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Postprandial Lipids In Diabetes and Pre-Diabetes- Role in Atherosclerosis

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Microangiopathy and in particular macroangiopathy contributes to excess morbidity and premature death in patients with type 2 DM¹. At diagnosis, patients with type 2 DM have a 3-4 fold higher risk for cardiovascular disease than non-diabetic persons^{2,3}. Risk factors for macroangiopathy in patients with type 2 DM include an elevated fasting hyperglyceride level, a low HDL cholesterol level, and accumulation of small dense low density lipoprotein (LDL) particles which are early oxidized and are atherogenic⁴. Epidemiological studies have reported a higher risk of coronary artery disease (CAD) in those with elevated fasting triglycerides in the serum. Fasting hypertriglyceridemia has also been consistently shown to be associated with type 2 DM and persons with visceral obesity. In a Finnish 7 year prospective study, high triglyceridemia (TG) levels (>203 mg/dl) were associated with a 2 fold increase in risk for CAD events. This shows that elevated TG level may be a better predictor of CAD than elevated LDL levels⁵⁻⁸.

Recent studies have shown that post-prandial handling of triglyceride rich lipoprotein (TRLs) is important for the propensity of endothelial dysfunction and atherosclerosis^{4,9-12}. Although fasting lipid and lipoprotein levels reflect steady state lipid metabolism even healthy subjects are in a state of post-prandial hypertriglyceridemia most of the time due to meal frequency¹¹. Serum triglycerides

are generally increased maximally by 3-4 hrs post-prandially in non-diabetic / healthy individuals and by 6-10 hrs in pre-diabetic and diabetics¹²⁻¹⁵. Once post-prandial lipidemia occurs it is exacerbated by the next meal and thus hypertriglyceridemia persists for the entire day. Clearly body's vasculature is exposed to post-prandial lipemia for most of the day. Therefore, it would appear logical that most of the endothelial dysfunction that finally leads to atherosclerosis should be taking place during post-prandial state^{1,9,14,16,17}.

Elevated postprandial lipemia has been seen in type 2 DM, prediabetes, first degree relatives of type 2 DM, obese and asymptomatic person with raised fasting serum triglyceride levels^{14,16}. Therefore measurement of lipid especially triglycerides in post-prandial state would be a more reliable and sensitive indicator to predict future cardiovascular risk.

In 1979, Zilversmit, proposed that postprandial accumulation of 'Triglyceride Rich Lipoproteins (TRL's) resulted from a reduction in the rate of clearance of the TG rich dietary remnant particles at the endothelial surface and promoted the development of atherosclerosis. Remnants of TRL's are certainly atherogenic in fat fed experimental animals and in humans with type III hyperlipoproteinemia^{9,18}. TRL's derived from

hypertriglyceridemic humans are toxic to endothelial cells and are taken up by macrophages resulting in foam cell formation. Moreover, case control studies have found an elevated level of postprandial TRL's in those with angiographically verified CAD as compared to normal controls^{19,20,21}. In persons with prolonged increases of plasma triglycerides, either fasting or postprandial, the process of lipid exchange would enrich the triglyceride rich particles in cholesteryl ester and thereby make these particles more atherogenic.

Studies involving measurements of specific triglyceride rich lipoprotein fractions have provided support for the hypothesis that particular types of triglyceride rich particles may be directly atherogenic.

Farideh, Helen and Michael studied the acute effect of low and moderate fat intakes on post-prandial lipemia. Based on a observation over a 7 day period involving more than 3000 eating occasions, they have shown that on 26% of occasions fat ingestion was below 5 gm, on 41% of occasion it was between 5-20 gm and only 33% occasions, fat intake was above 30 gm. They observed that any meal intake with fat content >15 gms would elicit a post-prandial lipemic response (triacylglycerol concentration) that will affect endothelial function and is capable of affecting the composition and concentration of HDL and LDL. He also concluded that sex had no effect on post-prandial lipemia if other compounding features are matched²². Therefore, it can be concluded that in diabetic and prediabetic individuals who already harbour risk factors for increased endothelial dysfunction, even moderate intake of fat (>15 gms) would be a catastrophe leading to increase in CV morbidity and mortality.

Murphy et al showed that doses of 20 g fats were capable of eliciting a plasma genetic inhibiting polypeptide (GIP) augments insulin mediated stimulation of lipoprotein lipase, the enzyme that catalyses plasma TAG clearance. Thus, there is impaired post-prandial clearance of TAG in diabetic

and pre-diabetic individuals due to either insulin resistance or decreased insulin secretion (secretory defect is IGT individuals)²³.

The high TRL's associated with alimentary lipemia lead to activation of factor VII and increased levels of PAI-1²⁴. Though, it does not lead to any thrombus formation in itself, the procoagulated state augments the potential for thrombus formation in event of plaque rupture.

Taskinen et al studied post-prandial hypertriglyceridemia and insulin resistance in normoglycemic, normotriglyceridemic first degree relatives of patients with type 2 DM. They found that these subjects exhibited post-prandial hypertriglyceridemia after a mixed meal (meal containing 49% fat, 36% carbohydrate, 14% protein), which suggests an inherited defect in post-prandial lipid metabolism¹. This defect probably linked to insulin resistance in first degree relatives¹. Activation of PI3-kinase enzyme is required for initiating insulin action which in turn is necessary to suppress the release of endogenous VLDL cholesterol²⁵. An impaired cellular activation of PJ-3 kinase has been suggested to be responsible for PPL as one of the mechanisms in diabetic, pre-diabetic and healthy first degree relatives of type 2 DM^{26,27}.

Studies from our institute clearly shows association of post-prandial lipemia with endothelial dysfunction in type 2 diabetic individuals, irrespective of fasting triglyceride levels^{15,16}. This was independent of glycemic control and insulin sensitivity but was related to the interaction of diabetic state and obesity. This was observed both in older type 2 diabetic as well as young ketosis resistance subjects¹⁶.

In a study in Prediabetes, significant elevated PPTGs were demonstrated only in Newly detected Diabetes following OGTT and not in the pprediabetic groups.

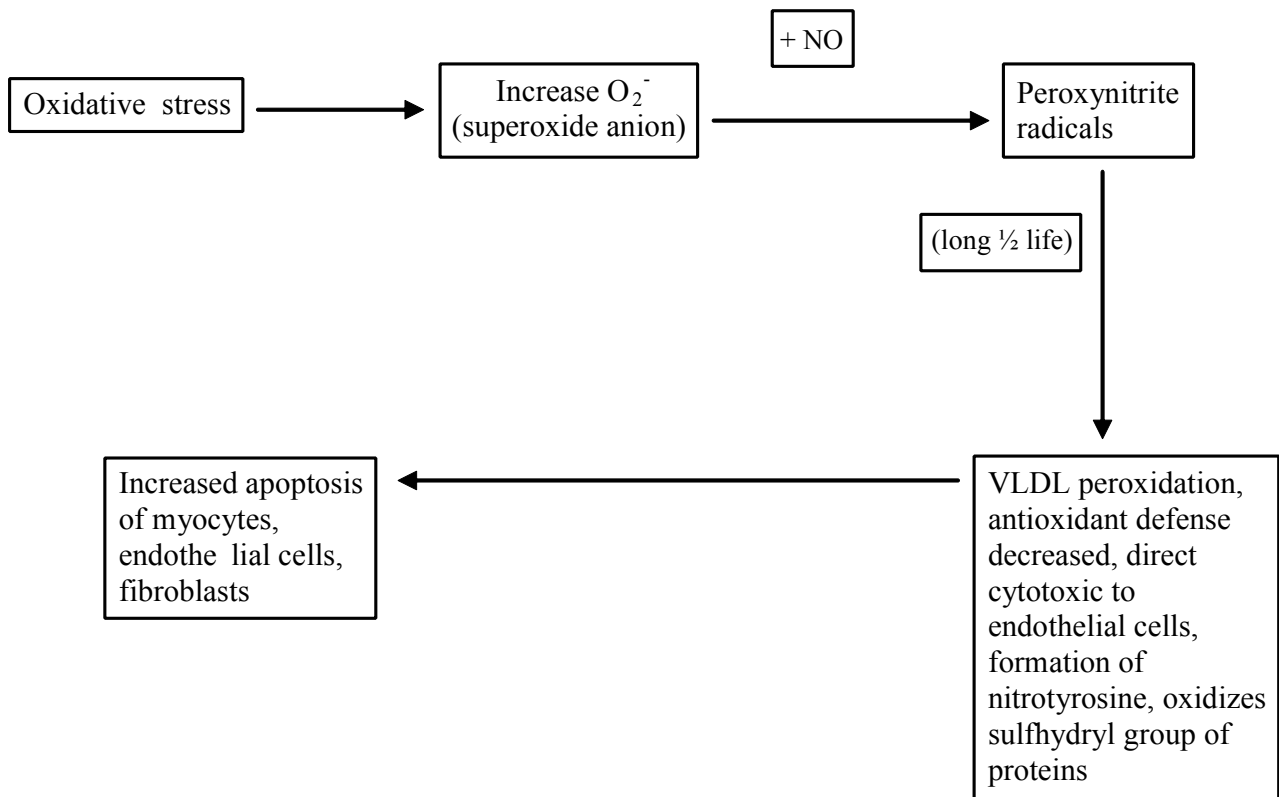
Presently one of the study is being carried out to demonstrate post-prandial lipemia in prediabetics (i.e. impaired fasting glucose and impaired glucose tolerant subjects) and to find its association with

endothelial function and presence of family history of type 2 DM. Results of this study will be available by April 2008.

Antonio et al studied post-prandial hypertriglyceride and hyperglycemia as an independent evidence for endothelial dysfunction and oxidative stress generation in diabetic and non-diabetic adults. They concluded that meal absorption is a complex phenomenon and post-prandial hypertriglyceridemia and hyperglycemia and simultaneously present in the post-absorptive phase, particularly in children and also in subjects with impaired glucose tolerance. When hyperglycemia and hypertriglyceridemia were simultaneously present, there was greater impairment of endothelial function as compared with that observed during either hyperglycemia or hyperglyceridemia alone suggesting a cumulative effect on endothelial cells²⁸. This event is mediated through production of an oxidative stress as depicted in Figure given below²⁹:

Konukoglu studied endothelial dysfunction in prediabetes, i.e. impaired glucose tolerant subjects. He found that NO levels significantly decreased in prediabetic as compared to controls (healthy subjects). TBARs (thiobarbituric acid reactive substances) were elevated in IGT, Cu-Zn superoxide dismutase, which acts as an antioxidant were significantly reduced in prediabetic. Thus, they concluded that pre-diabetic state is a stage of enhanced oxidative stress which can lead to increase in endothelial dysfunction³⁰.

Gofman and colleagues have shown that IDL (intermediate density lipoprotein) particles are strong determinants of endothelial dysfunction and hence atherosclerosis as compared to LDL particles³¹. MARS (monitored atherosclerosis regression study) trial suggest that triglyceride rich lipoprotein particles particularly small VLDL and IDL are involved in atherosclerosis progression more than LDL³².



Triglyceride enriched Apo B containing lipoproteins especially nitrosylated VLDL has been isolated from human atherosclerotic lesion, supporting the fact for direct involvement of TRL's in atherosclerosis^{29,33}.

Both intestinally and hepatically derived TRL's contribute to the post-prandial lipemia after a meal in diabetic and pre-diabetic individuals. Additionally post-prandial saturation of the common chylomicron and VLDL removal pathway has also been attributed.

Insulin resistance is a well known fact in type 2 DM, prediabetics and in first degree relatives of type 2 DM and it has direct effect on decreasing the expression of lipoprotein lipase on endothelial surface³⁴. This may contribute to delayed clearance of TRL's as it is widely accepted that the amount of lipoprotein lipase available at the endothelial surface is the rate limiting factor in TG hydrolysis³⁴. Plasma free fatty acids have been found to be elevated in postprandial state in these individuals, which in turn inhibits lipolysis and weakens the binding of lipoprotein lipase to TRL's and endothelium bound heparan sulphate^{35,36,37}.

In view of large number of studies in type 2 DM and few ongoing studies in pre-diabetics and first degree relatives of type 2 DM, post-prandial lipemia particularly post-prandial hypertriglyceridemia have been linked with endothelial dysfunction and subsequent macrovascular disease. Studies from our institute in type 2 DM individuals support the association of post-prandial lipemia and endothelial dysfunction, no association was found between PPLO and carotid IMT^{14,16}. Present study is being carried out in our institute to find out relationship between post-prandial lipemia and endothelial function in pre-diabetic individuals and whether family history of type 2 DM has any bearing on increase in post-prandial lipemia or endothelial function. Results of this study will be available by April 2008.

While a large number of studies support a key role for postprandial lipemia in endothelial dysfunction

and atherosclerosis, the precise relationship between the two is somewhat clear in type 2 diabetics and obese individuals but not in prediabetics and first degree relatives of type 2 DM.

Keeping in view of all the studies that have been done so far in context of post-prandial lipemia, it can be concluded that post-prandial lipemia especially post-prandial hypertriglyceridemia may be an independent risk factor for endothelial dysfunction and future cardiovascular morbidity and mortality in not only diabetics but it also extends to prediabetics, obese and first degree relatives of type 2 DM. Therefore we should focus on devising new strategies to control post-prandial lipid metabolism to prevent future cardiovascular risk either by lifestyle modifications or pharmacotherapy.

Summary

Post-prandial lipemia (i.e. delayed clearance of TRL's – triglyceride rich lipoproteins, chylomicron remnants, VLDL in post-prandial state) has been emerging as an independent and one of the early markers of endothelial dysfunction and subsequent cardiovascular morbidity in diabetic, pre-diabetic and non-diabetic individuals. Several studies in diabetic individuals have shown that an elevated fasting triglyceride level and subsequent PPL is associated with excess cardiovascular morbidity and mortality. However, only a few studies are available in context of pre-diabetic individuals. One of the studies on healthy, normoglycemic, normotriglyceridemic male first degree relatives of patients with type 2 Diabetes Mellitus (DM) exhibits post-prandial lipid intolerance and insulin resistance despite having normal fasting triglyceride and glucose levels. It may be attributed to reduced efficiency of endovascular lipolysis due to reduced levels of lipoprotein lipase, abnormal lipoprotein particles, elevated level of apo C-III, impaired uptake of TRL remnant particles by the liver or an inherited defect of impaired post-prandial suppression by insulin or hepatic release of endogenous VLDL particles in first degree relatives of type 2 DM patients (either pre-diabetic or normoglycemic

individuals). Studies from our institute have clearly shown that post-prandial hypertriglyceridemia is present in type 2 DM patients with a wide range of age and body mass index and that it is associated with endothelial dysfunction and post prandial oxidative stress. Subsequently, we have also studied this abnormality in prediabetes also. One of the studies being carried out currently in our institute is to demonstrate post-prandial lipemia (hypertriglyceridemia) in prediabetic subjects (without or without family history of Type 2 DM) and to find its association with endothelial function. It has been proposed that post-prandial lipemia in non-diabetic, pre-diabetic, diabetic or obese individuals has an independent and cumulative effect in determining endothelial dysfunction and oxidative stress may be the common mediator of this phenomenon. All these recent observations, suggest that post-prandial lipemia (hypertriglyceridemia) is an independent risk factor for cardiovascular morbidity and mortality, particularly among diabetic and pre-diabetic individuals. This opens up avenues for developing strategies to target post-prandial lipemia particularly hypertriglyceridemia to prevent future cardiovascular risk in patients with Diabetes ,Pre-diabetes and in first degree relatives of type 2 DM patients.

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