Post Prandial Dyslipidemia

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ABSTRACT

Fasting hypertriglyceridemia is now recognized as an independent marker and risk factor for coronary heart disease (CHD). The ATP-III guidelines of NCEP suggest treatment of this dyslipidemia. Postprandial dyslipidemia is now being recognized as a marker of insulin resistance syndrome and its related lipid abnormalities. It essentially implies disproportionate rise in postprandial triglyceride levels. This is akin to impaired glucose tolerance and is metabolically related to insulin resistance and thus clinically related to visceral obesity. Other features of obesity related dyslipidemia including low HDL levels and increased small dense LDL particles are accompaniments of postprandial dyslipidemia and are already well recognized risk factors for CHD. There are no standard guidelines regarding levels which define postprandial dyslipidemia. In some large studies a postprandial triglyceride (TG) concentration of more than 220 mg% has been taken as abnormal.

Postprandial dyslipidemia has been proposed as an independent marker and risk factor for CHD. In fact a study from Japan shows that it correlated more closely to carotid intimal media thickness than fasting TG levels. It essentially implies inability of body metabolism in presence of insulin resistance to handle postprandial lipid load. We thus need to look at randomly done triglyceride levels with which some patients come to us, we should not ignore these as abnormal collection methods since we now have data and do recognize that even postprandial rise of triglyceride levels beyond 220 to 240 mg% is a marker of CHD. This approach is similar to our recognition of high postprandial blood sugar levels with normal fasting blood sugar levels.

Traditionally, we are all used to conduct fasting lipid profile estimations since the TG levels are markedly affected by meals and it takes 8-10 hours of fasting state for a steady state to be reached. Total cholesterol levels are not affected by fasting or postprandial states and can be conducted at random. However, since LDL levels are derived from mathematical calculations dependent on TG levels so total lipid profile is only done in fasting state although some good labs do direct LDL estimation now. All guidelines for classification, detection and management of dyslipidemias recommend fasting lipid profiles for a uniform pattern and we do need to stick to this for all routine purposes.[1]

However, disturbances in postprandial lipemia have been observed in subjects with Type 2 Diabetes Mellitus (DM) and in those with visceral obesity or features of metabolic syndrome. We need to be conscious and aware of the relevance of this phenomenon of postprandial dyslipidemia.[2,3]

SIGNIFICANCE

Fasting hypertriglyceridemia is regarded as an independent risk factor for CHD.[1,4,5] In a meta-analysis of six large prospective studies Hokanson and Austin et al found strong associations between triglyceride concentration measured in fasting state and CHD with a 76% increase in risk for women and 32% for men for every 1 mmol/l increase in triglyceride levels. The increased risk of CHD remains significantly elevated for both sexes even when adjusted for HDL concentration.[6]

In 1979 Zilversmit first proposed that triglyceride-rich liproproteins (TRL) seen in postprandial dyslipidemias play an independent role in atherosclerosis.[7] Since then many studies have shown the role of postprandial lipoprotein particles in the development of CHD. In fact some studies have shown that postprandial hyperlipidemia may be a better discriminant of the presence of CHD than fasting TG Levels.[8] There is no large epidemiological study available showing that postprandial hyperlipidemia is an independent risk factor for CHD. However, it has been shown that postprandial hypertriglyceridemia was more closely correlated to carotid intima-media thickness than fasting TG levels.[9,10]

BLOOD LIPIDS

The two major lipids in plasma are cholesterol and triglycerides. Cholesterol is a major component of cell membrane. It is also a precursor of steroid hormones and bile acids. Triglycerides are produced by esterification of glycerol with three fatty acid

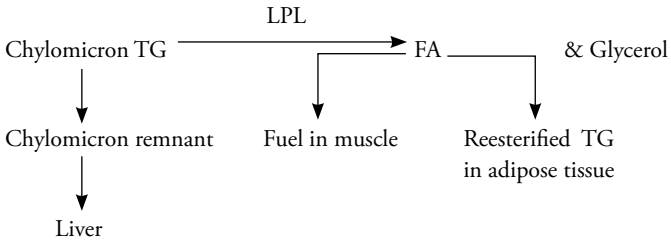

Fig. 1 : The exogenous pathway of absorption of lipids and initial metabolism.

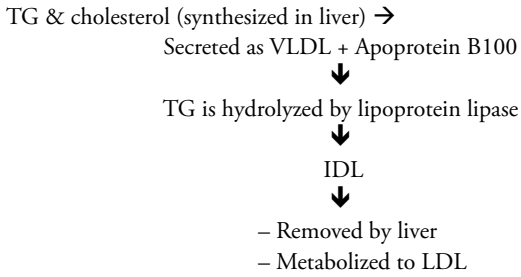

Fig. 2 : The endogenous pathway of synthesis in liver and further metabolism.

molecules. Triglycerides are body's major energy stores specially in adipose tissue. The TGs and cholesterol are insoluble in aqueous environment of the plasma and are solubilized by their incorporation into lipoproteins. Lipoprotein consists of a central core of insoluble lipid (TG & cholesterol-ester) and an outer monolayer that has protein called apoprotein which give the complex their names. The major lipoproteins are :

Chylomicrons

VLDL – Very Low Density Lipoprotein

IDL – Intermediate Density Lipoprotein

LDL – Low Density Lipoprotein

HDL – High Density Lipoprotein

Lipoproteins serve to transport absorbed dietary fat and endogenously synthesized cholesterol and TG. There are three main pathways of lipoprotein metabolism.

1. Exogenous pathway
2. Endogenous pathway
3. Reverse cholesterol transport

Exogenous Pathway

Following digestion, absorption and reesterification the TGs and cholesterol are packaged in the jejunal enterocyte with apoprotein B48 to form chylomicrons. These are the largest lipoprotein. Chylomicrons enter circulation via intestinal lymphatics and thoracic duct. The exogenous pathway is shown in Fig. 1.

Endogenous Pathway: The endogenous pathway is as shown in Figure 2.

LINK WITH OBESITY AND HYPERINSULINEMIA

Central obesity is the main cause of the resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia which are in turn responsible for most if not all of the associated lipoprotein abnormalities.[11] Obesity related dyslipidemia has three major components.[12]

1. Increased fasting and postprandial triglyceride-rich lipoprotein (TRLs).
2. Decreased HDL.
3. Increased small, dense LDL particles.

They are mostly found together in insulin resistant and obese individuals and possibly a common fundamental metabolic defect explains these abnormalities.[13]

After secretion triglyceride-rich lipoproteins from the intestine (chylomicrons) and from the liver (VLDL) are hydrolysed by enzymes located on the endothelium of capillary-rich tissues.[14] Lipid abnormalities in obesity differ from non-obese subjects in that the plasma concentration of cholesterol is not normally elevated. Rather there is typically an accumulation of TG-rich lipoproteins. It is unclear whether in obesity, a defect in secretion, hydrolysis, and/or particle uptake is responsible for concomitant hypertriglyceridemia and which lipoprotein type contributes most significantly.[15] Postprandial dyslipidemia is said to be a contributing factor of increased triglycerides in obesity and several labs have reported an elevated TG response in obese subjects after an oral fat load.[16,17]

It is not the poorly hydrolyzed chylomicrons but the remnant lipoproteins that have undergone lipolysis that contribute. These have a greater arterial uptake and retention.[18] We know that insulin stimulates lipoprotein lipase activities in some tissues.[19] The insulin resistant state of obesity seems to contribute to postprandial dyslipidemia due to reduced lipolysis by endothelial lipases.[20] A reduced hydrolytic capacity results in accumulation of large TG-rich lipoproteins.[21]

Also insulin is a potent stimulator of LDL receptor expression[21] which is the mechanism by which chylomicron remnants are cleared[14,22]. This results in smaller and denser remnant lipoproteins.

It has also been shown that slower clearance of TRLs from circulation postprandially results in low fasting levels of HDL. The HDL formation is closely associated with total cholesterol catabolism.[23]

Elevated TG concentration promotes cholesterol ester exchange reactions mediated by cholesterol-ester transfer protein (CETP).[24] In postprandial hypertriglyceridemia the HDL particles are TG enriched by CETP-mediated exchange with TRL. Such TG enriched HDL particles are cleared more rapidly from the circulation leading to low serum HDL levels. So the dyslipidemia of diabetic and insulin deficiency is interlinked and comprises of fasting and postprandial hypertriglyceridemia and low HDL.[24]

A number of studies have shown positive association between central obesity, insulin resistance and glucose metabolism. Possibly a similar association regulates chylomicron metabolism. So the postprandial dyslipidemia in visceral obesity seems to be due to decreased clearance by high affinity pathways.[3,15,25-27]

Visceral adipose tissue has been shown to be a more important therapeutic target than the normalization of glycemia per se among high risk individuals with IGT.[28]

LEVELS

There are no official guidelines to define postprandial TG range. On the basis of studies a postprandial TG concentration of ≥ 220 mg% at 4, 6 or 8 hours has been taken as abnormal.[29]

It has been shown in Western population that TG of ≥ 120mg% has 100% sensitivity and 80% specificity for an abnormal postprandial TG response.[29] Postprandial hypertriglyceridemia is not a uniform abnormality. Its exact pathophysiological cause is not known. It is likely a polygenic phenomenon although the phenotype is one.[30,31] The baseline TG levels do impact on postprandial response. Also the HDL-C levels are a predictor of this response. Mechanistically a delayed TG clearance postprandially seems to result in low HDL-C even in subjects with low fasting TG concentration.[32-34]

Thus postprandial hyperlipidemia is being increasingly recognized as a marker for CHD. It essentially implies postprandial hypertriglyceridemia. It is related metabolically to the insulin resistance state and thus to visceral obesity, impaired glucose tolerance and syndrome X. It is important because of its link with other features of dyslipidemia of insulin resistance characterized by low HDL and increased small dense LDL particle which are well recognized markers of CHD.[12] In view of the above, some authorities are advocating that postprandial hypertriglyceridemia be targeted with lipid lowering drugs.[35] However, the lack of reference ranges and variability of postprandial lipid measurements presently detract from their routine clinical use. However, further studies are required and we are learning more into the complexity of dyslipidemia and its markers specially with reference to highly atherogenic dyslipidemia of insulin resistance.[24]

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