Stearidonic Acid: Is There a Role in the Prevention and Management of Type 2 Diabetes Mellitus?1–3

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Abstract

Obesity and its related comorbidities are major public health concerns in the United States with over two-thirds of adults and one-third of children classified as overweight or obese. The prevalence of type 2 diabetes mellitus (T2DM) has similarly risen to an estimated 25.8 million, which accounts for a staggering $174 billion in annual healthcare costs. Identification of dietary interventions that protect against the development of T2DM would markedly reduce the medical and economic consequences of the disease. Hence, we review current evidence supporting a role of (n-3) PUFA in T2DM and explore potential therapeutic implications of stearidonic acid (SDA). The low consumption of fish in the US along with a reduced efficiency to interconvert most plant (n-3) PUFA highlights a need to find alternative sources of (n-3) PUFA. The efficient biological conversion of SDA to EPA underscores the potential implications of SDA as a source of (n-3) PUFA. The full therapeutic efficacy of SDA remains to be further determined. However, recent data have suggested a protective role of SDA consumption on markers of dyslipidemia and inflammation. The AHA recommends that healthy individuals consume oily fish at least twice per week and individuals with a history of cardiovascular disease consume 1 g of EPA+DHA/d. These goals will likely not be met by the typical American diet. Therefore, SDA may represent a sustainable alternative to marine-based (n-3) PUFA and may have novel therapeutic efficacy regarding the development of T2DM. J. Nutr. 142: 635S–640S, 2012.

Introduction

Obesity and its related comorbidities are major public health concerns in the United States with over two-thirds of adults and one-third of children classified as overweight or obese (1). The prevalence of T2DM6 has similarly risen to an estimated 25.8 million (or 8.3% of the US population), which accounts for a staggering $174 billion in annual healthcare costs (2–4). The efficacy of current pharmaceutical therapies to treat T2DM is limited by its multi-factorial pathology. Specifically, a group of metabolic abnormalities, often referred to as metabolic syndrome, is implicated in the development of obesity-associated T2DM. These risk factors, which include visceral obesity, dyslipidemia, hypertension, thrombosis, inflammation, and insulin resistance (5), are now recognized to precede frank diabetes. These pathologies also represent primary mediators of cardiovascular-related mortality in diabetic patients (5). Thus, identification of dietary interventions that protect against the development T2DM would markedly reduce the medical and economic consequences of the disease. Herein, we review current in vivo evidence supporting a role of (n-3) PUFA, including EPA and DHA, in the prevention and treatment of T2DM and related pathologies. Furthermore, we explore the potential therapeutic implications of the (n-3) PUFA, SDA.

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6 Abbreviations used: ALA, α-linolenic acid; CVD, cardiovascular disease; GLA, γ-linolenic acid; LA, linoleic acid; SDA, stearidonic acid; T2DM, type 2 diabetes mellitus.
Therapeutic implications for dietary intake of (n-3) PUFA in the development of T2DM

Numerous systematic reviews, meta-analyses (6–22), and primary publications (23–57) have addressed the use of dietary (n-3) PUFA in the prevention and management of obesity-related comorbidities, including T2DM and CVD. Many of these in vivo studies have also assessed the efficacy of (n-3) PUFA on attenuation of related metabolic pathologies, such as dyslipidemia, hypertension, inflammation, and insulin resistance. Herein, we explore potential therapeutic implications of the (n-3) PUFA and review the major findings of various studies.

Several reviews (9,13,16–18,20) have addressed the use of dietary (n-3) PUFA, including fish intake and fish oil supplementation on the development of T2DM and its related pathologies. McEwen et al. (18) concluded that a plethora of evidence exists to support an association between fish consumption and a reduction in risk factors for T2DM, including thrombosis (41–44), dyslipidemia (12,14,19), inflammation (6,23,26,45), and hypertension (30–32,52). Furthermore, the authors noted that a decrease in these metabolic abnormalities may also reduce CVD-related mortality in diabetic individuals (18). More recently, evidence has suggested the potential role of fish oil or EPA supplementation in the attenuation of insulin resistance, which is a hallmark of T2DM (13). Fedor and Kelley (13) also highlighted that discrepancies in clinical data may be attributed to variations in study design, including target population, macronutrient composition, source of (n-3) PUFA, and analytical methods used for determination of insulin sensitivity. Alternatively, Rodkowska (20) suggested that fish oil supplementation does attenuate dyslipidemia in diabetic individuals, whereas the influences of fish oil on glycemic control, hypertension, and inflammation remain less definitive. Nonetheless, these reviews (6–22) and primary publications (23–57) collectively support the use of (n-3) PUFA for attenuation of pathologies associated with T2DM.

Recent work (16) has implicated that fish oil may protect against the development of T2DM through modification of the obese phenotype. More specifically, consumption of (n-3) PUFA may protect against dyslipidemia, impaired glucose tolerance, and insulin resistance through a reduction in body fat and adipocyte hypertrophy (16). Similarly, Lombardo et al. (17) demonstrated that fish oil intake reduced total adiposity and fat cell size in a preclinical rodent model of T2DM. Corresponding with these effects was an improvement in glucose and lipid metabolism. A meta-analysis on the impact of fish oil intake on glycemic control and lipid parameters in diabetic individuals reported that plasma (n-3) PUFA concentration were negatively associated with total body fat (40). Moreover, it is suggested that the antiobesity effects of fish oil were associated with an improvement in plasma TG as well as a mild but significant reduction in fasting blood glucose concentration (40). Overall, these studies suggest that dietary (n-3) PUFA may attenuate T2DM and related pathologies through a reduction in obesity or modifications of adipocytes.

Low-grade inflammation is a primary risk factor in the development of T2DM (58). Makhoul et al. (38,39) demonstrated that the (n-3) PUFA concentration (i.e., EPA and DHA) in RBC was negatively associated with serum C-reactive protein (CRP) concentration in overweight and obese individuals. It is well established that (n-6) PUFA, such as arachidonic acid, are precursors for eicosanoid synthesis (26,59,60). These lipid derivatives exhibit significant proinflammatory properties, which are often targeted by pharmaceutical agents (61,62). Moreover, EPA and DHA act as antagonists of the eicosanoid synthesis by blocking (n-6) PUFA incorporation into phospholipids (61,62). Additional antiinflammatory properties of (n-3) PUFA may be mediated through specific cell surface receptors, including a novel G protein-coupled receptor, GPR120 (45). Stimulation of these receptors with EPA or DHA may attenuate insulin resistance through a reduction in tissue-specific inflammation. Additionally, dietary (n-3) PUFA may ameliorate inflammation through modification of PPARγ and Toll-like receptor signaling in adipose tissue (51). Collectively, these findings indicate a strong relationship between (n-3) PUFA consumption and a reduction of low-grade inflammation in individuals diagnosed with T2DM.

Recent work (63) has demonstrated that the beneficial effects of (n-3) PUFA consumption on T2DM may be attributed to improvements in lipid metabolism. For instance, lipid accumulation in nonadipose tissue such as heart, skeletal muscle, pancreas, and liver, is associated with development of T2DM, CVD, and nonalcoholic fatty liver disease. The consumption of (n-3) PUFA protects against these metabolic disparities through attenuation of dyslipidemia (12,14,64) and ectopic lipid accumulation in diabetic subjects (46). Moreover, EPA and DHA supplementation directly reduce lipid accumulation in pancreas, liver, and heart, which blunts the progression of T2DM, nonalcoholic fatty liver disease, and CVD-related mortality (63). Although the mechanisms involved are poorly understood, it is now apparent that consumption of (n-3) PUFA can improve markers of lipid metabolism and related pathologies associated with T2DM.

It is now evident that dietary (n-3) PUFA represents a potential therapy for attenuation of the diabetic phenotype (6–57). Despite these findings, there remain several inconsistencies regarding the efficacy of (n-3) PUFA to improve metabolic dysfunction in T2DM. These disparities may reflect differences in experimental design or study populations. In particular, the type and amount of dietary (n-3) or (n-6) PUFA can reduce the activity of Δ6-desaturase and thus impair interconversion of EPA and DHA in vivo (Fig. 1). This is especially apparent in subjects provided diets with high ALA and/or LA content (61). The efficiency of Δ6-desaturase is also highly variable in humans, with women exhibiting the greatest activity (61). In addition, the severity of metabolic dysfunction within diabetic individuals (i.e., hyperglycemia) is reported to affect Δ6-desatase activity and reduce interconversion of (n-3) PUFA (7,8,65–70). There are many other physiological or dietary confounders that affect the interconversion and biological activity (i.e., antidiabetic properties) of EPA and DHA (7,8,65–70). These issues will need to be addressed to fully determine the efficacy of fish intake or fish oil supplementation in protecting against metabolic dysfunction in humans with T2DM. Nonetheless, the collective evidence supports the utilization of dietary (n-3) PUFA as a therapeutic intervention for the prevention and management of T2DM and its related pathologies.

Therapeutic implications for SDA in the development of T2DM

SDA (18:4) is an (n-3) PUFA typically found at low quantities in the diet (71–73). It is generated through the desaturation of ALA (18:3) by Δ6-desaturase (Fig. 1). For this reason, and unlike ALA, dietary SDA does not require Δ6-desaturase activity for EPA synthesis. In the typical diet, SDA is supplied by through marine sources, although the concentration of SDA in fish is limited, highly variable, and can range from 0.9 to 3%, depending on the species of fish (i.e., salmon, mackerel,
Cod, menhaden, herring, and sardine. Negligible amounts of SDA are also found in certain algae and plant species (71–73). Plant oils, such as echium, borage, and currant, represent the predominant nonmarine source of SDA in the food supply (62). Echium oil, derived from the seeds of *Echium plantagineum*, is one of the richest plant sources of SDA, containing 3.5–9.0% (62). Commonly consumed vegetable oils contain negligible SDA (62,74). Recently, SDA-enriched vegetable oils have been produced through biotechnological modification. For example, transgenic soybean plants (62,74) have been generated through targeted incorporation of Δ6-desaturase and Δ15-desaturase genes (Fig. 1). The resulting soybeans produce oil markedly higher in (n-3) PUFA content (Table 1). Specifically, the composition of the oil is ~15–30% SDA and 5–8% GLA. The oil is also moderately higher in ALA and palmitic acid with lower oleic and LA contents relative to traditional soybean oil (Table 1). At this point, there are no readily available plant-based oils that have this unique fatty acid profile.

Recent animal and human studies have demonstrated that SDA can increase RBC concentrations of EPA with a greater efficiency than ALA (75–77). It has been demonstrated that the enrichment of RBC with EPA and DHA reflect other tissue membrane (n-3) PUFA content and this enrichment is expressed as the (n-3) index (78–80). The (n-3) index has been found to strongly correlate with a reduced risk of CVD such as sudden cardiac death (78–80). An (n-3) index (i.e., percentage of EPA/DHA in RBC) of ≥8% is recommended to protect against metabolic disease (81), such as T2DM and CVD (78–80). Recent studies (75–77) have demonstrated that dietary SDA substantially improves this clinical marker more efficiently than ALA supplementation. James et al. (77) further suggested that consumption of 1 g of SDA is equivalent to 300 mg of dietary EPA in terms of the (n-3) index. These findings demonstrate the potential importance of SDA-enriched soybean oil as a more sustainable alternative to marine-based EPA and DHA (82).

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Soybean</th>
<th>SDA soybean</th>
<th>Flaxseed</th>
<th>Canola</th>
<th>Corn</th>
<th>Cottonseed</th>
<th>Olive</th>
<th>Echium oil</th>
<th>Peanut</th>
<th>Safflower</th>
<th>Sunflower</th>
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<td>% total fatty acids by weight</td>
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<tr>
<td>14:0 (myristic)</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
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<td>16:0 (palmitic)</td>
<td>7.0–12</td>
<td>9–13</td>
<td>P</td>
<td>4</td>
<td>11</td>
<td>22</td>
<td>13</td>
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<td>11</td>
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<td>18:0 (stearic)</td>
<td>2.0–5.5</td>
<td>2.0–5.5</td>
<td>P</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3.7</td>
<td>2</td>
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<td>18:1 (oleic)</td>
<td>19–30</td>
<td>10–20</td>
<td>18</td>
<td>62</td>
<td>28</td>
<td>19</td>
<td>71</td>
<td>15.9</td>
<td>48</td>
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<td>48–65</td>
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<td>16</td>
<td>22</td>
<td>58</td>
<td>54</td>
<td>10</td>
<td>18.8</td>
<td>32</td>
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<td>5–10</td>
<td>9–12</td>
<td>57</td>
<td>10</td>
<td>1</td>
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<td>28.4</td>
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<td>12.5</td>
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1 ALA, α-linolenic acid; GLA, γ-linolenic acid; LA, linoleic acid; SDA, stearidonic acid.
2 From (97).
3 From (98).
4 From (99).
5 From (100).
6 From (88).

**TABLE 1** Compositional comparison of SDA soybean oil, echium oil, and common vegetable-derived food oils

**FIGURE 1** Metabolism of PUFA and key interconversion of (n-9), (n-6), and (n-3) PUFA. In humans, Δ6-desaturase is considered the rate-limiting step in converting ALA to EPA. The type and amount of dietary (n-3) or (n-6) PUFA can reduce the activity of Δ6-desaturase and thus impair interconversion of EPA and DHA in vivo. This is especially apparent in participants provided diets with high ALA or LA content. The efficiency of Δ6-desaturase is also highly variable in humans. In addition, the severity of metabolic dysfunction within diabetic individuals is reported to negatively affect Δ6-desaturase activity and reduce interconversion of (n-3) PUFA. To bypass the compromised desaturase genes, transgenic soybean plants (SDA-enriched soybean) were recently generated through targeted incorporation of Δ6-desaturase and Δ15-desaturase genes. The resulting soybeans produce oil markedly higher in SDA and GLA and lower in LA and ALA (Table 1). It may be possible that SDA and its potential benefits should be considered as a sustainable alternative to marine-derived omega-3 fatty acids.
the fishing industry (6,60,62) have provided the need for more viable and cost-effective strategies to increase consumption of (n-3) PUFA. Thus, SDA-enriched soybean oil is uniquely positioned due to its established manufacturing process and more efficient conversion of SDA to EPA and DHA in humans.

There are limited studies (62,71,75–77,83–90) examining the impact of SDA consumption on the development of T2DM and/or its related pathologies. To date, only a few studies have directly utilized SDA-enriched soybean oil (75–77,85) and these studies have been primarily focused on the verification of changes in tissue EPA content or modification of the (n-3) index. Hence, the current understanding of the antidiabetic properties of SDA relies on data from studies of alternative SDA plant oils that contain less SDA and have different fatty acid profiles. In particular, Surette et al. (88) reported that participants consuming 15 g/d of echium oil for 4 wk had a lower serum TG concentration, similar to fish oil. The hypolipidemic effect of echium oil was recently supported using a genetic rodent model of dyslipidemia (90). Further, mice (apoB100-only LDLrKO) fed echium oil exhibited a decrease in plasma TG and VLDL concentration. There was also a significant hepatoprotective effect in echium oil-fed animals, which was evident by a decrease in liver TG content and downregulation of several genes involved in hepatic TG biosynthesis. The authors concluded that echium oil may provide a botanical alternative to fish oil regarding plasma TG and VLDL concentration.

The link between obesity-related comorbidities, such as T2DM and low-grade systemic inflammation, is well established (58). It was also reported that the (n-3) index is negatively associated with the serum CRP concentration (38,39). More recently, SDA-containing plant oils were shown to have marked antiinflammatory properties (77,87,87). Miles et al. (86) demonstrated that SDA intake (1.0 g/d) in combination with GLA (0.9 g/d) increased the EPA content in circulating immunocytes, including neutrophils and macrophages. Similarly, Wu et al. (91) observed that supplementation of blackcurrant seed oil (high in GLA, ALA, and SDA) reduced PG E2 production, which exhibits significant proinflammatory effects in humans. It may be possible that SDA and GLA consumption, individually or in combination with each other, could elicit marked antiinflammatory properties in vivo (8,62,67,86,87,91–94). However, further investigation is necessary to fully elucidate these effects in the development of T2DM as well as the potential benefit of SDA-enriched soybean oil.

In conclusion, the low consumption of marine-based (n-3) PUFA in the US along with a reduced efficiency to interconvert ALA in vivo has amplified the need to find alternative dietary sources or precursors of EPA and DHA (6–8,59,61,62,65,67). Thus, the efficient conversion of SDA to EPA in humans emphasizes the potential usefulness of SDA-enriched soybean oil (76,77,85). So far, consumption of this oil in humans has been shown to result in its effective conversion to EPA, whereas only marginal amounts are metabolized to DHA (76,77,85), which may reflect the low Δ6-desaturase activity required for the synthesis of DHA (7,8,59,61,67). As established in this paper, the therapeutic implications of SDA-enriched soybean oil remain to be fully determined. However, recent data (62,71–73,75–77,78–84,88,90,95,96) has suggested a protective role of SDA consumption on markers of dyslipidemia and inflammation. Recently, the generation of transgenic soybeans has produced unique oil containing 15–30% SDA, 5–8% GLA, and 9–12% ALA (Table 1). This particular fatty acid profile is unique to SDA-enriched soybean oil and is more effective at improving the (n-3) index compared to traditional soybean or other common plant oils (76). The AHA recommends that healthy individuals consume oily fish (i.e., salmon, tuna, mackerel, herring, and trout) at least twice per week and individuals with a history of CVD are advised to consume 1 g of EPA+DHA/d. These goals will likely not be met by the typical American diet. Therefore, SDA-enriched soybean oil may represent a sustainable and efficient alternative to marine-based (n-3) PUFA and could have novel therapeutic uses regarding the development of T2DM and related pathologies.

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