Carbohydrate diets, postprandial hyperlipidaemia, abdominal obesity & Asian Indians: A recipe for atherogenic disaster

After a fatty meal, intestinal (chylomicrons and chylomicron remnants containing apolipoprotein) and liver-derived triglyceride rich lipoproteins contribute to postprandial increase in lipids. Along with fasting hyperlipidaemia, excess postprandial lipid levels (postprandial hyperlipidaemia; PPHL), independent of other cardiovascular risk factors, have been implicated in the pathogenesis of atherosclerosis and considered to be a component of insulin resistance syndrome (metabolic syndrome). Greater than 80 per cent increase in postprandial triglycerides over the fasting value has been suggested as cut-off point for significant postprandial hypertriglyceridaemia based on its significant association with insulin resistance.

Postprandial state affects the physical characteristics and composition of lipoprotein particles, principally mediated by the effects of cholesteryl ester transfer protein (CETP) and hepatic lipase. CETP catalyses the transfer of cholesteryl esters from high density lipoprotein (HDL) and low density lipoprotein (LDL) to chylomicrons, very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL), and reciprocal transfer of triglycerides. The conversion of triglyceride-enriched LDL particle into small dense LDL by the action of hepatic lipase additionally influences the magnitude and duration of PPHL. While fasting hypertriglyceridaemia is closely associated with PPHL, some data suggest that each is associated with different set of determinants. For example, dietary imbalance and alcohol intake appear to be more important determinants of PPHL than fasting hypertriglyceridaemia. Importantly, depending upon the timing and duration of meals, postprandial hyperlipidaemic state may persist for 15 to 18 h, making it potentially more atherogenic than fasting hyperlipidaemia alone.

Recent research shows close association of PPHL with atherosclerosis. PPHL is closely correlated with carotid intima-media thickness in normolipidaemic and hyperlipidaemic individuals independent of other risk factors. Higher daytime triglyceridaemia with similar fasting triglyceride levels was observed in subjects with premature coronary artery disease (CAD) as compared to their first-degree relatives without CAD. Indeed some evidence suggests that postprandial plasma triglyceride levels (3-4 h post-meal) predict future myocardial infarction better than fasting triglyceride levels.

How does PPHL induce atherosclerosis? It is associated with alterations in several atherogenic factors; increase in intestinally-derived chylomicrons and their remnants, increase in VLDL and remnants secreted by liver, decrease in HDL, and increase in small dense LDL particles which are more susceptible to oxidation. In addition, it is associated with increased activity of factor VII (a procoagulant effect), and increase in the level of plasminogen activator inhibitor-1 (an anti-fibrinolytic effect). The effects of PPHL on sub-clinical inflammation and adiponectin, important for atherogenesis and insulin resistance respectively, remain to be investigated. Accumulation of chylomicron remnants (apo B48 and apo B100-containing particles) with prolonged PPHL results in their migration through the vessel wall into the subendothelial space and initiation of atherosclerosis. Further, triglyceride-rich lipoproteins hydrolyzed by lipoprotein lipase raise levels of fatty acid anions in the vicinity of endothelium, disrupting its integrity and causing dysfunction, and also potentiate tumour necrosis factor-α mediated endothelial injury. Another mechanism for accelerated atherosclerosis in subjects with postprandial hypertriglyceridaemia is increase in circulating adhesion molecules.
Research in PPHL is a particularly important issue for ethnic groups with high tendency to develop metabolic syndrome, dyslipidaemia and CAD, such as Asian Indians and Hispanics. Dyslipidaemia in Asian Indians is usually characterized by hypertriglyceridaemia, low levels of HDL, and high levels of small dense LDL (a cluster of abnormalities termed as atherogenic dyslipidaemia) which frequently occurs in conjunction with PPHL \(^{9-12}\). Excess abdominal adiposity, commonly observed in Asian Indians\(^{13-15}\), may be another important factor that may cause PPHL\(^{16}\), and is associated with increased levels of postprandial insulin and free fatty acids. Not only the prevalence of abdominal obesity is high in Asian Indians, but the total mass of subcutaneous and intra-abdominal fat is higher than white Caucasians\(^{13,15,17-21}\). In white Caucasians, “hypertriglyceridaemic waist” phenotype (individuals having fasting hypertriglyceridaemia and high waist circumference) is associated with significantly greater postprandial triglycerides and CAD\(^{22}\). It appears that subjects with excess visceral adipose tissue may have decreased post-heparin plasma lipoprotein lipase activity due to either defects in insulin secretion or insulin resistance, thus impairing clearance of triglycerides during postprandial state\(^{16}\).

PPHL after high fat meal is well documented. High carbohydrate content (\(>55\%\) energy) in diets also causes hypertriglyceridaemia, despite low fat content. Beneficial effects of very low-carbohydrate diet in improving PPHL and other components of metabolic syndrome have been reported\(^{23}\). In Asian Indians, postprandial hypertriglyceridaemia in treated patients with type 2 diabetes was principally seen in those consuming high carbohydrate and low fat diets\(^{24}\). However, comparative dietary studies with other ethnic groups have not been done, and different carbohydrate containing dietary articles have not been tested. Both these important issues have been dealt in the study of Ezenwaka and Kalloo\(^{25}\) on healthy and diabetic East Indian (ethnic population with ancestral origin from Indian subcontinent) and African subjects, published in the current issue of the journal. Interestingly, these investigators showed that subjects had highest tendency to develop hypertriglyceridaemia with brown bread meal followed by diets containing rotis and rice. Moreover, these effects were particularly seen in East Indian diabetic patients. These findings dispel a popular notion in South Asians that brown bread is better than other two dietary articles, and that rotis are better than rice, for maintaining healthy metabolism in non-diabetic individuals, and is beneficial for diabetic patients. Importantly, rotis and rice are frequently consumed by South Asians originating not only from India, but also by populations living in Pakistan, Bangladesh, Sri Lanka, Nepal, Mauritius, and many countries in Middle East. Brown bread, on the other hand, is available in India only in major cities and mostly consumed by persons belonging to urban middle- or high-income groups. The persons living in rural areas either consume rotis or rice as staple dietary items.

Although novel, the observations of Ezenwaka and Kalloo\(^{25}\) are based on a short-term diet study of seven days and should be deemed as preliminary. A closer look at the dietary composition also reveals subtle difference in the total carbohydrate and fat contents of the diets, both being higher in the diet containing brown bread due to addition of cheese. The investigators should have considered several body composition variables while analyzing PPHL data. For example, the magnitude of PPHL depends on the BMI of the individuals; high carbohydrate diets (76\% energy) with markedly low fat content (8\% energy) resulted in 30 per cent increase in the postprandial triglycerides in CAD patients with BMI > 28 kg/m\(^2\), while there was no change in those with BMI < 28 kg/m\(^2\)\(^{26}\). Ezenwaka and Kalloo\(^{25}\) have not clarified the differences of BMI and waist circumference between East Indian subjects and subjects of African origin. The quality of the study would have been further enhanced if abdominal fat content, both subcutaneous and intra-abdominal, was measured precisely by magnetic resonance imaging, and the variables were adjusted between the two ethnic groups when analyzing the data.

Individual or population difference of postprandial hypertriglyceridaemia in response to diet may be due to genetic, hormonal and/or environmental factors. Among genetic factors apolipoprotein E genotype has been most frequently studied. In Japanese men apo E phenotype E3/4 was associated with an impaired postprandial triglyceride-rich lipoprotein metabolism.
relative to apo E3/3 phenotype when matched for intra-abdominal visceral fat accumulation\textsuperscript{27}. In non-obese Korean men, the presence of the C allele in the APOA5 promoter region at position 1131 significantly contributed to PPHL\textsuperscript{28}. A study on limited number of subjects suggests that postprandial lipaemic response is modified by polymorphism at codon 54 of fatty acid-binding protein 2 gene\textsuperscript{29}. Similarly, peroxisome proliferators-activated receptor-\(\gamma\) may impact postprandial handling of lipoproteins\textsuperscript{30}. These data suggest that gene-diet interactions are important for handling of lipoproteins in the postprandial period. Studies along these lines in Asian Indians might be useful.

Despite the growing literature on PPHL, several issues remain unanswered. First, the precise cut-off point for PPHL is not yet known. Second, how important is PPHL in the causation of CAD in Asian Indians? Heterogeneous etiological factors for CAD preclude simple answers to this question. PPHL should be viewed as an important cardiovascular risk factor in the realm of abdominal obesity and metabolic syndrome in Asian Indians. Whether it contributes independently to the risk of CAD in Asian Indians remains to be investigated. Third, should PPHL be investigated routinely? No guidelines are available on this issue. One could presume that PPHL is present in patients with fasting hypertriglyceridaemia. It would be rational to investigate for PPHL in those with normal fasting lipid levels but having abdominal obesity. Fourth, what are the treatment options for PPHL in Asian Indians? Diet and physical exercise should be advised to reduce abdominal obesity and insulin resistance. An important issue would be how low should be a low carbohydrate diet to effectively prevent PPHL? Further studies should also clarify which carbohydrate diets that have fewer propensities to cause PPHL should be avoided. The observations of Ezenwaka and Kalloo\textsuperscript{25} should be critically tested in further trials. Diet-gene interactions of PPHL should be investigated although practical implications are limited. Several drugs could improve postprandial lipoprotein metabolism, including \(\omega\)-3 fatty acids, (HMG Co-A) reductase inhibitors, and thiazolidinediones, however, usefulness of these drugs in those with PPHL alone remains to be investigated. Finally, whether reduction of PPHL leads to reduction of cardiac- and all-cause mortality in all ethnic groups including Asian Indians is yet an unresolved issue.

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References


