Targets for Intervention in Dyslipidemia in Diabetes

GERALD H. TOMKIN, MD

Treatment for dyslipidemia in diabetes reduces cardiovascular events. Diabetes is associated with major abnormalities in fatty acid metabolism. The resulting disturbance results in an abnormal lipoprotein cascade from the large chylomicron through to the small HDL particle. This suggests that drugs that alter formation of the chylomicron particle might have a very important role in diabetic dyslipidemia. Achieving normal glycemia will reverse the abnormalities in fatty acid metabolism, but this is difficult, particularly as the disease progresses. Genes that regulate cholesterol absorption and excretion have been described (Niemann Pick C1-like 1 [NPC1-L1] and ATP binding cassette proteins [ABC] G5 and G8). An effective NPC1-L1 inhibitor (ezetimibe) improves the reduction in cholesterol caused by statins. Agonists of ABCG5 and G8 may become important in the treatment of dyslipidemia. Microsomal triglyceride transfer protein (MTP) is responsible for the assembly of the chylomicron and VLDL particles. New MTP inhibitors, acting only on the intestine, are exciting possible treatments. The advisability of sitosterol-enriched foods to lower cholesterol may have to be reassessed for patients with diabetes, since these products may lead to an increase in chylomicron sitosterol in diabetic patients. More successful treatment of diabetic dyslipidemia is essential if we are to reduce the burden of cardiovascular disease so commonly found in diabetes.

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ATHEROSCLEROSIS AND BLOOD GLUCOSE CONTROL

— World diabetes day in November 2006 again focused the world's attention on diabetes. As the editorial in *The Lancet* (1) states, the personal, social, and financial burden resulting from the chronic complications of type 2 diabetes, which become commonplace after 10–15 years of disease, will be enormous. Two large prospective cohorts have shown that the risk of cardiovascular disease is lowest when the blood glucose is between 4 and 4.9 mmol/l; this concentration has been called optimum concentration (2,3). Cardiovascular mortality risk increases continuously with blood glucose, from concentrations well below conventional thresholds used to define diabetes (4). The largest percentage increase in risk occurs in the pre-diabetes range. Although there is no doubt about the association between blood glucose and atherosclerosis, only a few studies have been able to show an improvement in cardiovascular outcome by reduction in blood glucose. This may be because of the great difficulty in lowering blood glucose over time, even in an intensely treated environment. The Diabetes Control and Complications Trial (5) in type 1 diabetes only managed to reduce A1C to a mean of ~7.0% in the intensively treated group compared with 9.0% for the conventional therapy group in the 6.5 years (mean) of intensive treatment. However, the follow-up Epidemiology of Diabetes Interventions and Complications trial (6) suggested cardiovascular benefit, even though at the end of the study there was little difference between A1C levels in the intensively treated patients compared with the original control group. In the U.K. Prospective Diabetes Study (7) trial in type 2 diabetes, intensive treatment only succeeded in reducing A1C in the first year. By the end of the study, there was at most a 2-year difference in A1C between the intensively treated patients and the control group; thus, the intensively treated patients caught up with the control group within 2 years with regard to their worsening hyperglycemia. In both groups, after the first year, A1C levels rose in parallel over the years. Expressed in another way, A1C for the third 5-year period had risen to 8.1% (7.0–9.4%) in the intensively treated group, whereas in the usual treatment group, this elevated A1C level occurred already in the second 5-year period (8.4% [7.2–9.4%]). This demonstrates the difficulties in controlling blood glucose over a long period of time, even in highly motivated patients who agreed to take part in trials.

ATHEROSCLEROSIS AND DIABETIC DYSLIPIDEMIA

— The treatment of dyslipidemia in diabetes, on the other hand, has been shown to reduce cardiovascular events in both primary and secondary prevention in a very consistent manner since the Scandinavian Simvastatin Survival Study (4S) was first published in 1997 (8). That study examined 202 diabetic and 4,242 nondiabetic patients with cardiovascular disease (coronary heart disease [CHD]) treated with simvastatin or placebo for 4–5 years. The relative risk of total mortality in the treated group was 0.57 and major CHD events was 0.45. It was concluded that the absolute benefit of cholesterol lowering in diabetic patients may be greater than that in nondiabetic patients with CHD because the diabetic patients have a higher absolute risk of atherosclerotic events and CHD (9). The most recent large intervention study for primary prevention in type 2 diabetes, the Collaborative Atorvastatin Diabetes Study (CARDS) (10), demonstrated that 10 mg atorvastatin was beneficial. The trial had to be terminated 2 years earlier than specified because the prespecified early stopping rule for efficacy had been met. The study demonstrated that over a median follow-up of 3.9 years, patients with no documented previous history of cardiovascular disease who had a mean LDL cholesterol concentration of 3.02 ± 0.7mmol/l were significantly protected against cardiovascular events by 10 mg atorvastatin.

From the Department of Diabetes and Endocrinology, Trinity College Dublin, Dublin, Ireland.

Address correspondence and reprint requests to Professor Gerald H. Tomkin, Diabetes Research Foundation, Clontra, Quinns Rd., Shankill, Co Dublin, Ireland. E-mail: gerald.tomkin@tcd.ie.

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Abbreviations: apo, apolipoprotein; CHD, coronary heart disease; MTP, microsomal triglyceride transfer protein; NEFA, nonesterified free fatty acid; PPAR, peroxisome proliferator–activated receptor.

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DIABETES AND HYPERTRIGLYCERIDEMIA — The evidence that hypertriglyceridemia is also a risk factor for cardiovascular disease is strong. The Paris study (11) in 943 men with diabetes or impaired glucose tolerance found that triglyceride was a risk factor for CHD, although that study did not confirm it to be independent of cholesterol. More recently, the Hoorn study (12) has shown hypertriglyceridemia to be an independent risk factor in those patients with abnormal glucose metabolism. Reduction of triglyceride with fibrates has demonstrated coronary angiographic benefit in the Diabetes Atherosclerosis Intervention Study (DAIS) study (13). In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (14), fenofibrate was not associated with a significant reduction in primary events, but there was a significant 24% reduction in nonfatal myocardial infarction, outcome of first myocardial infarction, or CHD death. The secondary outcome of total cardiovascular disease events (the composite of cardiovascular disease death, myocardial infarction, stroke, and coronary and carotid revascularization) was significantly reduced by fenofibrate. It should be noted that by the end of the study, 17% of the placebo patients were taking nonstudy lipid-lowering agents (mostly statins) compared with 8% in the fenofibrate group ($P < 0.001$).

In routine clinical practice, hypertriglyceridemia is the most frequent lipoprotein abnormality found in uncontrolled diabetes. In the U.K. Prospective Diabetes Study (15), in 3,041 newly diagnosed type 2 diabetic patients, the authors found that plasma triglyceride levels at entry were 2.46 mmol/l (0.86–7.1). In The Heart Protection Study (16), patients with diabetes had triglycerides of 2.3 + 1.6 mmol/l compared with nondiabetic patients of 2.0 + 1.3 mmol/l. A study (17) was undertaken in 2005 to assess whether fasting plasma glucose levels can help to identify young healthy normoglycemic individuals at increased risk of type 2 diabetes. The study, which surveyed 13,000 young defense force recruits in their late teens and again a decade later, found that higher fasting glucose levels within the normal range did constitute an independent risk factor for type 2 diabetes. Perhaps more importantly, the study also demonstrated that raised triglyceride levels was a strong predictor of diabetes in those patients who had fasting blood glucose levels of 4.5–5.0 mmol/l.

CAUSE OF HYPERTRIGLYCERIDEMIA IN DIABETES — The reason for the elevated triglycerides in diabetes is complex and stems from a disturbance in fatty acid metabolism, a derangement that is so profound that it has been suggested that diabetes should not be called mellitus but rather lipidus (18). Indeed, high nonesterified free fatty acid (NEFA) levels have been shown to confer in nondiabetic subjects an increased risk of type 2 diabetes. In 1969, Shafrir and Gutman (19) investigated NEFA suppression after a glucose load in 50 control subjects and 96 patients with impaired glucose tolerance or diabetes. They divided the subjects into quartiles depending on their blood glucose levels: fasting and 2 h after glucose load. As glucose tolerance worsened, even in the normal subjects, fasting NEFA levels increased to the highest levels, and the least suppression ability was found in those with impaired glucose tolerance. Shafrir and Raz (18), in their review "Diabetes: Mellitus or Lipidus?", referred to the late Denis McGarry (20), who hypothesized that if Minkowski had been aware of the ketone odor of urine rather than its sweetness, the importance of the derangement in fat metabolism in diabetes would have been noticed sooner! The importance of the disturbance in lipid metabolism in diabetes comes not only through the downstream effect on triglycerides and HDL, but also through the life-threatening events that can occur when heart NEFAs become excessive. In 2001, Jouven et al. (21) demonstrated that circulating NEFA levels were a predictive risk factor for sudden death. The theory of the dangers of elevated NEFAs was first raised by Kurien and Oliver (22), and the theory was revisited in a recent article by Oliver (23). It is possible that the benefits in mortality outcome seen in the intensive care unit and the coronary care unit (24) with intensive blood glucose lowering using insulin is partly due to suppression of NEFAs. The cause of the disturbance in fatty acid metabolism is in part genetic and in part due to lifestyle. In 2004, Petersen et al. (25) examined a group of young fit male subjects who had a family history of diabetes and evidence of insulin resistance and compared them to a similar group without family history or insulin resistance. The authors measured mitochondrial phosphorylation and found a reduction of ~30% in the insulin-resistant subjects, suggesting that this may be an important genetic defect that results in the accumulation of intramyocellular fat. The authors found no evidence of a difference in whole-body lipolysis nor was there any difference in insulin-induced suppression of localized rates of lipolysis in subcutaneous fat. This has been challenged to some extent. In agreement with the above study, Bell et al. (26), who examined palmitate uptake, demonstrated that there was no evidence of an increase in muscle malonyl CoA, an inhibitor of fatty acid oxidation. They found that basal palmitate oxidation across the leg was not different in type 2 diabetic patients compared with control subjects. They found that palmitate uptake was significantly greater in type 2 diabetic subjects and suggest that this may be a key contributing factor to increased fatty acids being shunted toward storage in muscle. The authors concluded that the intramyocyte cellular fat accumulation may be a secondary rather than a primary defect in type 2 diabetes. In 2004, Iozzo et al. (27) investigated whether there was impairment of liver free fatty acid fractional extraction and/or uptake in patients with impaired glucose tolerance. They examined 10 male subjects with impaired glucose tolerance and compared them to eight healthy men. They found that liver fractional NEFA extraction was significantly reduced in the impaired glucose tolerance patients, and this fractional extraction was inversely related to plasma glucose.

High blood glucose levels are the result of damaged β-cell function. In addition, high blood glucose levels also damage β-cell function, thus leading to a vicious cycle. The first lipid abnormality to become apparent in pre-diabetes seems to be the raised fatty acids, and it is clear that NEFAs impair glucose signaling of insulin secretion in the β-cell. Until recently, it was not thought that LDL played a part in the deterioration of β-cell function. The β-cell has been shown to have an LDL receptor, and it is possible that diabetic LDL, which is more easily oxidizable and is glycated, may add to β-cell damage (28). An intriguing finding that supports the concept of LDL being associated with the destruction of the β-cell comes from the West of Scotland Coronary Prevention (WOSCOP) study (29), which showed that statin therapy may prevent diabetes. This interrelationship between blood glucose and lipids in tissue damage is seen, not only in the β-cell, but also in the arterial wall and it is the complications of diabetes, and particularly the

vascular complications of diabetes, that account for the high mortality associated with the condition. The suggestion that there will be an epidemic of diabetes by 2025 and that we can therefore expect a massive increase in macrovascular disease has focused attention on the mechanisms by which diabetes promotes atherosclerosis to such an extent. Although diabetes is often associated with hypertension, this review focuses only on dyslipidemia as the cause of atherosclerosis.

LDL IN DIABETES — LDL is the major cholesterol-carrying lipoprotein in that the ratio of cholesterol to protein is 2:1. It is important to note that the half-life of LDL is in days, whereas the triglyceride-rich lipoproteins, which carry much less cholesterol/particle, have a half-life in hours. Hence, the ability of each lipoprotein subclass to carry cholesterol to the atherosclerotic plaque is similar. Because most attention has been paid to LDL as the most important lipoprotein, we will now analyze this in more detail. LDL composition is shown in Fig. 1. Compositional changes in diabetes may account for much of the increased atherogenicity found in diabetes. Some years ago, we showed that the ratio of esterified to free cholesterol was increased in the LDL particle from diabetic patients (30). The implications of this finding was that the oxidizability of the LDL would be increased and it is oxidized LDL that delivers cholesterol to the atherosclerotic plaque in an unregulated way through uptake by the macrophage. We and others then showed that oxidized LDL was increased in diabetes (31–34). The fatty acid composition of the LDL plays an important role in the oxidizability. The major polyunsaturated fatty acid in the LDL particle is linoleic acid, and this is increased in diabetes, perhaps because of a decrease in the activity of 5a-desaturase, which is insulin sensitive. There is a strong correlation between linoleic acid in the LDL particle and oxidizability of LDL (32,33), and this is an important reason for promoting a monounsaturated fatty acid diet rather than a polyunsaturated fatty acid diet for the diabetic patient. The uncontrolled diabetic state lends itself to increased oxidation because of the increased free radical formation in diabetes (35,36), and it is therefore a disappointment that the antioxidant vitamin E was not successful in preventing atherosclerosis in the Heart Protection Study (37). In that study, 20,000 U.K. adults with CHD, other occlusive arterial disease, or diabetes were randomly selected to receive antioxidant treatment or placebo over a 5-year period. The study found no evidence of benefit in either 5-year mortality or the occurrence of any vascular disease. The diabetic patients fared no better than their nondiabetic counterparts. Much has been written about the reason for failure to demonstrate benefit from antioxidants. It is probable that free radical production and its neutralization require tissue levels of antioxidant that cannot be achieved by oral supplementation. Another mechanism whereby the LDL particle becomes increasingly atherogenic is through the increased glycation of the particle, with the glycation being directly related to the degree of hyperglycemia, and glycation appears to make the LDL particle more sensitive to oxidation (31). Oxidation may damage glucose with concomitant production of free radicals (34), and glycation of LDL has been shown to be associated with an increase in free radical production (35,36). The glycation appears to increase non–receptor-mediated uptake of the LDL particle, and our group has shown an increase in LDL clearance in diabetes (38). For these reasons, one would expect improvement in diabetic control to lead to improvement in cardiovascular outcome in diabetes. This has been shown in the Epidemiology of Diabetes Interventions and Complications study (6), which demonstrated significantly less cardiovascular events in those patients assigned to intensive treatment when the cohort was analyzed in an observational study some 22 years after the initial Diabetes Control and Complications Trial was started (5).

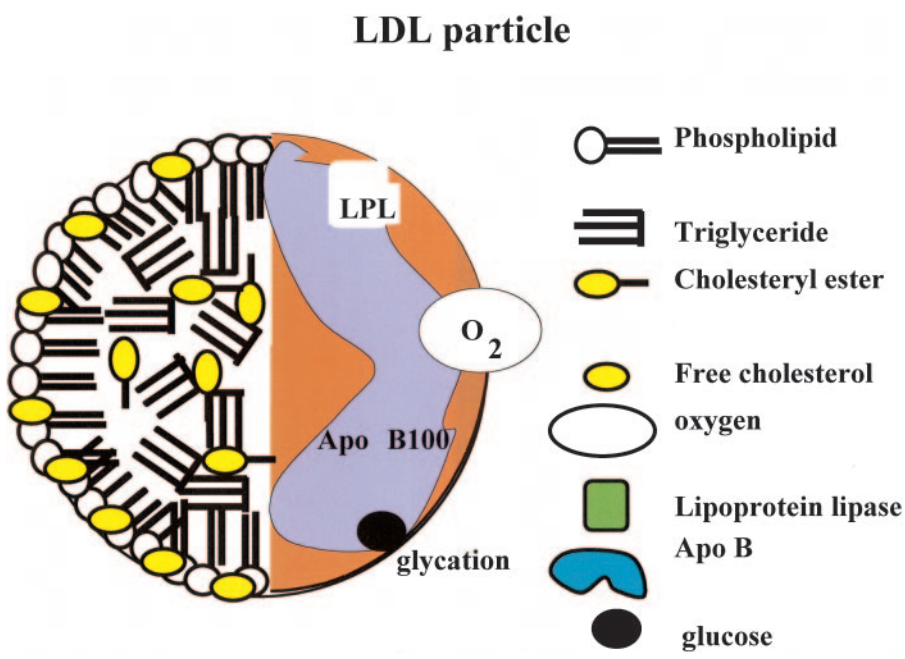

Figure 1—*The LDL particle is composed of an inner hydrophobic core made up of triglyceride and the fatty acid tails of the phospholipids and cholesterol esters. The surface is made up of free cholesterol, the phospholipids head, and one apo B100 molecule. LDL may be modified by oxidation and glycation and may attach molecules, such as to lipoprotein lipase and free fatty acids.*

The role of modification of LDL in antibody formation has been studied over the past few years with conflicting results, since it was first suggested that modified LDL is immunogenic and associated with circulating antibodies (39). We demonstrated an increase in LDL antibodies in diabetic patients (40), and numerous observational studies have shown an association with atherosclerotic disease. Several studies, however, have failed to show an association or have shown an inverse relationship between plasma levels of autoantibodies to LDL and atherosclerosis (41,42), although induction of tolerance to oxidized LDL has been shown to ameliorate atherosclerosis in animals (43).

HDL PROTECTS LDL — Defense of LDL against oxidation also comes from the paroxinase activity of HDL, and the low HDL in diabetes may be another factor leading to the increased oxidation of LDL. Not only is HDL quantity diminished in diabetes, but HDL composition is altered with higher triglyceride (44). It

has recently been demonstrated that HDL from type 2 diabetic patients was less effective in counteracting the inhibition of endothelium-dependent vasorelaxation induced by oxidized LDL than control HDL (45). In that study, there was a strong inverse correlation between the triglyceride content of the HDL and the ability to suppress inhibition of vasodilation that was induced by oxidized LDL. The mechanism by which HDL protects against atherosclerosis is thought to be through modulation of LDL oxidation by the action of paraoxinase 1 (PON-1). The group from Manchester (44) recently showed that HDL from type 2 diabetic patients was deficient in its ability to metabolize oxidized palmitoyl-arachidonylphosphatidy L-choline, a major product of LDL oxidation and a PON-1 substrate. The ATP binding cassette protein transporter ABC-A1 mediates the transfer from cells to apolipoprotein (apo) A1, the major protein in HDL. Passarelli et al. (46) demonstrated that precursors of advanced glycation end products can impair ABC-A1–mediated cholesterol removal from cells. Because advanced glycation end products have been implicated in the development of diabetic vascular disease (36,47), this seems to be one mechanism that occurs in diabetes leading to low HDL and increased atherogenesis. Recently, there has been a great deal of interest in the role of C-reactive protein, an acute phase protein, in the generation of atherosclerosis. It has been suggested that another inflammatory protein, serum amyloid A, may also be involved in the atherosclerotic plaque. Serum amyloid A appears to attach itself to the HDL particle and may play a role in the retention of HDL particles in the atherosclerotic tissue (48).

The initial metabolic disturbance in diabetes and pre-diabetes is an abnormality in fatty acid metabolism. Correction through exercise and alteration in diet has been shown convincingly in at least two studies to prevent the progression from impaired glucose tolerance to type 2 diabetes (48,49). The large Finnish study examined 522 middle-aged overweight subjects with impaired glucose tolerance and randomized them either to a lifestyle intervention or control group. The study demonstrated a cumulative incidence of diabetes of 11% in the intervention group compared with 23% in the control group, giving a 58% risk reduction over a 3.2-year period (50,51).

FATTY ACIDS AND INSULIN SECRETION

— Diabetes and indeed impaired glucose tolerance results in defects in insulin secretion, and it is therefore interesting to examine the relationship between fatty acids and insulin secretion. Xiao et al. (52) recently demonstrated the effect of different fat emulsions on glucose-stimulated insulin secretion and insulin sensitivity and clearance. They found that polyunsaturated fatty acids resulted in a reduction in absolute insulin secretion, whereas saturated fat induced insulin resistance. The authors concluded that the results supported the concept that saturated fatty acids impaired β-cell function. Exploring the problem in a different way, Poynten et al. (53) examined the relationship between circulating lipids, fatty acids, and fat oxidation. They found that circulating fatty acids could predict whole-body insulin sensitivity independently of abdominal fat, total body fat, and muscle lipids. The authors concluded that fasting NEFA levels were an independent predictor of insulin sensitivity. It seems clear that in the acute phase fatty acids stimulate insulin secretion, the stimulation being augmented by high glucose. In the chronic phase, however, it is well documented that fatty acids impede insulin secretion and cause, at least in in vitro studies, both apoptosis and necrosis of the β-cell. It has been suggested that high circulating NEFAs and triglycerides induce triglyceride accumulation in the pancreatic islets. The associated rise in cytoplasmic NEFAs cause a rise in ceramide formation and induce iNOS, resulting in nitric oxide–mediated β-cell apoptosis (rev. in 54 and 55). Peroxisome proliferator–activated receptor (PPAR)-α plays an important role in the regulation of cellular uptake, activation, and β-oxidation of fatty acids. The natural ligands for PPARs are mostly long-chain fatty acids. In pancreatic islets, exposure to long-chain fatty acids increases PPAR-α expression and may play a role in sustaining β-cell secretory capacity. However, in hyperglycemia, PPAR-α mRNA may be suppressed, and this suppression may be a component of glucotoxicity (56). PPAR-γ is expressed in many cell types. The natural ligands are several unsaturated fatty acids. A major effect of PPAR-γ is stimulation of fatty acid storage in adipose tissue and alteration in the size of the adipocytes, thereby reducing insulin resistance. PPAR-γ also negatively regulates transcription of several genes that impair insulin action. In pancreatic islets, thiazolidinediones, which are PPAR-γ agonists, have been shown to increase glucokinase and GLUT2 expression and activity (57), and this may also be a mechanism whereby the thiazolidinediones improve insulin resistance and delay the onset of diabetes (58).

THE LIPOPROTEIN CASCADE

— Because fatty acids play such a major role in the metabolic disturbance of diabetes, it is perhaps not surprising that the major disturbance in lipoprotein metabolism in diabetes is found in the triglyceride-rich lipoproteins, stemming from abnormalities in chylomicron synthesis and clearance. The disturbance is reflected in both quantity and quality. The atherogenicity of the chylomicron has been investigated over the years (59), and the evidence is supported by the finding of chylomicron particles in the atherosclerotic plaque (60) and the discovery that the macrophage has a specific apo B48 receptor (61), Apo B48, synthesized only in the intestine in humans. It is the solubilizing protein for the chylomicron and distinguishes it from the apo B100–containing triglyceride-rich VLDL synthesized in the liver. Apo B48 is increased in uncontrolled diabetes postprandially, and improvement in diabetic control leads to normalization (62). Chylomicron composition is probably abnormal in diabetes (63), although precise measurement of individual particle composition is difficult. Clearance is delayed, at least in animal studies, because of a deficiency of apo E on the particle, which also occurs in human diabetes (64). Defective action of lipoprotein lipase, an insulin-dependent enzyme, is another reason for delay in clearance of the particle. Because the chylomicron is preferentially taken up by the liver in competition with VLDL, the abnormality in chylomicron metabolism leads directly to defective clearance of VLDL by the liver and results in further hypertriglyceridemia because of an increase in VLDL.

REGULATION OF THE CHYLOMICRON

— The synthesis of the chylomicron particle (Fig. 2) in the intestine is altered because of abnormalities in cholesterol absorption and de novo synthesis. Although there is some controversy as to whether cholesterol absorption is increased or decreased in diabetes and type 1 may be different from type 2 diabetes (65,66), HMG-CoA reductase,

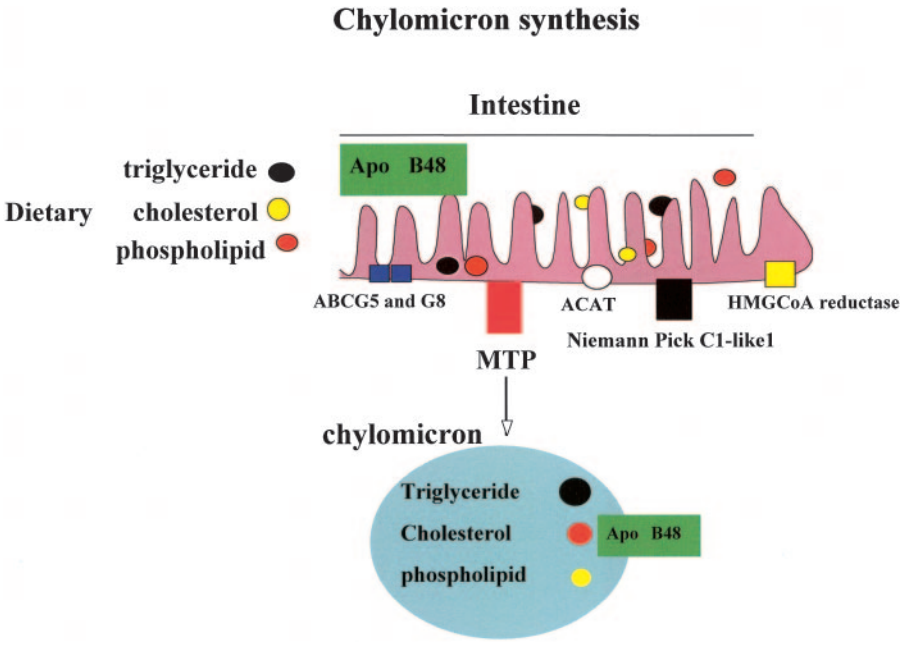

Figure 2—*In the intestine, cholesterol from dietary and billiary sources together with newly synthesized cholesterol for which HMG-CoA reductase is the rate-limiting enzyme is esterified by the enzyme ACAT and assembled, together with triglycerides, phospholipids, and apo B48 under the influence of MTP to form the chylomicron particle. Niemann Pick C1-like 1 (NPC1-L1) promotes cholesterol absorption by transfer of cholesterol across the membrane and ABCG5 and G8 regulate chylomicron cholesterol by promoting re-excretion from the intestinal villi.*

the rate-limiting enzyme for cholesterol synthesis, is increased in both the intestine and the liver in animals, suggesting an increase in de novo cholesterol synthesis (67,68). Expression of Niemann Pick C1-like 1 mRNA (the protein that regulates cholesterol absorption) (69) has been shown to be increased in diabetes (68,70,71), suggesting an increase in cholesterol absorption, recognizing that the cholesterol may come from dietary cholesterol or recycled cholesterol from the bile. The regulation of cholesterol absorption is further influenced by the ABCG5 and G8 proteins, which work in concert but perhaps also separately to pump absorbed cholesterol back into the lumen of the intestine and in the liver to pump cholesterol into the bile (72). ABCG5 and G8 have been shown to be reduced in diabetes in both liver and intestine (70,71). Microsomal triglyceride transfer protein (MTP) assembles the chylomicron in the intestine and the VLDL particle in the liver. MTP has been shown to be increased in the intestine in the diabetic patient (70,73); thus, many steps in the synthesis of the chylomicron and VLDL particle are abnormal in diabetes. The implications for the increase in the triglyceride content of the triglyceride-rich particles are to produce an LDL particle of abnormal composition and size (74).

PLANT STEROLS AND DIABETES

— Plant sterols have become popular in the treatment of high cholesterol, since numerous studies have demonstrated their ability to lower cholesterol by ~10% when taken in yogurt, margarine, etc. One might question the advisability of using these products in type 2 obese diabetic patients on the grounds of calories, since to eat 2.5 g of plant sterols a day, the subject needs to eat ~300 kcal of the margarine (and that does not even count the bread, biscuits, etc., on which the margarine is spread). A more serious concern, however, is the knowledge that sitosterolemia is associated with severe atherosclerosis. Sitosterolemia is caused by a defect in the ABCG5 and G8. Many polymorphisms have now been described. The decrease in ABCG5 and G8 found in diabetes suggests that, in diabetes, there may be an increase in chylomicron sitosterol when sitosterol-enriched margarine is used, and a small study has confirmed this (75).

TARGETS

— It can be seen from the above introduction to the lipid abnormalities that occur in diabetes that there are many new targets to attack to diminish the dyslipidemia of diabetes (Table 1). Meticulous control of hyperglycemia will inevitably result in normalization of lipoprotein and fatty acid metabolism, but this is unachievable for the majority of our patients at present. Drugs that alter the synthesis of the chylomicron particle may prove useful in the future. Targets include NPC1-L1 inhibitors, ABCG5 agonists, and MTP inhibitors (76). Intestinal Acyl coenzyme A: cholesterol acyltransferase (ACAT) inhibitors (77), which prevent esterification of ACAT (necessary for cholesterol absorption), may prove successful, but it is disappointing that the CETP inhibitors that raise HDL have not improved outcome (78). Clearance of apo B–containing particles may be improved by an increase in apo E and is another pathway for investigation (64). Apo A1–like particles that might improve the ability for reverse cholesterol transport is another area of interest (79). The understanding of the dyslipidemia of diabetes and the tissue damage that occurs will continue to stimulate the development of new treatments for diabetes.

Table 1—*Potential targets to normalize the dyslipidemia of diabetes*

Inhibition of NPC1-L1
Stimulation of ABCG5/G8
Inhibition of intestinal MTP
Inhibition of intestinal ACAT
Stimulation of synthesis of apo E and apo A1

NPC1-L1, Niemann Pick C1-like 1.

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