sources of DHA and EPA, while ALA mainly originates from plant products [9].

Dietary composition plays an important role in reducing risk of diabetes [13]. The role of dietary fat in T2DM has been reported for many decades. It has been stated that populations in which people have high intakes of fish had lesser risk of diabetes, because of the effect of n-3 PUFAs in controlling and even preventing the diabetes [12]. Owing to the fact that n-3 PUFAs are an important component of phospholipids in cell membrane, they can have fundamental effects on insulin transduction signals [10,14]. Also, n-3 PUFAs may control the expression of various metabolic genes *e.g.* genes involved in glucose metabolism [15].

This paper aimed to review the epidemiological and clinical studies regarding the effects of dietary n-3 PUFAs on T2DM and insulin sensitivity. Moreover, we discussed the limitations of these studies and the possible further researches in this field.

2. Epidemiological studies

Table 1 summarizes the results of some epidemiological studies regarding the effects of dietary n-3 PUFAs on T2DM. Epidemiological studies have demonstrated a lower prevalence of impaired glucose tolerance and T2DM in populations with consumption of fish products [16,17]. n-3 PUFAs may decrease insulin resistance trough a number of mechanisms such as decrease in plasma triglycerides and perhaps small dense lipoproteins [5]. It has been proved that substituting SFAs with unsaturated fats such as n-3 PUFAs may have beneficial effects on insulin sensitivity and may reduce the risk of T2DM incidence from impaired glucose tolerance state [18,19].

2.1. Prospective cohort studies

Intake of n-3 PUFAs originating from various marine sources is either unrelated to diabetes incidence or modestly increases its risk as testified by prospective cohort studies [20–22]. In contrast, total and n-6 PUFAs seem to have protective effects [22,23]. In an EPIC-Norfolk cohort study, consumption of one or more portion/week of shellfish (as a source of n-3 PUFAs) increased the risk of diabetes [24]. The reported risks might be due to unhealthy oils rich in both saturated and *trans* fatty acids used for frying fish or shellfish, environmental contamination of marine products, the type and amount of cooking fat used, and the possible accompanying condiments with which these products are often served such as mayonnaise or butter [13,25]. In contradiction to the above mentioned results, epidemiological studies among Alaskan Eskimos (known for a very high intake of n-3 PUFAs) has shown a low prevalence of diabetes [16,26].

In a 30-year follow up survey of Dutch and Finnish cohort of the Seven Countries Study, it was found that an increase of 8 g/1000 kcal in fish consumption (from 7 to 15 g/1000 kcal) inversely affected the blood glucose level [19]. Other studies reported that consuming one or more portion *versus* less than one portion/week of fish (either white or oily fish) was associated with a lower risk of diabetes [17,24]. In contrast, several studies demonstrated that n-3 PUFAs did not reduce the risk of T2DM [20,21,23,27]. A large prospective study reported that the relative risk of T2DM was slightly higher for women who had 5 servings or more of fish meal/week compared to those who had one serving/month, after adjusting the other dietary and lifestyle risk factors [20]. It was suggested that some toxins such as dioxins and methyl mercury may interrupt the insulin actions [13]. Furthermore, high-dose consumption of n-3 PUFAs can lower glucose utilization and increase glucagon stimulated C-peptide [28]. In one study, the role of n-3 PUFAs originating from either marine or non-marine sources on the development of T2DM was investigated. It was found that consumption of marine sources of n-3 PUFAs (range, 0.11–0.6 g/day) was not associated with T2DM risk. However, non-marine sources of n-3 PUFAs (range, 0.27 to 1.06 g/day) decreased the risk of T2DM [21]. A case-cohort study, nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, reported that lean fish consumption (range of intake, 38.1–139.7 g/week) and total fish consumption (range of intake, 19.8–244.4 g/week) were not associated with incidence of T2DM, but fatty fish intake (range, 4.1–102.6 g/week) had weakly inverse association with this disease [29]. A recent meta-analysis on 24 prospective cohort studies found that marine n-3 PUFAs have beneficial effects on the prevention of T2DM in Asian populations, but not in Western populations [30]. This contradiction might be due to differences in gene–diet interaction, life style and fish cooking methods [13,31].

Contradicting data are reported about the effects of dietary n-3 PUFAs on T2DM. However, the anti-inflammatory effects of n-3 PUFAs on cell membrane function and also insulin transduction signalling has been proved [5]. Therefore, the exact role of n-3 PUFAs intake from various foods in T2DM merits further investigations.

2.2. Cross-sectional and case–control studies

Case–control and cross-sectional studies have reported that recently diagnosed diabetic patients and subjects with undiagnosed T2DM consumed higher SFAs than healthy subjects. It might be due to not having the chance to change their diet compared with diabetic patients who had dietary treatment due to their disease [31]. Cross-sectional studies in which clamp technique is used to measure insulin sensitivity and fatty acid composition in skeletal muscle demonstrated a direct relationship between insulin action and the proportion of long-chain n-3 PUFAs. Moreover, these studies found an inverse relationship between SFA content of the membrane and insulin sensitivity [32,33]. A large cross-sectional study of elderly Swedish men indicated that linoleic acid content of adipose tissue could be a good biomarker of n-6 PUFAs intake which was a protective factor for diabetes [34].

It is important that cross-sectional and case–control studies require cautious interpretation because of multiple sources of bias and the existence of confounders [31]. Furthermore, epidemiological studies using food frequency questionnaires or food records have a lower reliability compared with those in which biomarkers of intake such as fatty acid pattern in plasma or biological membranes are used to assess dietary fat intake [24,27].

3. Clinical studies

Several human clinical trials on the effects of n-3 PUFAs among participants with T2DM are summarized in Table 2. Most studies showed no effect of n-3 PUFAs supplementation on insulin sensitivity [35–38]. In these studies, the doses of fish oil and n-3 PUFAs supplement (EPA + DHA) were 3–3.6 g/day and 1.2–1.68 g/day, respectively, with the treatment duration of 8–12 weeks. Some studies declared the adverse effects of n-3 PUFAs supplementation in high doses (≥5 g/day) [28,39]. However, beneficial effects of n-3 PUFAs supplements on insulin sensitivity are reported in few studies [40,41]. Due to the small sample size in these 2 studies, the results of these studies cannot be reliable. In another study, Ramel et al. [42] showed that consumption of fish oil capsules (provided 1.3 g/day of n-3 PUFAs) for 8 weeks decreased fasting blood glucose and insulin resistance in 278 overweight and obese participants.

Table 1
Epidemiological studies on effects of dietary n-3 PUFAs on type 2 diabetes mellitus (T2DM).

Study design	Time of follow-up	Method of evaluation	Source of n-3 PUFAs	Results
Feskens et al. [17] 175 men and women aged 64–87 y in a prospective cohort study	4 years	Cross-check dietary history	Fish	Habitual consumption of small amount of fish reduced the risk of T2DM
Meyer et al. [18] 35988 women aged 55–69 y in a prospective cohort study	11 years	Frequent food questionnaire	Total dietary PUFAs intake	Substitution of SFAs with n-3 PUFAs reduced the risk of T2DM Vegetable fat inversely related to T2DM
Feskens et al. [19] 338 middle-aged men in a prospective cohort study	20 years	Cross-check dietary history	Fish products	SFAs were associated with impaired glucose tolerance test and T2DM Fish consumption decreased the risk of T2DM
Kaushik et al. [20] 152100 women and 42504 men aged 26–78 y in a prospective cohort study	14–18 years	Frequent food questionnaire	Total dietary PUFAs intake	SFAs intake positively related to incidence of T2DM Fish intake was not associated with the risk of T2DM
Brostow et al. [21] 43176 men and women without chronic diseases aged 45–74 y in a prospective cohort study	6 years	Frequent food questionnaire	Marine and non-marine sources of n-3 PUFAs intake	Non-marine sources of n-3 PUFAs decreased the risk of T2DM Marine sources of n-3 PUFAs were not associated with the risk of T2DM
Djouss et al. [22] 36328 women, mean age 54.6 y in a prospective cohort study	17 years	Frequent food questionnaire	Total dietary PUFAs intake	Higher intake of n-3 PUFAs ($\geq$ 0.2 g n-3 PUFAs/day or $\geq$ 2 servings of fish/day) increased the risk of T2DM
Van Woudenberg et al. [23] 4472 men and women aged $\geq$ 55 y in a prospective cohort study	15 years	Frequent food questionnaire	Fish and supplement	Fish consumption or EPA and DHA supplements were not associated with T2DM
Patel et al. [24] 21984 men and women aged 40–79 y in a prospective cohort study	10.2 years	Frequent food questionnaire	Seafood	Fish consumption reduced the risk of T2DM High- dose consumption of shellfish increased the risk of T2DM
Hodge et al. [27] 3737 adults aged 36–72 y in a prospective cohort study	4 years	Assessment of plasma and phospholipids biomarkers	Total dietary PUFAs intake	SFAs and T2DM incidence were directly associated No relation between n-3 PUFAs and T2DM incidence
Patel et al. [29] 12403 incident diabetes cases and 16835 adults from 8 European countries in a case-cohort study	3.99 million person-year	Country-specific food questionnaires	Fish	Total fish and lean fish consumption were not associated with incidence of T2DM Fatty fish consumption was weakly inversely associated with incidence of T2DM
Borkman et al. [32] 27 patients aged $\leq$ 65 y undergoing coronary artery surgery + 13 normal men in a cross-sectional study	–	Clamp technique for insulin sensitivity evaluation Assessment of fatty acid composition in skeletal muscle	–	PUFAs were inversely associated with insulin resistance in patients PUFAs were directly associated with insulin sensitivity in normal subjects
Pan et al. [33] 52 men aged $\leq$ 44 in a cross-sectional study	–	Clamp technique for insulin sensitivity evaluation Assessment of fatty acid composition in skeletal muscle	–	PUFAs were directly associated with insulin action
Iggman et al. [34] 795 men, mean age 71 y in a cross-sectional study in ULSM cohort study	–	Assessment of biomarkers in adipose tissue biopsies	Essential PUFAs biomarker	Lower amount of PUFAs in adipose tissue was associated with insulin resistance

Table 2
Clinical studies on effect of n-3 PUFAs on type 2 diabetes mellitus (T2DM).

Study design	Type, dose, and source of n-3 PUFAs	Timeframe	Results
Studies with beneficial effects			
Waite et al. [40] 5 subjects in an intervention study	Fish oil supplements (440 mg DHA + 660 mg EPA)	60 days	Increase insulin sensitivity Decrease plasma glucose response
Tsitouras et al. [41] 6 men and 6 women aged > 60 y in an intervention study	Consumption of 720 g of fatty fish/week plus 15 ml of sardine oil/day	6 weeks fatty fish accompanied by 8 weeks sardine oil	Increase in insulin sensitivity
Ramel et al. [42] 278 overweight and obese subjects in a controlled study of parallel design	Randomized to 4 energy-restricted diet (−30% of energy intake) Control group: no seafood Lean fish group: 150 g cod 3 times a week (0.26 g/day n-3 PUFAs) Fatty fish group: 150 g salmon 3 times a week (2.1 g/day n-3 PUFAs) Fish oil group: daily DHA/EPA capsules (1.3 g/day n-3 PUFAs)	8 weeks	Consumption of fish oil decreased fasting blood glucose, insulin resistance, and plasma triglyceride Weight loss was also a predictor of improve
Studies with no effects			
Giacco et al. [35] 162 healthy individuals in a parallel design	Subjects randomly divided to 2 groups Rich in MUFAs Rich in SFAs Within each group there was a second randomization to fish oil (3.6 g/day) or placebo	3 months	No change in insulin sensitivity, insulin secretion or glucose tolerance in both groups No change in body weight
Kabir et al. [36] 27 women with T2DM without hyper-triglyceridemia in a controlled study of parallel design	3 g/day of fish oil (1.8 g/day n-3 PUFAs) or placebo (paraffin oil)	2 months	No change in fasting blood glucose and insulin level
De Luis et al. [37] 30 subjects with T2DM, mean age 55 y in an intervention study	930 mg EPA + 750 mg DHA daily	12 weeks	No change in fasting insulin or glucose level
Tierney et al. [38] 417 participants with metabolic syndrome in a study of parallel design	Subjects randomly divided to 4 isoenergetic diets High SFAs High MUFAs High-complex carbohydrates supplemented with n-3 PUFAs (1.2 g/day) High-complex carbohydrates supplemented with placebo	12 weeks	Reducing SFAs had no effect on insulin sensitivity MUFAs and n-3 PUFAs had no effect on insulin sensitivity
Barre et al. [43] 18 participants with T2DM, mean age 60 y in a parallel design	Flaxseed oil, 5 g/day (60 mg/kg/day of α-linolenic acid) Safflower, 1 g/day	3 months	No effect on fasting blood glucose or insulin level compared with safflower oil
Taylor et al. [44] 34 participants with T2DM aged 51–54 y in a controlled study of parallel design	Subjects randomly divided to 3 groups No flaxseed Milled flaxseed (13.32 g/day) Flaxseed oil (12.13 g/day)	12 weeks	Milled flaxseed and flaxseed oil increased n-3 PUFAs in plasma phospholipids No effect on glycemic control in well-controlled type 2 diabetic patients
McManus et al. [45] 11 subjects with T2DM, aged 58–64 y in a cross-over study	Fish oil (35 mg/kg/day of 20:5 n-3 and 22:6 n-3) Linseed oil (35 mg/kg/day of 18:3 n-3)	3 months	No significant difference observed in weight, fasting glucose and insulin level
Studies with adverse effects			
Mostad et al. [28] 26 subjects with T2DM without hyper-triglyceridemia in a controlled study of parallel design	Intervention group: 17.6 ml/day fish oil (5.9 g of n-3 PUFAs) Control group: 17.8 ml/day corn oil (8.5 g of linoleic acid)	9 weeks	Increase in fasting blood glucose and insulin level Decrease in glucose utilization
Mostad et al. [39] 26 overweight participants aged 40–75 y in a controlled study of parallel design	Intervention group: 5.9 g/day fish oil Control group: 8.5 g/day corn oil (18:2 n-6)	9 weeks	Decrease in insulin sensitivity compared with control group

We concluded that further investigations are needed to confirm the results of the studies with beneficial effects.

The plant-base n-3 PUFAs which contain more α-linolenic acid than DHA and EPA, showed no beneficial effects on serum glucose and insulin response [43,44]. In another study, a comparison between the effects of marine-source n-3 PUFAs and plant-base n-3 PUFAs demonstrated no difference in improving insulin sensitivity between the mentioned sources [45].

A meta-analysis of 11 clinical trials asserted that n-3 PUFAs intervention (dose, 0.138–4 g/day; duration, 8–24 weeks) had no effect on insulin sensitivity [46]. In another meta-analysis of 18 randomized, placebo-controlled trials in type 2 diabetic patients, it was concluded that fish oil supplementation (range, 3–18 g/day; mean of intervention duration, 12 weeks) lowered triglycerides, but had no effects on glycemic control [47].

Overall, clinical trials have claimed that n-3 PUFAs can ameliorate plasma triglycerides, but seem to have no beneficial effect on insulin response and glycemic control [35–38,43]. The diet both in developed and developing countries contains higher amount of n-6 PUFAs [13,31]. Therefore, the subjects participated in the trials may require higher fish oil doses which are associated with higher n-3 and lower n-6 PUFAs content, to demonstrate the potential protective effect of n-3 PUFAs on insulin sensitivity. Additionally, the effect of n-3 PUFAs on insulin sensitivity is difficult to be evaluated because of the difficulties in finding a good and reliable marker for insulin sensitivity. Measurement of fasting blood glucose and insulin are not recommended as a good biomarker for insulin sensitivity, because they explain less than 40% of insulin sensitivity variance observed in a population and 13% of the insulin sensitivity variance in normal-weight participants [48]. Some reference methods such as frequently sampled intravenous glucose tolerance test, euglycemic-hyperinsulinemic clamp, and insulin suppression test are more reliable procedures in determining the degree of insulin sensitivity, but are more expensive and require large number of participants to have a meaningful dietary intervention study [49].

Adequate intervention duration is also important to detect a real clinical outcome. In most of the mentioned clinical studies (Table 2), the duration of interventions was between 8 and 12 weeks. The authors think that a longer period of intervention duration is needed to have an appropriate insulin response.

4. Conclusion

It is suggested that the epidemiological studies evaluate the preventive effects of dietary n-3 PUFAs on T2DM, whereas, clinical trials assess their therapeutic effects to ameliorate the condition. This would suggest avenues of investigations to be pursued.

In evaluating the effect of n-3 PUFAs on insulin sensitivity, it is difficult to have a final conclusion due to the contradictory results reported in different trials. The contradicting results might be due to the fact that several factors such as genetic, life style and different dietary patterns may influence the effect of n-3 PUFAs on insulin sensitivity and glycemic control. However, because of the beneficial effects of n-3 PUFAs on inflammation and obesity which are the risk factors in T2DM, the need for further exact trials on the subject is evident. The authors think that the acquired results from the investigations concerning no effect of n-3 PUFAs on T2DM might be due to the following limitations and therefore more clear and realistic experiments are needed:

(a) Inherent limitations of case–control and cross-sectional studies due to several sources of bias.
(b) Small sample size in some clinical trials.
(c) Lack of information about the background diet in some clinical trials.
(d) Limitations on the use of more exact and reliable reference methods in evaluating insulin sensitivity.
(e) Insufficient intervention duration in some clinical studies.
(f) Unrecognized optimum doses of n-3 PUFAs for an acceptable insulin response.

To overcome some limitations, it is advisable to organize a database of volunteers who are currently consuming n-3 PUFAs supplements and track their health status and serum biochemical indices over a long period. Moreover, simultaneous effects of n-3 PUFAs with other parameters should be considered.

Dietary approaches to stop hypertension (DASH) eating pattern can play an important role in reducing inflammation as a risk factor of T2DM. This dietary plan emphasizes the intake of fruits and vegetables; and is one of the therapeutic patterns to ameliorate T2DM [50]. Therefore, the n-3 PUFAs originating from vegetable sources which are non-expensive alternatives to the marine sources could be a challenging field for further investigations. It should be noted that there is lack of data on this subject.

Contributors

Tina Jafari declare that I participated in the collection of data and writing the manuscript. I have seen and approved the final version. Leila Azadbakht declare that I participated in providing the idea of the manuscript, reading the manuscript and commenting on manuscript. I have seen and approved the final version. Aziz A. Fallah declare that I participated in the manuscript design and structure. I have seen and approved the final version.

Competing interest

The authors declare that there are no conflicts of interest.

Provenance and peer review

Not commissioned, externally peer reviewed.

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