# Polyunsaturated Fatty Acids in the Management of Lipoprotein Abnormalities in Diabetes Mellitus*

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## INTRODUCTION

Atherosclerotic complications, particularly coronary heart disease (CHD) are the leading cause of death in subjects with diabetes mellitus. Abnormalities of plasma lipid and lipoprotein concentrations are common in both insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), [1].

IDDs who are well controlled or on optimal therapy have normal cholesterol and triglyceride concentrations. The plasma high density lipoprotein (HDL) are normal or elevated. Thus, it can be concluded that IDDs in general, demonstrate an antiatherogenic pattern [2].

IDDs, who are untreated or inadequately treated, have elevations in the fasting, as well as postprandial triglyceride levels in association with reduced lipoprotein lipase activity. The low density lipoprotein (LDL) cholesterol rises because of the effect of insulin deficiency on LDL receptor function. Diabetes when complicated by ketoacidosis demonstrates lipemic serum which is secondary to elevations in the chylomicrons and VLDL, the HDL concentration in these situations is lowered [3, 1]. Insulin therapy rapidly restores the LPL activity and corrects the abnormalities of the VLDL metabolism but the resonse of HDL occurs more slowly [4].

IDDS complicated by nephropathy demonstrate a rise in the Lipoprotein A (Lp a) concentrations, the latter is currently thought to be a marker for premature atherogenesis (CHD) [5]. In overt nephropathy, the concentrations of total cholesterol, triglycerides, VLDL and LDL are elevated, whereas those of HDL and apo A1 reduced [6]. In addition to the quantitative changes in the lipoprotein concentrations described, qualitative changes in the structure and composition of the lipoprotein may be observed in relation to VLDL subclasses, LDL composition and the distribution of surface and core lipids in lipoprotein particles [7].

Non-insulin-dependent diabetics (NIDDs) are associated with an atherogenic lipid profile; their serum triglycerides are 1.5 to 3.0 times higher than their matched controls and they have reduced HDL concentrations (10-20%). VLDL overproduction by the liver leads to hypertriglyceridemia. The primary defect is presumed to be resistance to insulin stimulated glucose uptake. Decompensation of glucose tolerance can be avoided if the beta cell of the pancreas is capable of secreting increased amounts of insulin and in this situation hyperinsulinemia is capable of maintaining near normal glucose tolerance. When insulin resistant patients with NIDDM lose the capacity to maintain hyperinsulinemia, frank decompensation of glucose tolerance occurs, and fasting hyperglycemia supervenes. In these patients ambient insulin levels are comparable to those of normal persons. In addition to being normoinsulinemic and hyperglycemic, these patients have higher than normal circulating levels of free fatty acids, presumably because they are also resistant to the ability of normal insulin levels to regulate plasma free fatty acid metabolism. Thus, the elevated plasma free fatty acid concentrations in the presence of normal circulating insulin levels lead to an increase in hepatic VLDL - TG synthesis. Also, the VLDL particles are abnormally rich in triglycerides and have a high triglyceride - apolipoprotein B ratio. These particles are cleared more slowly than normal VLDL and from intermediate density lipoproteins that are not converted to low density lipoprotein (LDL) but compete with LDL at the hepatocyte level for the LDL receptor. Triglyceride rich VLDL is taken up by smooth muscle to induce foam cell formation and facilitate the process of atherogenesis [8, 9]. The apoproteins responsible for the delipidation and uptake of VLDL may be glycosylated [10], leading to a delay in VLDL clearance. Furthermore, the lipoprotein lipase and hepatic lipase activity may be decreased in poorly controlled diabetics, these factors tend to potentiate the hypertriglyceridemia encountered in NIDDM subjects. Restoration of normoglycemia in NIDDM subjects by intensified insulin regimens tends to improve the triglyceride \ apo B composition and normalise VLDL composition [1, 11, 12].

The HDL-cholesterol concentration in NIDDs is reduced. This is due to a reduction in the amount of

cholesterol in the HDL particles, which are rich in triglycerides [13]. The apolipoprotein A-I is decreased relative to apo A-II in NIDDM subjects. Because HDL2 (the cardioprotective HDL subfraction) has more apo A-I than apo A-II, the decrease in total HDL may underestimate the true atherogenic potential associated with the diabetic state. It has been demonstrated that intensified insulin therapy reduces the VLDL concentrations but has a minor effect on total HDL. However, on examining the HDL subfractions, the HDL2 cholesterol increases significantly (21%), where as the HDL3 fraction decreases (13%). Thus, the benefits of insulin therapy are undermined if only its effect on total HDL is monitered [14].

Most subjects with NIDDM are reported to have subtle abnormalities in the composition of lipoproteins that cannot be detected from measurements of lipoprotein concentrations. These include the presence of large VLDL particles with a high triglyceride - apo B ratio. The VLDL subclasses are elevated and appear to be enriched in free and esterified cholesterol [11]. In poorly controlled NIDDM patients the LDL 3 fraction was elevated whereas the LDL 2 fraction was lower than in control subjects.

The LDL 2 fraction represents normal LDL whereas LDL 3 fraction comprises small dense particles which are atherogenic. Treatment tends to improve the compositional alterations of lipoproteins but not fully correct them despite improvements in glycemic control and normalisation of the lipoprotein concentrations. [4].

## POLYUNSATURATED FATTY ACIDS (PUFAs) IN DIBETES MELLITUS

The PUFAs are fatty acids with one or more double bonds and are 16-20 C in length. They may be of plant origin (Oleic, Linoleic and Linolenic acids) or of animal origin (eicosapentaenoic, docosa-hexaenoic and arachidonic acids).

Linoleic acid is a w-6 fatty acid which is present in many vegetable oils and is predominantly the fatty acid in safflower oil. It is an essential fatty acid necessary for the synthesis of key prostaglandins (PGE1 and E2 series) and leukotriene. These substances play a vital role in biochemical processes involved in atherogenesis. Linoleic acid when exchange for saturated fatty acids in diet have a propensity to reduce both, cholesterol as well as triglycerides. The mechanisms by which it reduces

the lipids, include the enhanced excretion of cholesterol, enhancing the fractional clearance of LDL by reducing the number of lipoprotein particles and increasing the activity and the number of LDL receptors. Linoleic acid decreases the conversion of VLDL to LDL promoting the clearance of VLDL remnants; this, alongwith the reduced secretion of VLDL may be responsible for lowering the plasma triglycerides. The intake of linoleic acid may be associated with premature greying of hair, cholelithiasis, immunosupression, oncogenecity, a decrease in the HDL cholesterol concentration and alterations in the lipid composition of the cell membrane. The consequences of the latter effect remain to be determined. These features limit the usage of large quantities of linoleic acid in the management of hyperlipidemias.

The omega 3 fatty acids are obtained from ocean fish and animals e.g. salmon, mackerel, whale and seal. The fish oils when substituted for saturated fatty acids in the food of diabetics lower the circulating levels of VLDL triglycerides by one or more of the following mechanisms, viz., a reduction in the absorption of dietary fatty acids, enhanced lipoprotein lipase activity and a reduction in the hepatic VLDL synthesis and secretion. LDL composition is abnormal in diabetic subjects and is usually smaller and denser than normal. Fish oil administration may improve cholesterol/apoB in diabetic subjects. The various fish oil preparations available in the market are listed in Table 1.

**Table 1**
**Commercially avialble fish oil preparations**

| Product | Fat (g/capsule) | EPA | DHA (mg/capsule) | Chol |
|---|---|---|---|---|
| MaxEPA | 1.0 | 180 | 110 | 6.00 |
| Super EPA | 1.0 | 300 | 190 | 0.08 |
| n-3 PUFA | 1.0 | 340 | 35 | 0.95 |
| RES-Q1000 | 1.0 | 300 | 200 | 1.00 |
| Sardine oil | 1.2 | 300 | | |

EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid,
Chol: cholesterol, PUFA: polyunsaturated fatty acid.

The fish oils are prescribed when dietary restrictions fail to alleviate the hyperlipidemia by $\leq 50\%$ over a period of six weeks. Two capsules of MaxEPA (which are locally available) are administered twice a day and the serum lipids are reviewed after an interval of six weeks.

A major concern during fish oil administration in diabetic patients is their potential deleterious effect on circulating levels of LDL and HDL, i.e. elevation in the concentration of total and LDL cholesterol and a modest increase in the HDL cholesterol. The LDL: HDL cholesterol ratio is usually increased. The increase in the HDL cholesterol is primarily accounted for by an increase in HDL2 with little change in HDL3 levels. The use of fish oils in diabetics, particularly NIDDM has been associated with impairment in glycemic control [15]. Despite these caveats, the cumulative data as of today encourages the use of natural dietary sources of omega 3 fatty acids in menus of IDDM and NIDDM patients.

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