Maturitas 74 (2013) 303–308

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

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

Tina Jafari[a], Aziz A. Fallah[b], Leila Azadbakht[a,*]

[a] Food Security Research Center and Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord 34141, Iran

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.

Contents

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),

* Corresponding author at: Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Tel.: +98 311 792 2791; fax: +98 311 6682509.
E-mail address: azadbakht@hlth.mui.ac.ir (L. Azadbakht).

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.