Post-prandial Hypertriglyceridaemia

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Cholesterol is essential for the maintenance of cellular membrane, production of steroid hormones and bile acids and triglyceride (TG) to supply energy during metabolic needs or storage there after in the muscles and adipocytes. But excess of lipids in blood can lead to its deposition in the vascular wall resulting in atherosclerosis of which most lethal is when it involves the cerebral or coronary arteries. The atherosclerotic process mainly depends upon the dysbalance between different components of lipids.

Lipid metabolism has two pathways -

a. The exogenous pathway which start from intestinal absorption of dietary fat and cholesterol.

b. The endogenous pathway that starts with VLDL production from the liver. The exogenous pathway is dominant in the well-fed state and endogenous pathway in the fasted state.

Excess of dietary fat or cholesterol originating from environmental factors or from hereditary factors produces lipoprotein imbalance and subsequent atherogenesis. Lipoprotein abnormalities initiate the process of atherosclerosis but complication associated with plaque rupture or erosion are exacerbated by worsened lipid levels. Hyperlipedema leads to endothelial dysfunction whereas HDL level improves it. Excess of LDL cholesterol stimulates the atherosclerotic process but higher HDL induce its regression. Similarly thrombogenicity potential depend upon LDL and HDL values in the adverse or favorable way respectively.

The necessity for treatment of high cholesterol particularly LDC-C are well established. But the correlation between hypertriglyceridaemia and cardiac risk factors are not clear. The National Cholesterol Education Programme (NCEP) has recommended 3 categories of triglyceridaemia.

1. Normotriglyceridaemia = <150mg / dl
2. Borderline hypertriglyceridemia = 150-200mg/dl
3. Hypertriglyceridaemia = >200mg/dl

Values which are higher than normal limits show association with risk of pancreatitis. TG has a molecular structure of 3 fatty acids and 3 carbon glycerol. TG is sparingly soluble in plasma and therefore circulates in the blood in the center of lipoproteins (mainly chylomicrons) and very low density lipoprotein (VLDL). According to the balance of supply and demand, TG is stored in adipocytes, muscles and liver TG is converted to fatty acids by lipoprotein lipase for cellular utilization. TG is also used as a source of energy than glucose in chronically exercising cardiac and heart muscles of long distance runners.

Common causes of hyper-triglyceridaemia are

a. Primary
   - Chylomicronaemia
   - Familial lipoprotein lipase deficiency

b. Secondary
   - Oestrogen, Tamoxifen, Hypothyroidism
   - Diabetes mellitus Type 1, Type 2.

C. Associated Diseases
   - Liver diseases
   - Obesity
   - Lipodystrophy
   - Gaucher’s and Glycogen storage diseases

Hypertriglyceridaemia in diabetes can occur in both type1 and type 2 diabetes. In type1 diabetes hypertriglyceridaemia results from

a. Increased fatty acids return to the liver due to deficient insulin inhibition of adipose tissue hormone sensitive lipase.

b. Impaired plasma removal of TG by lipoprotein lipase which depends upon insulin level

c. Lack of stimulation of HDL synthesis by insulin.

In type 2 diabetes the classical dyslipidaemia seen in our country are hypertriglyceridaemia with low HDL level and with or without hyper-cholesterolaemia. Hypertriglyceridaemia results from

a. Increased hepatic supply of substrates for TG synthesis

b. Decreased production of lipoprotein lipase

c. Heightened production of apo CIII due to insulin resistance, insulin treatment increases LPL activity in vivo by increasing LPL gene transcription and/or decreasing enzyme inactivation.

As the proportion of conversion of VLDL to LDL is decreased, LDL level is not very high but are smaller and denser hence more atherogenic.

Microvascular and macrovascular complications contribute to excess mortality and morbidity in diabetes. Patients with type 2 diabetes at diagnosis have significant number of these complications and have a 3-4 fold higher risk for cardiovascular disease than non-diabetics. Elevated fasting triglyceride, low HDL and smaller – denser – oxidized LDL particles are the risk factors for atherogenesis and macrovascular disease. Elevated TG lever are a better predictor of coronary artery disease than elevated LDL levels.

So long the main focus was fixed to the fasting TG levels but recently studies have shown postprandial TG level is also a determinant of endothelial dysfunction and atherosclerosis. Human beings are mostly on fed state than fasting state because of multiple meals and in between snacks. Normal
people with steady fasting TG level often show postprandial hypertriglyceridaemia due to multiple meals.\(^6\) TG level remain elevated after meal upto 3-4 hours in healthy population but upto 6-10 hours in pre-diabetic and diabetes.\(^7\) Once elevated, the serum TG level are further stimulated by next meal and vascular endothelium are mostly exposed to the effect of TG during postprandial state than fasting state, and endothelial damage occur during this time mostly.\(^8\)

Postprandial hyperlipidaemia are not only seen in presence of diabetes or prediabetes but also in first degree relatives of type2 diabetes, in obese persons and asymptomatic persons with higher fasting TG in postprandial stage should be an important guide. Case control studies have shown high post prandial TG level in patients with angiography proved coronary artery disease than normal population.\(^9\)

In diabetic and pre-diabetic persons who are already prone to endothelial dysfunction, even moderate intake of fat (>15G/day) lead to heightened serum TG level and increased cardiovascular morbidity and mortality.\(^10\) In diabetic and pre-diabetic, there is also impaired postprandial clearance of triacyl glycerol due to either insulin resistance or inadequate insulin secretion.\(^11\)

The pro-coagulant activity is exaggerated by hyperlipidaemia leading to thrombus generation and plaque rupture. The defect of postprandial lipid abnormality related to insulin resistance is found to be inherited by first degree relatives of type2 diabetes patients.\(^12\)

Indian study has also shown association of postprandial lipaemia with endothelial dysfunction irrespective of fasting hypertriglyceridaemia.\(^13\) This was not related to diabetic control and insulin sensitivity but was related to the interaction of diabetic state and obesity.

Studies have also shown that if hyper glycaemia and hypertriglyceridaemia is present simultaneously in postprandial phase, they exert additive effect on damage to endothelial cells than anyone if present alone.\(^14\) Monitored atherosclerosis regression study(MARS) has established that TG rich lipoprotein like VLDL and IDL are more responsible in the progression of atherosclerosis than LDL particles.\(^15\) From human atherosclerosis lesions, TG enriched apo β particles have also been identified establishing the direct link of TG with atherosclerosis.\(^16\)

Insulin resistance as seen in type2 diabetes, prediabetes, obesity etc, decreases expression of lipoprotein lipase on endothelial surface.\(^17\) This lead to impaired TG hydrolysis and delayed clearing from the endothelium. Free fatty acids which are raised in postprandial phase are higher in this conditions and inhibits lipolysis and inhibits the action of lipoprotein lipase on TG rich lipoproteins and endothelium bound heparan sulphate.\(^18\)

Multiple western studies and study by Madhu et al from India\(^a\) have correlated postprandial hypertriglyceridaemia and endothelial dysfunction and subsequent macrovascular diseases. But they could not establish any relation with carotid intima media thickness.\(^19\)

Khoury DE et al studied the postprandial metabolic and hormonal responses of obese dyslipidemic subjects with metabolic syndrome(MS) to test meals, rich in carbohydrate, fat or protein. The sustained postprandial hypertriglyceridaemia of MS subjects after all meals suggests defective catabolism of triglyceride-rich lipoproteins. The greater postprandial increases in plasma insulin and glucose in MS relatively to control subjects indicate decreased insulin sensitivity, not revealed in the faster state.\(^20\)

Till now no strong evidence persist in correlation of hypertriglyceridaemia with prediabetes and first degree relatives of type2 diabetes.

In this issue of JAPI, Kumar V et al have compared the status of hypertriglyceridaemia in diabetics with and without macrovascular disease and normal control. They observed that, postprandial hypertriglyceridaemia and delayed clearance of TG were seen after fat meal in patients with type2 diabetes mellitus particularly in presence of macrovascular disease. They have also noted significant postprandial hypertriglyceridaemia in absence of fasting hypertriglyceridaemia.

This may be considered, as identifying the defect at an early stage which if allowed to progress will also develop fasting hypertriglyceridaemia.

Several studies are establishing that postprandial hypertriglyceridaemia is an independent predictor for cardiovascular mortality and morbidity in diabetes and prediabetes. Probably we have to now think for focusing a postprandial lipid level (in addition to fasting) for estimation and treatment target as we practice for blood sugar values. We should also think that whether we will routinely perform the both or will only perform post prandial TG estimation if fasting TG level is normal at least in selected cases based on the risk factors. We will have to wait for large multi center,double blind comparative trial for final answer.

References

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