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POLYUNSATURATED FATTY ACIDS FAMILY *N*-3 – PROOXIDANT OR ANTIOXIDANT FACTOR IN DIABETES MELLITUS? – A REVIEW

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Oxidative stress is considered as a likely causative factor in the development of insulin resistance leading to diabetes mellitus. Meals rich in lipids disturb the redox balance in humans. Some nutrients such as *n*-3 long-chain polyunsaturated fatty acids may enhance the oxidative processes, however many studies underline their possible beneficial effect in the prevention and treatment of diabetes mellitus. N-3 polyunsaturated fatty acids are obtained not only from naturally occurring foods but also from pharmaceutical *n*-3 supplements. Possible roles played by essential fatty acids, in the oxidative processes in diabetes mellitus, are discussed in light of recent evidence and available methods.

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases affecting millions of people worldwide. The report of The World Health Organization indicates that the prevalence of diabetes for age-groups was estimated to be 2.8% in 2000, and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [Wild *et al.,* 2004].

Oxidative stress is one factor which increases the side effects of long-lasting or badly controlled type 2 diabetes mellitus. Many studies have documented that the increased oxidative state, observed in patients with type 2 diabetes, is due to increased oxygen derived free radicals, such as hydrogen peroxide [Jain *et al.,* 2002; Halliwell, 2002]. Hydrogen peroxide leads to the activation of stress kinases such as c-Jun N-terminal kinase, p38, I kappaB kinase, and extracellular receptor kinase 1/2. This activation is accompanied by a down-regulation of the cellular response to insulin, leading to a reduced ability of insulin to promote glucose uptake, and glycogen and protein synthesis [Bloch-Damti & Bashan, 2005].

Hyperglycemia and free fatty acids are associated with increased mitochondrial reactive oxygen species production and, as a consequence, increased oxidative stress [Bloch-Damti & Bashan, 2005; Ursini & Sevanian, 2002]. Prolonged exposure to reactive oxygen species (ROS) affects transcription of glucose transporters: whereas the level of glucose transporter-1 (GLUT1 – protein that facilitates the transport of glucose across the plasma membranes) is increased, GLUT4 levels (responsible for insulin-regulated glucose disposal in adipose tissues and striated muscle) are reduced. While studies in animal models of diabetes have demonstrated that administration of antioxidants improves insulin sensitivity. Therefore oxidative stress is presently accepted as a likely causative factor in the development of insulin resistance [Bloch-Damti & Bashan, 2005].

Many dietary factors influence oxidative stress; therefore analysis of the diet should be of primary importance [Sies *et al.,* 2005; Wander & Du, 2000; DeFilippis & Sperling, 2006]. Dietary fat has been implicated in the development of insulin resistance. Some studies suggest that consumption of high levels of total fat from the diet can result in greater whole-body insulin resistance [Lovejoy, 2002; Haag & Dippenaar, 2005; Petersen & Shulman, 2002; Boden, 2003]. Moreover, the high levels of dietary fat can impair insulin sensitivity, independent of body weight changes [Kahn & Pedersen, 1993]. In addition, it appears that different types of fat have different effects on insulin action. Saturated and certain monounsaturated fatty acids have been implicated in causing insulin resistance, whereas polyunsaturated, especially *n*-3 polyunsaturated fatty acids (PUFA), largely, do not appear to have adverse effects on insulin action [Lovejoy, 2002]. Furthermore, clinical studies in patients with diabetes mellitus have demonstrated many beneficial effects of *n*-3 polyunsaturated fatty acid consumption [DeFilippis & Sperling, 2006]. Their cardio-protective effect occurs without adverse effects on glucose control or insulin activity, in subjects with type 2 diabetes. Polyunsaturated *n*-3 fatty acids lower blood pressure and improve the lipid profile [Woodman *et al.*, 2002]. They also improve endothelial function and reduce platelet aggregation, these findings encourage their use in daily food consumption, especially in patients with cardiovascular diseases [Julius, 2003; Vanschoonbeek *et al*., 2003; Sethi *et al*., 2002]. The increased consumption of *n*-3 long chain – polyunsaturated

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fatty acids (LC-PUFA), together with reduced intake of saturated fat may reduce the risk of conversion from impaired glucose tolerance to type 2 diabetes in overweight subjects [Nettleton & Katz, 2005].

Despite the benefits of dietary treatment with marine *n*-3 polyunsaturated fatty acids in cardiovascular disease there remains concern, with respect to their increased potential for peroxidation [Johansen *et al.*, 1999]. Unsaturated bonds, characteristic of long-chain n-3 fatty acids, and found in eicosapentaenoic acid (EPA 20:5*n*-3) and docosahexaenoic acid (DHA 22:6*n*-3), can promote the oxidation process [Woodman *et al.*, 2002; Johansen *et al.*, 1999; Dierckx *et al.*, 2003; Ceriello, 2005; Pedersen *et al.*, 2003], and seem to be the molecules most susceptible to free radical attack [NRC, 1989]

To date, data from *in vivo* studies are inconclusive [Jain *et al.,* 2002; Johansen *et al.*, 1999; Pedersen *et al.*, 2003; Kesavulu *et al*., 2002]. However, supplementation with fish oils has been proposed as a non-pharmacological way to correct the atherogenic lipid abnormalities found in patients with diabetes mellitus. Therefore, this article will review the literature surrounding *n*-3 polyunsaturated fatty acids, to investigate their significance during dietary intervention therapy and also investigate their role during oxidative stress.

POSTPRANDIAL OXIDATIVE STRESS

When considering dietary intervention in subjects with diabetes mellitus, oxidative stress should be considered. Oxidative stress refers to an abundance of free radicals or highly reactive oxygen species that can result from lipid peroxidation, this process describes an imbalance between the pro-oxidant load and the antioxidant defenses. This imbalance may be a consequence of excess oxidative load or of inadequate supply of nutrients [Sies *et al.,* 2005; Ursini & Sevanian, 2002]. Because in Western societies, a significant part of the day is spent in the postprandial state Sies *et al.* [2005] underlined the meaning of postprandial oxidative stress. This is a subform of nutritional oxidative stress, which ensues from sustained post-meal hyperlipidaemia and/or hyperglycemia and is associated with an increased risk of developing atherosclerosis, diabetes, and obesity [Sies *et al.,* 2005]. Postprandial oxidative stress is characterised by an increased susceptibility towards oxidative damage after consumption of a meal rich in lipids and/or carbohydrates [Ursini & Sevanian, 2002]. Thus, macronutrients have an effect on the redox balance within humans. After dietary absorption, unsaturated fatty acids are incorporated into VLDL and ultimately LDL; these molecules may be the target for oxidative modification and therefore have the potential to be atherogenic. Also, molecules may be consumed from the diet in a pro-oxidant form, for example if lipid hydroperoxides are absorbed from the diet they will contribute to the pro-oxidant load. Studies have demonstrated that in hyperlipidaemia and hyperglycemia there is an association between increased oxidative damage and decreased antioxidant status [Bae *et al.,* 2002].

Thus, postprandial oxidative stress has been implicated in the pathogenesis of diabetic complications [Dierckx *et al.,* 2003; Ceriello, 2005; Halliwell, 2002; Adeghate, 2004; Sanusi, 2004; Okouchi *et al.,* 2005; Pantsulaia, 2006; Sima, 2006; Tsai *et al.,* 2004] including its involvement in the development of atherosclerosis [Schulze *et al.,* 2004]. In atherosclerosis an important background risk factor is postprandial hyperglycemia. Blood glucose increases after a meal and is a predictor of cardiovascular risk, as, due to oxidative stress, it may have a direct toxic effect on the vascular endothelium and this is independent of other cardiovascular risk factors such as hyperlipidaemia [Griendling & FitzGerald, 2003]. Hyperglycemia is also a major etiological factor in the development of diabetic cardiomyopathy. Increased blood glucose concentration promotes the production of reactive oxygen (ROS) and nitrogen species (RNS). The release of these reactive particles induces oxidative stress leading to abnormal gene expression, faulty signal transduction and apoptosis of cardiomyocytes [Adeghate, 2004]. Cardiovascular complication including myocardial infarction is one of the main causes of death in diabetic patients [Adeghate, 2004; Sanusi, 2004].

Hyperglycemia also leads to the most common late complication of diabetes – diabetic polyneuropathy [Pantsulaia, 2006; Sima, 2006]. An elevated blood glucose level is the cause of neuronal apoptosis and is accompanied by increased oxidative stress [Vincent *et al.,* 2005]. Repetitive postprandial hyperglycemia enhances not only oxidative damage caused by ischemia-reperfusion, but can also destroy the primary sensory neurons, known as dorsal root ganglion neurons. Damage to these cells results in diabetic peripheral neuropathy [Frantz *et al.,* 2005].

Thus, dealing with the complications of toxic blood glucose concentration and its consequence, oxidative stress, are a major clinical target.

POLYUNSATURATED *N*-3 FATTY ACIDS – PRO-OXIDANT OR ANTIOXIDANT FACTOR?

Despite the reported benefits associated with *n*-3 polyunsaturated fatty acids for cardiovascular disease, there remains concern that increased intake may lead to increased lipid peroxidation. Because *n*-3 LC-PUFAs are highly unsaturated, some authors underline that the increased consumption might increase oxidative stress. Oxidative stress is already associated with diabetes mellitus and supplementation with fatty acids may enhance the oxidative processes. These processes are connected with glycosylated LDL, which is particularly vulnerable to oxidation [Lyons & Jenkins, 1997; Young & McEneny, 2001]. There are suggestions that fish oil supplementation may further impair the oxidative resistance of LDL and lead to accelerated atherogenesis in diabetic patients [Johansen *et al.,* 1999; Lyons & Jenkins, 1997].

EPA and DHA can induce hyperlipidaemia as well as elevated plasma and tissue lipid hydroperoxide levels, in animals fed cholesterol-containing diets. Nevertheless, elevations in plasma hydroperoxide levels could readily arise from existing hydroperoxides associated with PUFA-rich foods, as they can from their propensity to undergo peroxidation after assimilation. LDL is a prominent target for postprandial oxidative modification [Dierckx *et al.,* 2003; Ceriello, 2005] and a study from a German group seems to confirm this hypothesis: in this study they demonstrated that the oxidizability of antioxidant-containing LDL (rate of lipid peroxida-

tion measured before total consumption of alpha-tocopherol, the major LDL antioxidant) correlated positively with its *n*-3 PUFA content. Therefore they concluded that the oxidizability of antioxidant-depleted LDL was largely determined by the PUFA content of the LDL [Kontush *et al.,* 1995]. Thus, the correlation between unsaturated fat intake and lipoprotein oxidation has been documented, therefore it is widely accepted that diets rich in PUFA lead to increased antioxidant demand [Halliwell, 2002; Sies *et al.,* 2005; NRC, 1989; Turpeinen *et al.,* 1995].

However, even clinical trials regarding supplementations with large doses of EPA and DHA are inconclusive. For example Pedersen and colleagues demonstrated that supplementation with 4 g daily of either type of fish oil for 8 weeks can increase both markers of *in vivo* oxidation and *in vitro* oxidation of LDL. In this study LDL was isolated by density gradient ultracentrifugation and oxidized *in vitro* with copper ions, malondialdehyde concentration in LDL (LDL-MDA) was used as a measure of *in vitro* oxidation, with the fish oils reducing both mean lag time and propagation rate [Pedersen *et al.,* 2003]. In another study (randomized double-blinded placebo-controlled trial), in addition to their normal diets, diabetic patients were supplemented with the same doses (4 g) of either EPA, DHA or olive oil per day for 6 weeks, results revealed beneficial effects on the lipid profile but adverse effects on short-term glycaemic control. Neither EPA nor DHA had any significant effects on glycated hemoglobin, fasting insulin, C-peptide, insulin sensitivity, secretin, or blood pressure. Serum triglycerides in the EPA and DHA groups decreased, but no significant changes were found in serum total, LDL, or HDL cholesterol [Woodman *et al.,* 2002]. Moreover, a study of Johansen and colleagues [1999] revealed that the supplementation of *n*-3 fatty acids decreased haemostatic markers of atherosclerosis for example, tissue plasminogen activator antigen and soluble thrombomodulin, whereas markers of inflammation were increased (soluble E-selectin and soluble vascular cell adhesion molecule-1) and therefore would contribute to increased cardiovascular risk in diabetic patients.

Conversely, a review by Das [2000] has underlined the inhibition of the synthesis and release of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-alpha) and interleukins: IL-1 and IL-2 by n-3 fatty acids. These cytokines are released during the early course of ischemic heart disease and they decrease myocardial contractility and induce myocardial damage, they enhance the production of free radicals, which can also suppress myocardial function. Based on this, it has been suggested that the principle mechanism of anti-inflammatory and cardioprotective action of *n*-3 fatty acids may be due to the suppression of interleukins and TNF-alpha synthesis and release [Das, 2000].

There are many studies that support the beneficial effects of fish oil supplementation, especially at low doses. Kesavulu *et al.* [2002] demonstrated that diabetic patients supplemented for two months with 1,080 mg of EPA and 720 mg of DHA per day, together with an anti-diabetic drug produced many desirable effects. After two months serum triglycerides decreased, HDL-cholesterol increased and lipid peroxide levels were significantly decreased. Among the erythrocyte antioxidant enzymes – glutathione peroxidase activity was also increased. Therefore, this study demonstrated that such treatment may lead to a decreased rate in the occurrence of vascular complications in diabetes [Kesavulu *et al.,* 2002]. The study of Jain *et al*. [2002] confirmed that parameters indicating oxidative stress such as raised lipid peroxides and conjugated dienes, together with reduced glutathione were found in subjects with type 2 diabetes. Another study assessed the effect of low dose *n*-3 polyunsaturated fatty acid substitution in subjects with type 2 diabetes, these subjects were randomized to either 180 mg EPA and 120 mg DHA or placebo, and their findings demonstrated reduced levels of parameters of oxidative stress, in the supplemented group. Moreover in the supplemented group there was a significantly greater improvement in glycaemic status, blood pressure and lipid profiles. Thus, substitution of low dose of *n*-3 polyunsaturated fatty acids for PUFA-6 (fatty acids found mainly in plant oils) seems to have significant beneficial effects not only on oxidative stress parameters but also on blood pressure and metabolic profile [Jain *et al.,* 2002].

Christensen and colleagues [2001] investigating if PUFA, derived from fish, reduced the incidence of sudden cardiac death (SCD) found that *n*-3 polyunsaturated fatty acids did have beneficial effects on 24-hour heart rate variability (HRV), in patients with diabetes mellitus. Patients' fish consumption was strongly related to their platelet *n*-3 PUFA content. In addition, patients with type 1 DM (diabetes mellitus) showed a close positive association between platelet *n*-3 PUFA content and 24-hour HRV, however, this association was not significant in patients with type 2 DM [Christensen *et al.,* 2001]. This finding may be partly explained by the increasing parasympathetic tone induced by *n*-3 polyunsaturated fatty acids that have positive influence on heart rate variability and protect the myocardium against ventricular arrhythmias. Increased parasympathetic tone and acetylcholine, the principle vagal neurotransmitter, significantly attenuates the release of TNF, IL-1beta, IL-6 and IL-18 [Das, 2000].

LIMITATION OF METHODOLOGY

As stated above, studies to date have been inconclusive regarding the involvement of *n*-3 polyunsaturated fatty acids in the treatment of type 2 diabetes [Jain *et al.,* 2002; Woodman *et al.,* 2002; Johansen *et al.,* 1999; Pedersen *et al.,* 2003; Kesavulu *et al.,* 2002; Das, 2000]. One reason for this may be due to the wide variety of parameters measured, together with the various types of methodologies employed in measuring these parameters. Therefore, the oxidative stress that is associated with patients with type 2 diabetes, especially those with the added complication of cardiovascular disease, requires more accurate measurement which would then allow evaluation of the involvement of fish oil supplementation. F_2-isoprostanes" (F_2-IsoPs), is a prostaglandin PGF_2-like product which is classed as a secondary peroxidation product and seems to be one of the most important markers of its class [Morrow & Roberts, 2002; Mori *et al.,* 1999]. F_2-IsoPs appears to be a significantly more accurate marker of the oxidative process in humans and animals, than other primary peroxidation ends products, such as conjugated dienes and lipid hydroperoxides. The isoprostanes are a unique series

of prostaglandin-like compounds formed *in vivo* from the free radical–initiated peroxidation of arachidonic acid, independent of the cyclooxygenase enzyme [Morrow & Roberts, 2002]. Thus, the quantization of F_2-isoprostanes provides a more reliable and useful assessment of *in vivo* lipid peroxidation and oxidant stress [Mori *et al.,* 1999*,* 2003].

The measurement of urinary F_2-isoprostanes, by gas chromatography-mass spectrometry, in a double-blind, placebo controlled trial in patients with type 2 diabetes, with hypertension provided evidence that daily supplementation with 4 g of purified EPA or DHA for 6 weeks reduced oxidative stress, *in vivo*. Post-intervention, urinary F_2-isoprostanes were decreased by 19% by EPA and 20% by DHA. Moreover the authors did not observe any change in inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). They therefore concluded that high doses (4 g) of either EPA or DHA reduced oxidative stress *in vivo* [Mori *et al.,* 2003]. This was further supported by the findings of an Australian group, who clearly demonstrated that *n*-3 polyunsaturated fatty acids, provided from daily fish meals, reduced oxidative stress *in vivo*. Both these intervention studies demonstrated that urinary F2-isoprostanes were significantly reduced by between 20-27% [Mori *et al.,* 2000].

In some studies it has been reported that intensive exercise increases lipid peroxidation [Watson *et al.,* 2005; Bailey *et al.,* 2001], while other studies have demonstrated that consumption of moderately high doses of fish oils (3.6 g/day *n*-3 LC-PUFA), even during acute exercise, has no influence on oxidative parameters. However, a study investigating the effects of short-term exercise (8-weeks) in subjects with type 2 diabetes and dyslipidaemia demonstrated that those subjects also taking regular fish meals (3.6 g/day *n*-3 LC-PUFA) had reduced levels of urinary F_2-isoprostanes [Mori *et al.,* 1999].

This response could further complement the known benefits of *n*-3 polyunsaturated fatty acids and exercise, favoring a reduced cardiovascular risk in diabetic patients [Mori *et al.,* 1999; Johansen *et al.,* 1999; Jarvinen *et al*., 2006]. Furthermore, exercise enhances parasympathetic tone, and the production of the anti-inflammatory cytokine IL-10, which may help explain the beneficial action of exercise in the prevention of cardiovascular diseases and diabetes mellitus [Das, 2000].

ANTIOXIDANTS

The available evidence suggests that double-blinded controlled clinical trials with antioxidants should be undertaken in order to develop strategies to delay the onset and ameliorate the development of type 2 diabetes [Halliwell, 2002]. It also seems that the appropriate levels of fat, as well as antioxidant vitamins in the diet are an important clinical goal. Low intake or impaired availability of dietary antioxidants, including vitamins E and C, carotenoids, polyphenols, and other micronutrients (*e.g.,* selenium) weakens the antioxidant network [Sies *et al.,* 2005; Wander & Du, 2000]. A study by a Belgian group investigating the antioxidant status in subjects with type 1 diabetes found that lipid peroxidation increased during the postprandial phase in parallel to glucose and triglyceride changes. However, blood antioxidants (such as ascorbate, retinol and α-tocopherol) followed a diverse pattern of change [Manuel-y-Keenoy *et al.,* 2005]. In a review of a large number of intervention studies Halliwell [2002] demonstrated the beneficial effects of vitamin E on endothelial function, retinal blood flow, and renal function (all factors which are abnormal in type 2 diabetes). This, together with the results from another study which demonstrated that postprandial oxidative stress was attenuated when dietary antioxidants were supplied together with a meal rich in oxidized or oxidizable lipids [Sies *et al.,* 2005]. To prevent *in vivo* oxidation of PUFA it is recommended that for each gram of PUFA consumed, 0.4 mg of RRR-α-tocopheryl acetate is needed [NRC, 1989].

FUTURE STUDY

Increased oxidative stress has been associated, not only with diabetes mellitus, but also with cardiovascular diseases, cystic fibrosis, cataract and infections [Julius, 2003; Vanschoonbeek *et al.,* 2003; Das, 2000; Manuel-y-Keenoy *et al.,* 2005; Woodman *et al.,* 2002, Ohia *et al.,* 2005; Rahman & Adcock, 2006]. The arousing interest in oxidative stress results from the detrimental influence free radicals has on lipids, endothelium and inflammatory factors however; this oxidative stress has also been implicated in the regulations of genes [Sethi *et al*., 2002]. It has been established that ROS influence the cellular redox state that leads to changes in intracellular thiols, especially glutathione, and thus demonstrates its role in the regulation of gene transcription [Wu *et al.,* 2004]. Antioxidants, such as polyphenols, modulate the expression of genes related to oxidative stress or antioxidant defenses [Moskaug *et al.,* 2004]. A variation in nutritional status leads to metabolic adaptations, which are affected by the individual genetic profile. Thus nutrigenomic approaches link nutrient supply and their resulting effects to a molecular basis of gene expression and may thus be the link between diabetic diet and oxidative stress [Bauer *et al.,* 2004].

CONCLUSIONS

Studies have revealed that fish oil supplements (4 g/day EPA or DHA) in patients with type 2 diabetes, lead to increased oxidation, both *in vivo* and *in vitro* [Woodman *et al.,* 2002; Pedersen *et al.,* 2003]. However, recent assessment of oxidative stress in subjects with hypertension and type 2 diabetes, demonstrated that consumption of 4 g per day of either EPA or DHA reduced the level of F_2-isoprostanes indicating reduced oxidative stress, *in vivo*. The same study revealed no change in inflammatory markers [Mori *et al.,* 2003], which had been reported previously by Johansen and colleagues [1999]. Other studies have concluded that low doses of fish oil (1,080 mg of EPA and 720 mg of DHA/day [Kesavulu *et al.,* 2002] or 180 mg EPA and 120 mg DHA/day [Jain *et al.,* 2002]) consumed by patients with type 2 diabetes had beneficial effects on markers of oxidative stress, as well as an improved metabolic profile. Thus, the interpretations of the influence of *n*-3 fatty acids on oxidative stress should be cautious with the particular considerations being paid to the dose administered and also the methods employed in measuring the inflammatory process. However, the measurement of F_2-isoprostanes seems to provide a reliable as-

sessment of *in vivo* lipid peroxidation and oxidant stress [Morrow & Roberts, 2002; Mori *et al.,* 1999, 2003].

Given the importance of insulin resistance in the development of diabetes and heart disease, establishing appropriate levels of fat in the diet is an important clinical goal. The European norms recommended by ISSFAL suggest that the energy percent from α-linolenic acid should range about 1.0% [Simpopoulos *et al.,* 1999]. The Nutrition Committee of the American Heart Association recommends at least 2 servings of fish per week to confer cardioprotective effects. Food sources of *n*-3 polyunsaturated fatty acids should include fish, especially fatty fish such as salmon, as well as plant sources such as flaxseed and flaxseed oil, canola oil, soybean oil, and nuts [Krauss *et al*., 2000]. The intake of 1 to 2 g/day *n*-3 LC-PUFA should be beneficial in the treatment of diabetes mellitus [Nettleton & Katz, 2005]. Finally, the pathogenic effect of glucose, possibly in combination with free fatty acids, may not only affect insulin sensitivity, insulin secretion, and survival, but may also play a role in the development of the secondary complications of diabetes [Robertson *et al.,* 2004; Green *et al.,* 2004; Evans *et al.,* 2003].

Thus dietetic therapy with the correct amounts of fatty acids seem to be one of the most important factors in the treatment of subjects with diabetes mellitus, as well as in the prevention of diabetes development, in patients with impaired glucose tolerance (IGT). However, the detailed relations between hyperglycemia and hyperinsulinemia, as well as the level of fatty acid intake and their influence on oxidative stress are still under research.

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