**REVIEW**

The Role of Consumption of Alpha-Linolenic, Eicosapentaenoic and Docosahexaenoic Acids in Human Metabolic Syndrome and Type 2 Diabetes- A Mini-Review

Douglas Edward Barre

Nutrition, Department of Health Studies, School of Education, Health and Wellness, Cape Breton University, Nova Scotia, CANADA B1P-6L2

Abstract: The human metabolic syndrome and its frequent sequela, type 2 diabetes are epidemic around the world. Alpha-linolenic acid (ALA, 18:3 n-3), eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3) consumption ameliorates some of these epidemics' features thus leading one to question if consumption of EPA and DHA, and their metabolic precursor ALA reduce the conversion of metabolic syndrome to type 2 diabetes and reduce the major cause of death in the metabolic syndrome and type 2 diabetes-myocardial infarction. Contributing to myocardial infarction are metabolic syndrome's features of dyslipidemia (including elevated total cholesterol and LDL-c), oxidation, inflammation, hypertension, glucose intolerance, overweight and obesity. Inflammation, glucose and lipid levels are variously influenced by disturbances in various adipocytokines which are in turn positively impacted by n-3 polyunsaturated fatty acid consumption. Type 2 diabetes has all these features though elevated total cholesterol and LDL-c are rarer. It is concluded that EPA and DHA consumption significantly benefits metabolic syndrome and type 2 diabetes primarily in terms of dyslipidemia (particularly hypertriglyceridemia) and platelet aggregation with their impact on blood pressure, glucose control, inflammation and oxidation being less established. There is some evidence that EPA and/or DHA consumption, but no published evidence that ALA reduces conversion of metabolic syndrome to type 2 diabetes and reduces death rates due to metabolic syndrome and type 2 diabetes. ALA's only published significance appears to be platelet aggregation reduction in type 2 diabetes.

Key words: metabolic syndrome, type 2 diabetes, omega 3 fatty acids, obesity, hypertension, dyslipidemia, hyperglycemia, adipocytokines

1 INTRODUCTION

In humans, metabolic syndrome is a frequent precursor to type 2 diabetes and the two share many features. Metabolic syndrome is characterized by persons with at least three of increased waist circumference (central abdominal obesity), hypertension, insulin insensitivity, elevated triglycerides, low high density lipoprotein cholesterol (HDL-c)\(^2\). Such features are accompanied by their sequelae of pro-thrombotic and pro-inflammatory (-oxidative) states\(^3\). Type 2 diabetes always features insulin insensitivity, dyslipidemia, hypertension, pro-thrombotic and pro-inflammatory (-oxidative) states and frequently increased waist circumference (central abdominal obesity)\(^4\). Such obesity decreases HDL-c and increases triglyceride, small dense (sd) LDL and total free fatty acid (FFA) blood plasma concentrations\(^5\). Elevated FFA manifests in insulin insensitivity resulting in decreased insulin efficiency\(^6\) in increasing blood plasma glucose concentrations resulting in oxidative stress, endothelial damage and hypertension. Endothelial damage encourages ingestion...
of sd LDL-c, into the arterial wall leading to atherosclerotic plaque formation and rupture. Such rupture causes platelet aggregation with subsequent thrombus and embolus formation culminating in myocardial infarction, the most frequent cause of death in type 2 diabetes. Human consumption of alpha linoleic (ALA, 18:3 n-3), eicosapentenoic (EPA, 20:5n-3) and docosahexanenoic (DHA, 22:6n-3) acids have the potential to decrease blood plasma concentrations of FFA and hence increase insulin sensitivity, lower blood plasma glucose concentrations and its sequelae-oxidative stress, endothelial damage and atherosclerosis (including plaque formation, rupture and subsequent platelet involvement). The active agents are EPA and DHA and so ALA is of interest because of its metabolism to EPA and DHA. The purpose of this mini-review is to give a brief critical overview of literature dealing with the effects of consumption of ALA, EPA, and DHA in human metabolic syndrome and type 2 diabetes including impact on conversion of metabolic syndrome to type 2 diabetes and death rates from myocardial infarction-the major cause of death in metabolic syndrome and type 2 diabetes. The influence of ALA, EPA, and DHA on levels of various adipocytokines (leptin, adiponectin, resistin, TNF-α, and IL-6) participating in the pathology of metabolic syndrome and type 2 diabetes is also examined.

2 ALA, EPA, DHA AND METABOLIC SYNDROME

EPA may be consumed in purified form, nutraceuticals (e.g. fish oil) and EPA containing foods (e.g. fish). Consumption of ALA results in its desaturation and elongation to EPA in the body. ALA may be consumed in purified form, nutraceuticals (e.g. flaxseed oil) and ALA containing foods (e.g. ground flaxseed).

There appear to be no studies on the specific impact of EPA on insulin insensitivity or its pre-cursor, elevated blood plasma FFA in the metabolic syndrome. Interestingly, in 3 studies the risk of type 2 diabetes (a sequela of metabolic syndrome) was lessened by increased fish intake and omega 3 fatty acid consumption. Nettleton and Katz (2005) have reviewed literature from Iceland showing a decreased prevalence of type 2 diabetes in males consuming increased EPA and DHA in the form of fish oils or 9-12 ounces of salmon/day to combat triglyceride elevations. However, Denke (2002) has suggested the use of 6-12 grams per day of EPA and DHA in the form of fish oils or 9-12 ounces of salmon/day to combat triglyceride elevations. However, she correctly points out that such a regimen may worsen glucose intolerance though it will also have the beneficial impact of diminishing platelet aggregation, the latter of which is a major contributor to myocardial infarction- a major cause of death in those with metabolic syndrome.

Indeed Nettleton and Katz (2005) noted that mortality from myocardial infarction in Icelandic females was not a measure of their levels in insulin sensitive tissues like muscle. Thus one might conclude that significant levels of ALA, EPA and/or DHA must be reached in insulin sensitive tissues for their effect to be felt. It could also be that ALA, EPA or DHA levels do not reach therapeutic levels in the studies showing no impact of ALA, EPA or DHA on insulin sensitivity.

EPA and DHA consumption have been studied regarding adipocytokines in metabolic syndrome in humans. EPA and DHA decrease TNF-α levels the effect of both being a decrease in insulin resistance. However Mori et al (2003), Jellema et al (2004) and Klein-Platat et al. (2005) indicated no impact of EPA or DHA on blood plasma IL-6 or TNF-α concentrations or their related fasting blood glucose management. EPA and DHA has been suggested to reduce blood levels of leptin and hence insulin insensitivity in metabolic syndrome. Krebs et al (2006) showed an increase in adiponectin (related to insulin sensitivity) in females exhibiting a metabolic syndrome like situation consuming increased EPA and DHA but yet no omega 3 fatty acid induced improvement in insulin sensitivity. ALA consumption has not been examined in connection with adipocytokines in the metabolic syndrome.

Though consumed ALA is converted to EPA and DHA there are no studies examining the impact of ALA consumption on the risk of acquiring type 2 diabetes. However, slower conversion of ALA to EPA and DHA via decreased delta-6 and -5 desaturase activity in metabolic syndrome persons as is the case with type 2 diabetics may negate any impact of ALA on slower conversion of metabolic syndrome to type 2 diabetes. The rates of ALA conversion should be studied in metabolic syndrome patients with a view to understanding of whether a progressive drop in delta -6 and -5 desaturase activity is an indicator of the risk of type 2 diabetes onset. The paper by Zamaria (2004) might lead one to suggest a significance of delta-6 and -5 desaturase activity in the conversion of metabolic syndrome to type 2 diabetes and has been proposed by Das (2005).

Denke (2002) has suggested the use of 6-12 grams per day of EPA and DHA in the form of fish oils or 9-12 ounces of salmon/day to combat triglyceride elevations. However, she correctly points out that such a regimen may worsen glucose intolerance though it will also have the beneficial impact of diminishing platelet aggregation, the latter of which is a major contributor to myocardial infarction- a major cause of death in those with metabolic syndrome. Indeed Nettleton and Katz (2005) noted that mortality from myocardial infarction in Icelandic females was...
inversely proportional to EPA consumption from milk.

Szapary and Rader (2001)\textsuperscript{23} as well as Cottrell et al. (2003)\textsuperscript{24} found that fish oils will reduce triglycerides while Barrett and Watts (2003)\textsuperscript{25} noted increased HDL-c. McCarty (1998)\textsuperscript{26} has indicated that EPA reduces synthesis of triglycerides in hepatocytes and thus lowers blood plasma concentrations of triglycerides\textsuperscript{27,28,29}. However, Klein-Platat \textit{et al.} (2005)\textsuperscript{12} have observed no relation between blood plasma levels of cholesteryl ester and phospholipids ALA, EPA or DHA and blood plasma triglyceride or HDL-c concentrations. Barrett and Watts (2003)\textsuperscript{25} have reviewed data indicating that DHA consumption increases HDL\textsubscript{c}-c compared to no change for EPA in overweight persons. Consequently the level of these omega-3 fatty acids in plasma cholesteryl ester and phospholipids fractions may not be capable of leveraging change in plasma triglycerides or HDL-c.

Unfortunately, LDL-c already elevated in metabolic syndrome is further mildly elevated with fish oil consumption\textsuperscript{25}. However, the risk of death in fish oil consumers is reportedly less\textsuperscript{31}, so elevation of the pro-atherosclerotic DHA would have to be done to confirm or reject the observation of Klein-Platat \textit{et al.}\textsuperscript{12} in metabolic syndrome. There appear to be no studies done feeding foods or oils containing ALA, EPA or DHA or pure ALA, EPA or DHA on blood pressure in metabolic syndrome.

There appear to be no publications on the specific impact, if any, of ALA, EPA or DHA consumption on LDL oxidation, glucose management, sd LDL-c, LDL-c, platelet aggregation, blood pressure, and obesity in metabolic syndrome. These areas need to be examined in the population as a whole and by gender to determine whether males or females are more responsive in various parameters to each of these omega-3 fatty acids.

### 3 EPA, DHA AND TYPE 2 DIABETES

Pure EPA lowers blood plasma triglyceride concentrations in type 2 diabetes\textsuperscript{30} as do fish oils\textsuperscript{36,37,38}. Jain \textit{et al.} (2002)\textsuperscript{39} and Pedersen \textit{et al.} (2003)\textsuperscript{40} noted an increase in HDL-c as the result of fish oil consumption. However, even at 1800 mg/d EPA-ethyl ester there was no change in triglycerides\textsuperscript{40,41}, suggesting that DHA is the active agent in fish oils regarding decreased triglycerides. Regardless of which fatty acid is responsible, fish oils lower triglycerides\textsuperscript{42} and this is supported by a meta analysis by Friedberg \textit{et al.} (1998)\textsuperscript{43} though it was noted that there is a significant though small rise in LDL-c but no change in HDL-c levels (supported by Anuzzi \textit{et al.} (1991)\textsuperscript{44} and Rivellese \textit{et al.} (1996)\textsuperscript{45}). Friedberg \textit{et al.} (1998)\textsuperscript{46}, Anuzzi \textit{et al.} (1991)\textsuperscript{47} and Rivellese \textit{et al.} (1996)\textsuperscript{48} found no change in cholesterol concentrations as the result of fish oil administration. Nakamura \textit{et al.} (1998)\textsuperscript{49} observed no changes in serum cholesterol levels but did not examine LDL-c as the result of EPA-ethyl ester administration. Jain \textit{et al.} (2002)\textsuperscript{39} found no change in total cholesterol but a drop in LDL-c apparently suggesting a redistribution of cholesterol from LDL to HDL. Popp-Snijders \textit{et al.} (1987)\textsuperscript{43} observed a decrease in plasma cholesterol and triglycerides using Super EPA fish oil. However, this seems to be an exception to the impact of fish oils in terms of total cholesterol and may be due to the higher percentage of EPA in the oil compared to regular fish oil studies. However, a meta analysis of fish oil studies by Montori \textit{et al.} (2000)\textsuperscript{36} indicated no changes in total cholesterol but the greatest increases in LDL-c in hypertriglyceridemic states and with higher doses of fish oils. This is borne out by Westerveld \textit{et al.} (1993)\textsuperscript{43} using EPA-ethyl esters who showed that higher EPA doses only produced a modest increase in LDL-c. However, Nettleton and Katz (2005)\textsuperscript{50} noted that omega-3 long chain fatty acids induced increases in LDL-c tend to be inconsistent and modest and that there are a few reports of significant increases in HDL-c in type 2 diabetics consuming n-3 long chain fatty acids. Additionally, the evidence for such HDL-c increases across the spectrum of
However, the Westerveld grams of fish oil/day (10, 48) noted a rise in fasting plasma glucose and HbA1c due to consumption of 10 or more grams of fish oil/day (48). Glauber et al. (1988) (48) noted a rise in fasting plasma glucose feeding fish oil delivering 3.3 g/d EPA and 2.2 g/d DHA. Interestingly high doses of fish oil (10 g/day) did not change FFA or glucose levels indicating that such deterioration must be due to other mechanisms (39). Yet Rivellese et al. (1996) (38) noted a significant decrease in FFA due to fish oil administration (2.7 g EPA/1.7 g DHA/d) yet no change in plasma glucose, insulin sensitivity or HbA1c again suggesting such changes in blood plasma glucose and/or HbA1c must be regulated by a mechanism other that blood plasma FFA level-mediated insulin sensitivity. However, more recent studies of doses of 1-2 g/day of omega 3 long chain polyunsaturated fatty acids showed no such deleterious impact (10) and this is supported by Montori et al. (2000) (50) whose meta analysis showed no change in HbA1c. Pure EPA has no effect on HbA1c in type 2 diabetics (35) as does fish oil for measures of plasma lipid oxidation (39). However, Pedersen et al. (2003) (39) confusingly notes that fish oil administration increases LDL oxidation (decreased lag time and propagation rate) compared to the corn oil placebo (yet there was no statistically significant change in the LDL malondialdehyde level-an in vivo measure of LDL oxidation). Yet, other markers of oxidative stress (IL-6, TNF-α, and c-reactive protein) are unchanged in type 2 diabetics due to the administration of purified EPA or DHA relative to olive oil placebo (36). Thus it would appear that purified EPA and/or DHA are less likely than fish oil to cause increased LDL oxidation, perhaps due to a lower polyunsaturated fatty acid load and hence oxidation potential.

Pure EPA lowers measures of platelet activation in type 2 diabetics (35). However, DHA but not EPA significantly reduced collagen-induced platelet aggregation and TxB2 formation compared to the olive oil placebo in type 2 diabetics (36). However, even at a daily dose of 1800 mg of EPA ethyl ester/d there was no change in platelet aggregation except for a decreased aggregation to the relatively weak agonists, ADP and platelet activating factor (41). Decreased aggregation was not seen with collagen stimulation (35). Collectively this data suggests that DHA alone or in fish oil is critical for reduction of platelet aggregation in type 2 diabetics.

There are no studies indicating the impact of pure ALA in type 2 diabetics on any of the parameters covered by this paper. However, Barre et al. (2005a, 2005b) (55, 56) have demonstrated that 60 mg/kg body weight of ALA in the form of flaxseed oil given for 3 months substantially increases bleeding time in both male and female type 2 diabetics (more so in males than females). McManus et al. (1997) (37) and Goh et al. (1997) (38) giving 35 mg ALA/kg body weight in the form of flaxseed oil for three months, failed to note any change in fasting triglycerides, cholesterol,
LDL-c, HDL-c insulin, and glucose. McManus et al. (1996) also noted no change in HbA1c.

There is an indication that increased fish consumption, pure EPA or DHA or fish oils may lower death rates in type 2 diabetics. However, it is not clear if such lowering may be specifically attributed to EPA and/or DHA in fish or fish oils or whether consumption of EPA or DHA represents other beneficial health and hence life-extending practices such as diet in general, exercise, cessation of smoking etc. No work has been done on impact of ALA, EPA or DHA in pure form or contained in oils or foods in terms of differential gender impact on the variables discussed in this section on diabetes except for the work of Barre et al. (2005a,b). There is no published evidence that pure ALA or ALA-containing oils or foods will reduce death rates in type 2 diabetics.

4 CONCLUSION

It is concluded that ALA, and its metabolic derivatives, EPA and DHA consumption benefits or has the potential to benefit metabolic syndrome and type 2 diabetes primarily in terms of dyslipidemia, inflammation, hypertension, platelet aggregation and the pro-oxidant state. Dietary ALA lowers markers of inflammation, though this has not been specifically published regarding metabolic syndrome or type 2 diabetes. There is no evidence that ALA, EPA and DHA have any impact on reducing central abdominal obesity. Consequently any beneficial effects of ALA, EPA and DHA are direct and not secondary to decreases in waist circumference. The effect of EPA and DHA consumption on metabolic syndrome’s progression to type 2 diabetes and the reduction of the mortality from atherosclerosis-induced myocardial infarction—the main cause of death in metabolic syndrome and type 2 diabetes has been suggested but such findings need to be subjected to further rigorous trials. Work needs to be done the impact (including gender) and hence potential gender-specific efficaciousness of ALA on the features of the metabolic syndrome and type 2 diabetes including mortality from these two phenomena and conversion of metabolic syndrome to type 2 diabetes. EPA and DHA need to be studied for gender-specific efficaciousness for the parameters discussed in this paper and for the mortality from these two phenomena and conversion of metabolic syndrome to type 2 diabetes. Further work also need to be done on the impact of ALA, EPA and DHA in modulating various adipocytokines to improve features of the metabolic syndrome and type 2 diabetes.

References

16. Mori, T.A.; Woodman, R.J.; Burke, V.A. et al. Effect of eicosapentaenoic and docosahexanoic acid on oxida-


42. Woodman, R.J.; Chew, G.T.; Watts, G.F. Mechanisms.


