The metabolic syndrome is recognized as an important risk factor for atherosclerosis and much attention has focused on its treatment. The dyslipidemia pattern in this syndrome is characterized by increased triglyceride levels, low HDL cholesterol levels, and a qualitative and sometimes quantitative change in LDL cholesterol levels. Although underlying mechanisms for this pattern are not fully understood, it is believed that insulin resistance resulting in an increased flow of free fatty acids from adipose tissue to the liver is a major contributor. The increased availability of fatty acids for triglyceride formation is a driving force for increased hepatic secretion of triglyceride-rich lipoproteins with secondary effects on HDL and LDL metabolism. Under normolipidemic conditions in humans, VLDL secretion is affected by triglyceride and cholesterol availability, and recent studies suggest an association between cholesterol synthesis and production of smaller VLDL particles (VLDL-2). While insulin suppresses the formation of large VLDL particles, it does not impact the production of the smaller VLDL-2 fraction.

Dietary modification with a reduction of saturated fat and cholesterol as well as focus on overall caloric intake is the foundation for treatment of dyslipidemia. The relationship between dietary fat intake and cholesterol absorption is well established, and responses to changes in dietary cholesterol are related to dietary saturated fat content. Thus, in a recent meta-analysis, a dietary cholesterol challenge of 100 mg from eggs resulted in a 70% higher increase in LDL cholesterol on a high versus a low saturated fat diet. However, the response in plasma lipid and lipoprotein levels to changes in dietary cholesterol content is highly individualized.

In addition to changes in dietary cholesterol intake, dietary-induced changes in endogenous cholesterol synthesis could contribute to this variation, as the latter pathway provides the majority of intestinal cholesterol available for absorption. So far, only a limited number of studies have addressed a possible link between cholesterol absorption and insulin resistance in human. Low cholesterol absorption and low plant sterol levels, used as indicators of cholesterol absorption efficiency, have been reported in patients with diabetes mellitus type 2 and in nondiabetic subjects with increased fasting blood glucose levels. In obese patients with type 2 diabetes mellitus, baseline cholesterol absorption and synthesis correlated with glucose and insulin levels. During weight reduction, cholesterol absorption increased in parallel with improvements in glucose metabolism parameters, suggesting that low cholesterol absorption could be an additional feature of the metabolic syndrome.

Recently, a relation between cholesterol absorption and body weight in patients with type 2 diabetes mellitus was reported; the more pronounced the degree of obesity, the lower the cholesterol absorption. Also in nondiabetic subjects, obesity is associated with reduced dietary cholesterol absorption, possibly due to an increased biliary cholesterol secretion. In a recent study on triglyceride-rich lipoprotein remnants, patients with the metabolic syndrome had a low campesterol/cholesterol ratio, indicative of reduced cholesterol absorption. This ratio was inversely correlated with plasma levels of triglycerides, remnant cholesterol and apo B-48. In parallel, cholesterol synthesis, as judged from the lathosterol/cholesterol ratio, was increased.

Interestingly, utilizing a dual stable isotope technique in a study on healthy individuals consuming a low-cholesterol, low-fat diet, a positive relationship between the amount of cholesterol absorption and fasting insulin, C-peptide or glucagon levels was found. Notably, there was no relationship between these parameters and relative cholesterol absorption. These findings suggest a different relation between cholesterol absorption in normolipidemic individuals and subjects with the metabolic syndrome. The possibility of differences in cholesterol absorption between different hyperlipidemic conditions was further underscored in a 4S subgroup study, demonstrating lower cholesterol absorption in hypertriglyceridemic patients with features of the metabolic syndrome compared with patients with isolated high LDL cholesterol. Collectively, these results are suggestive of differences in cholesterol absorption associated with the dyslipidemic pattern. It is tempting to conclude that such differences could affect response to dietary and/or pharmacological intervention. In support of this, cholesterol absorption and synthesis influenced response to treatment with statin and plant stanol ester margarine. Compared with patients with low baseline cholesterol absorption, a more pronounced decrease in total serum cholesterol levels was observed in patients with high baseline cholesterol absorption, although no data on lipoprotein cholesterol levels were provided.

Despite the general interest in the metabolic syndrome, relatively few studies have focused on the influence of insulin resistance on lipid and lipoprotein response to dietary inter-
vention. Knopp et al. found a decreased LDL cholesterol response to a low-fat diet in subjects with markers of insulin resistance. In another study, a reduced cholesterol intake from eggs resulted in larger serum cholesterol decrease in subjects with low body mass index and high HDL cholesterol, likely associated with high insulin sensitivity. There are also contradictory findings, as administration of 2 eggs/d resulted in a higher increase in LDL cholesterol in subjects with combined hyperlipidemia than in subjects with simple hypercholesterolemia. The study by Knopp and co-workers in this issue of the Journal has attempted to address some of these apparent discrepancies. The authors tested whether insulin resistance with and without obesity influenced the response in LDL cholesterol levels to egg feeding. By utilizing a randomized, double-blind, placebo-controlled, crossover design, 0, 2 and 4 egg yolks/d were given to 197 subjects, divided in three groups, insulin-sensitive, insulin-resistant, and obese insulin-resistant. Among insulin-resistant subjects, baseline LDL cholesterol levels were increased. The most pronounced plasma lipoprotein response to the addition of egg yolks was found among lean, insulin-sensitive subjects, with a higher increase in LDL cholesterol levels than for insulin-resistant subjects. Notably, a majority of the study subjects were women, and as insulin-resistant subjects were significantly older than the insulin-sensitive group, it is possible that menopausal state and/or hormone replacement therapy may have had an impact on the results. However, the findings are supportive of other studies suggesting decreased cholesterol absorption in the metabolic syndrome. Although no definitive answers are available regarding underlying mechanisms and many possibilities exist, it should be emphasized that cholesterol absorption and synthesis represents two important, interrelated regulatory mechanisms in cholesterol homeostasis, and both are affected by overall diet. Changes in one of the pathways may result in compensatory changes in the other, such as an increase in hepatic cholesterol synthesis observed during selective inhibition of cholesterol absorption. Further, inhibition of both these pathways by combination of statins, cholesterol synthesis inhibitors, and the recently available cholesterol absorption blocker ezetimibe, has proven synergistic in reducing LDL cholesterol levels. In addition, other so far relatively unexplored possibilities including genetic variability in cholesterol absorption may play a role. Sehayek et al. demonstrated a large variability in cholesterol absorption in response to dietary fat changes, and further, during high-fat diets, dietary cholesterol mass absorption varied markedly in response to dietary cholesterol intake. The authors suggested that genetically determined differences between individuals in the regulation of cholesterol absorption might be contributory.

While many studies have focused on cholesterol synthesis, plasma lipoprotein metabolism, and the interrelationship between bile acid and cholesterol metabolism, intestinal cholesterol absorption has been a relatively understudied area. Studies to date have demonstrated a considerable variability in cholesterol absorption in response to changes in dietary cholesterol intake. Additional studies are needed to explore underlying mechanisms and whether these observations will translate into more individualized diet recommen-

References


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