Postprandial Lipoprotein Metabolism in Diabetes Mellitus and Obesity

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Most studies of lipoprotein metabolism to-date have been performed in the fasting state. Studies of postprandial lipoprotein metabolism are now felt to be important for the following reasons:

1. Most of the day is spent in the postprandial and not the fasting state, considering that postprandial lipoprotein particles (chylomicron remnants) may be detected in the circulation for 12 hours and longer in normal individuals.

2. There is some in vitro evidence that chylomicron remnants may cross the endothelial surface, contributing to the development of the atheromatous plaque.

3. Influx of a large intestinal load of fat may unmask more subtle abnormalities in fat transport and clearance in the same way that an oral glucose tolerance test detects diabetes mellitus in an individual with normal fasting blood glucose.

4. There is a dynamic interaction between HDL and triglyceride-rich lipoprotein particles (TRL), with exchange of both core and surface lipid components. This exchange is exaggerated in the postprandial state when TRL are elevated, providing a useful model for the study of this interaction.

Over the past few years we have conducted a number of physiological studies in obese and diabetic individuals, examining postprandial lipoprotein metabolism and attempting to identify abnormalities that could be important in the development of atherosclerosis in this population. Since the major abnormalities in fasting lipoproteins in obesity and diabetes involve the triglyceride-rich lipoproteins and HDL, these clinical conditions lend themselves to the study of postprandial lipoproteins.

We used vitamin A ingested with a high fat meal to label chylomicrons and chylomicron remnants. Vitamin A is absorbed in its retinyl ester form, predominantly retinyl palmitate, and remains an integral part of the chylomicron and chylomicron remnant core until the remnants are taken up by hepatic remnant receptors. The retinyl esters do not recirculate with VLDL of hepatic origin and are not transferred to higher density lipoproteins to any appreciable extent in the early postprandial period. Larger chylomicrons were separated from smaller chylomicrons and chylomicron remnants by a single ultracentrifugal spin, separating particles larger and smaller than S₁₃₀₀₀.

Postprandial lipoprotein metabolism was studied in obese normolipidemic subjects compared to normal weight controls. Despite the selection of all subjects in the study for normolipidemia, the obese subjects had higher fasting triglyceride levels and lower HDL cholesterol levels than the controls. This is a well-described feature of obesity and is related predominantly to the higher VLDL production rate in obesity. There was a strong positive correlation between fasting triglyceride level and postprandial triglyceride response to the high fat meal in both groups and the postprandial triglyceride response was greater in obese than controls. A fair proportion of this elevation of TRL was not labelled with retinyl palmitate, suggesting that a significant contribution to postprandial lipemia is from VLDL of hepatic origin. We postulate that the elevation of VLDL in the postprandial state is due to increased competition for removal by a saturable lipolytic pathway when a fat load is absorbed. In addition to these findings, we analyzed HDL compositional changes in detail and found that HDL becomes enriched with triglycerides postprandially at the expense of cholesteryl ester, the degree of enrichment dependant on the magnitude of elevation of TRL. This HDL triglyceride enrichment was correlated with lower HDL cholesterol levels in the fasting state, but we were unable to determine from this study which was cause or effect (i.e. does triglyceride-enrichment of HDL lead to a more rapid removal of HDL particles or do low HDL levels lead to increased postprandial lipemia?).

A follow-up study in patients with non-insulin-dependent diabetes mellitus (NIDDM) was designed to determine whether there are potentially atherogenic postprandial abnormalities in NIDDM. We found that fasting

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hypertriglyceridemia in NIDDM is highly predictive of a constellation of postprandial abnormalities, many of which are potentially atherogenic. Hypertriglyceridemic NIDDM patients have increased postprandial lipemia, chylomicron remnant accumulation and delayed chylomicron clearance. These abnormalities are again most likely a result of the greater competition for removal of intestinal TRL in the face of an increased fasting VLDL pool size. In addition, abnormalities in the removal mechanism of fasting TRL become more evident in the postprandial state with the large influx of dietary fat. Free fatty acids (FFA) were markedly elevated postprandially in the hypertriglyceridemic NIDDM subjects, reflecting the lipolysis and release of FFA from the greater load of chylomicrons. Again in this study there was a strong correlation between fasting triglyceride level and postprandial triglyceride increment. HDL particles were enriched postprandially with triglyceride at the expense of cholesteryl ester, the degree of enrichment correlating with the magnitude of postprandial lipemia. Postheparin hepatic triglyceride lipase activity was elevated in the hypertriglyceridemic NIDDM subjects and this is another potential factor implicated in the lowering of HDL levels in these subjects. Interestingly, normotriglyceridemic NIDDM subjects did not demonstrate abnormalities in postprandial lipoprotein metabolism when compared with weight-matched non-diabetic controls.

Postprandial studies were performed in insulin-dependent diabetic subjects examining whether short term alteration in glycemic control and periprandial insulin replacement alters postprandial lipid metabolism. Subjects were studied in good and poor diabetic control by altering their insulin regimen over a 2 week period. Despite major differences in glycemic control, 2 weeks deterioration in glycemic control did not significantly raise fasting triglyceride levels and consequently postprandial lipid metabolism was unaffected. In addition, a low dose insulin infusion at the time of the meal compared to more physiological perimeal insulin replacement was sufficient to prevent increased postprandial lipemia in these subjects. There were, however, major differences in FFA levels postprandially depending on the level of insulin replacement at the time of the meal. FFA levels were markedly elevated postprandially when perimeal insulination was suboptimal. Postprandial FFA levels, therefore, appear to be a more sensitive index of insulination than triglycerides.

Finally, in order to examine the relationship between postprandial lipemia and HDL metabolism, non diabetic hypolalphalipoproteinemic (HA) patients with and without fasting hypertriglyceridemia were studied. Normotriglyceridemic HA patients were found to have a normal postprandial triglyceride response while co-existing fasting hypertriglyceridemia in HA subjects was associated with increased postprandial triglyceridemia. The hypertriglyceridemic HA patients had many metabolic features in common with our obese and NIDDM patients, including hyperinsulinemia and increased postprandial lipemia. Again in this study the postprandial triglyceride enrichment of HDL was a prominent feature and was increased even in the normotriglyceridemic HA subjects.

Since there is now in vitro evidence that triglyceride enrichment of HDL may facilitate catabolism of these particles, ultimately leading to lower HDL cholesterol concentrations, our future in vivo and in vitro studies will focus on this aspect of postprandial lipoprotein metabolism. This important relationship between TRL and HDL metabolism calls into question the significance of low HDL as a primary factor in the pathogenesis of atherosclerosis and suggests that low HDL may be a marker of a more complex aberration in TRL metabolism.

References


