Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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REVIEW

Diabetes and dyslipidemia: characterizing lipoprotein metabolism

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GH Tomkin[1,2]
D Owens[1,2]

[1]Diabetes Institute of Ireland, Beacon Hospital, [2]Trinity College, University of Dublin, Dublin, Ireland

Abstract: Premature atherosclerosis in diabetes accounts for much of the decreased life span. New treatments have reduced this risk considerably. This review explores the relationship among the disturbances in glucose, lipid, and bile salt metabolic pathways that occur in diabetes. In particular, excess nutrient intake and starvation have major metabolic effects, which have allowed us new insights into the disturbance that occurs in diabetes. Metabolic regulators such as the forkhead transcription factors, the farnesyl X transcription factors, and the fibroblast growth factors have become important players in our understanding of the dysregulation of metabolism in diabetes and overnutrition. The disturbed regulation of lipoprotein metabolism in both the intestine and the liver has been more clearly defined over the past few years, and the atherogenicity of the triglyceride-rich lipoproteins, and – in tandem – low levels of high-density lipoproteins, is seen now as very important. New information on the apolipoproteins that control lipoprotein lipase activity has been obtained. This is an exciting time in the battle to defeat diabetic atherosclerosis.

Keywords: obesity, type 2 diabetes, dyslipidemia, low-density lipoprotein, fibroblast growth factor, forkhead transcription factor O1, farnesyl X transcription factors

Introduction

Diabetes is still often considered a sugar-related disease, but the disease might well have been named diabetes lipidus if only lipids instead of sugar could have been tasted in the urine, as suggested by Shafrir and Raz.[1] Only in recent years has the devastating complication of the lipid-related disease atherosclerosis become more feared than the glucose-centric small vessel disease.[2–5] Whereas small vessel disease is very much related to hyperglycemia, large vessel disease has been difficult to attribute to dysglycemia. Many studies have failed to reduce cardiovascular disease (CVD) events by improvement in blood sugar control.[6–9] On the other hand, cholesterol-lowering treatment, in particular, statins, have been shown to have a major impact on cardiovascular events from the first statin trials in diabetic patients.[10–12] The pathways by which insulin regulates fuel usage are still being discovered. It is clear that there is a switch from glucose to fat metabolism overnight when, in the fasting state, insulin deficiency results in not only high serum glucose but also high serum triglyceride levels. The triglycerides are packaged in lipoprotein particles driving the cascade through abnormal chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and finally high-density lipoprotein (HDL) (Figure 1).

Correspondence: GH Tomkin
Diabetes Institute of Ireland, Beacon Hospital, Clontra, Quinns Road, Shankill, Dublin 18, Ireland
Email tomking@tcd.ie

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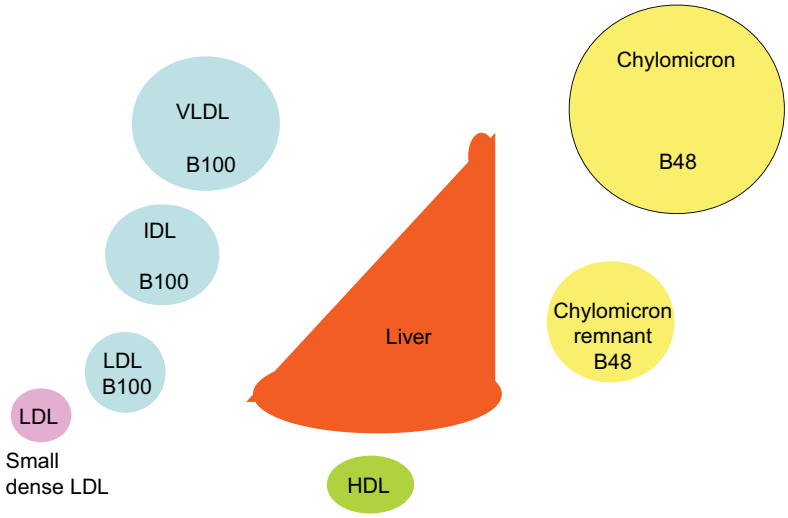

Figure 1 Lipoprotein cascade.
Notes: In the circulation, VLDL is gradually delipidated, resulting in increasingly smaller lipoprotein particles, ie, IDL, LDL, and small dense LDL. The intestinally derived chylomicron, characterized by presence of apoB48, is delipidated to form the chylomicron remnant, which is taken up by the liver.
Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

Fasting hypertriglyceridaemis is significantly associated with cardiovascular events and death.[13] A similar picture emerges when postprandial triglycerides are examined.[14–16] Starvation and bariatric surgery both have a profound effect on serum lipids.[17–19] Cholesterol is both absorbed and synthesized. Insulin regulates both these pathways, and since cholesterol synthesis is regulated through the bile acid cholesterol pathway, bile acids play a major part in cholesterol homeostasis.[20]

The purpose of this review is to explore the relationship among insulin resistance, diabetes, and dyslipidemia. We highlight areas of research that may lead to the discovery of possible new treatments to prevent premature heart disease in diabetes.

Insulin action

The secretion of insulin is glucose dependent. This is relevant in the fed state to prevent postprandial hyperglycemia. In fasting conditions, when the blood sugar is low, insulin is still needed; otherwise, free fatty acids will rise and hepatic glucose suppression will not occur, leading to hyperglycemia. In the fasting state, when blood sugars are low, fatty acids, not glucose, stimulate insulin secretion from the β cells.[21]

It has been shown that fatty acids acutely enhance insulin secretion, oxygen consumption rate, and extracellular acidification rate in human islets at fasting glucose concentrations, with monounsaturated fatty acids (MUFAs) being more potent than saturated fatty acids (SFAs).[22] Cen et al[22] suggest that the high fatty acids in their study may account for the hyperinsulinemia in patients who have raised fatty acids but normal blood sugars. In overnutrition, insulin initially manages to store the excess calories in the adipose tissue. This process breaks down at some stage and fatty acids collect in the liver and the muscle, leading to insulin resistance, and a vicious cycle arises in which the pancreas fails to deliver sufficient insulin to cope with the increased demands. This leads to even more difficulty in disposal of the fatty acids, and then the lack of inhibition of glucose release in the liver leads to hyperglycemia against a background of raised fatty acids. The high glucose level inhibits β-oxidation via a product of the glycolytic pathway, malonyl coenzyme A (Co-A), and fatty acids are directed toward formation of triglycerides.[23] In the long term, the rise in free fatty acids has a detrimental effect on the β cells, leading to apoptosis.[24]

Diacylglycerol and insulin resistance

Diacylglycerol (DAG) is the precursor for triglyceride biosynthesis. The DAG kinases (DAGKs) are a group of kinases that regulate signal transduction via protein kinase C (PKC), Ras and Rho family proteins, and phosphatidylinositol 5-kinases.[25] Elevated DAG content is linked with the development of insulin resistance in type 2 diabetes.[26,27] DAGK delta activity and total DAG level are reduced in skeletal muscle from type 2 diabetic patients.[28,29] Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is a central regulator of energy metabolism. Metformin, the most commonly used drug to treat type 2 diabetes, activates AMPK to suppress gluconeogenesis.[30] AMPK also suppresses gluconeogenesis by the downregulation of FoxO1 target genes.[31] Transforming growth factor beta (TGF-b)/daf-16 (FoxO1) interact

with AMPK to regulate metabolic and nutrient sensory pathways and glucose metabolism.[32,33] Yadav et al[33] have shown that that TGF-b1 signaling suppressed the liver kinase B1 (LKB1)–AMPK axis, thereby facilitating the nuclear translocation of FoxO1 and activation of key glucogenic genes regulating glucose-6 phosphatase and phosphoenolpyruvate carboxykinase both in the fasting state and in type 2 diabetes. PKC blocks AMPK activation.[34] Nutrient excess in type 2 diabetes or obesity elevates DAG levels and PKC activity, in addition to impairing insulin sensitivity.[35] AMPK activity is reduced in insulin-resistant and obese animal models.[36] AMPK is involved in lipid metabolism through acetyl-CoA carboxylase and malonyl-CoA decarboxylase.[37,38] Jiang et al[39] have shown that DAGK delta deficiency impairs AMPK and lipid metabolism, as well as influencing skeletal muscle energetics. It seems that DAGK delta is a major player in the reduction in lipid oxidation and the insulin resistance found in type 2 diabetes (Figure 2).

Bile acids

There is a third player in this process, namely, the bile acids. The two primary bile acids are chenodeoxycholic and cholic acids. They are synthesized in the liver, conjugated with taurine or glycine, and excreted in the bile.[20] They aid fat absorption through their ability to form micelles, thus solubilizing fat and cholesterol.[40] An increase in dietary cholesterol suppresses cholesterol synthesis and a decrease in dietary intake increases de novo synthesis in the liver. The bile acid-activated receptors play an important regulatory part in not only maintaining lipid, but also glucose, homeostasis.[41–43] Chenodeoxycholic acid, which is an important farnesoid X receptor (FXR) agonist, lowers the biliary secretion of cholesterol, and reduces the cholesterol saturation of LDL through reduced clearance of plasma apolipoprotein B (apoB).[44] Hepatic microsomal cholesterol 7 alpha hydroxylase (CYP7A1) and 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase activities were reduced and specific LDL receptor binding was also reduced.[45–47] Ghosh et al[48] have shown that chenodeoxycholic acid reduces plasma clearance of LDL, somewhat mitigated by a decrease in LDL production. Proprotein convertase subtilisin/kexin type (PCSK9), apoA1, apoC111, lipoprotein (a), triglycerides, and insulin levels were reduced. This is of interest because FXR agonists have been shown to prevent the development of insulin resistance in animals.[49]

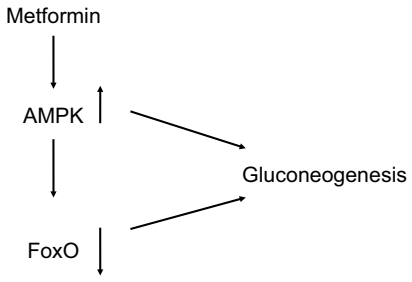

Figure 2 Metformin stimulates AMPK, which downregulates gluconeogenesis both directly and through downregulation of FoxO.
Abbreviation: AMPK, adenosine monophosphate-activated protein kinase.

Glucose-dependent insulinotropic polypeptide (GIP) stimulates insulin secretion. The action of GIP is impaired in type 2 diabetes. GIP has been shown to lower nonesterified fatty acid (NEFA) concentration in obese type 2 diabetic patients despite diminished insulinotropic activity. GIP has also been shown to increase subcutaneous adipose tissue triglycerides. Reduction in NEFA concentration with GIP correlated with a reduction in adipose tissue insulin resistance.[50]

Fibroblast growth factors (FGFs)

FGF 15/19 and FGF 21 play an important role in metabolic regulation.[51–53] Both molecules have demonstrated ability to lower serum glucose, triglyceride, and cholesterol levels; improve insulin sensitivity; and reduce body weight.[54,55] FGF 19 activates FGF receptor 4 (FGFR4), the predominant receptor expressed in the liver, and regulates bile acid homeostasis.[53,56–57] FGF 21 has recently been shown in mice to antagonize the action of FGF 15/19.[53] Zhang et al[53] have found, as expected, that overexpression of either FGF15 or FGF 21 reduced body weight, fasting glucose level, and insulin level, as well as decreasing plasma triglyceride and cholesterol levels. FGF 15 lowered the bile acid pool, but unexpectedly, the authors report that they found that FGF 21 increased the bile acid pool size through the beta-Klotho/FGFR4 complex. CYP7A1 catalyzes the first and rate-limiting step in the classic bile acid pathway.[58] Cyp7A1 is tightly regulated by a negative feedback loop mediated by FGF 15/19.[59,60] Overexpression of FGF15 significantly reduces Cyp7A1 mRNA.[53] In contrast, FGF 21 overexpression results in CYP7A1 upregulation, suggesting that bile acid synthesis was the reason for the increased bile acid pool size in these animals. Serum FGF 21 has been shown to be increased in obesity.[61] The authors have shown that there was a positive correlation between adiposity, fasting insulin, and triglycerides and a negative correlation with HDL cholesterol. Logistic regression analysis demonstrates an independent association between serum FGF 21 and the metabolic syndrome.[61] FGF 21 has been shown to be raised in type 2 diabetic patients with nonalcoholic fatty liver disease.[62] More recently, Alonge et al[63] have shown that glucagon and

insulin cooperatively stimulate *FGF 21* gene transcription by increasing the expression of activating transcription factor 4. It has also been shown that FGF 21 is a superior biomarker to other adipokines.[64] The authors suggested that serum FGF 21 might be considered an alternative to the oral glucose tolerance test.[64] An FGF 21 analog has been shown to be superior to glargine insulin and a glucagon-like peptide-1 (GLP1) agonist liraglutide in reducing hemoglobin A1c (HbA1c) and improving glycemic control, insulin resistance, serum lipids, and liver function states in type 2 diabetic db/db mice (Figure 3).[65]

The FGF 21 analog LY2405319 has shown, in a 28-day proof-of-concept study[66] in type 2 obese diabetic patients, significant improvement in lipids, with favorable effects on body weight, fasting insulin, and adiponectin. There was a trend toward glucose lowering.[66] Another analog, PF-05231023, has been shown – in type 2 diabetes – to decrease body weight, improve lipoprotein profile, and increase adiponectin levels. The drug had no effect on glycemic control. The drug had effects on multiple markers of bone formation and resorption, and it increased insulin-like growth factor-1 (IGF-1). In adults, FGF 21 has been shown to be raised.[64] In Chinese children aged between 6 and 18 years, the opposite has been described, with deficiency – rather than resistance – being found.[67] The authors suggest that in children, FGF 21 deficiency – rather than resistance – contributes to insulin resistance and hypoadiponectinemia. Interestingly, leptin has recently been shown to increase FGF 21 levels in Wistar rats and in human-derived hepatoma HepG2 cells.[68] Thus, the pathways between bile, cholesterol, glucose, and fat metabolic processes are linked, but there are still many discoveries yet to be made. Looking at the problem the other way, a deficiency of insulin leads to hyperglycemia, hypertriglyceridemia, and hypercholesterolemia, apart from abnormal bile acid metabolism, which affects the apoB-containing lipoproteins, and an interconnected decrease in HDL.

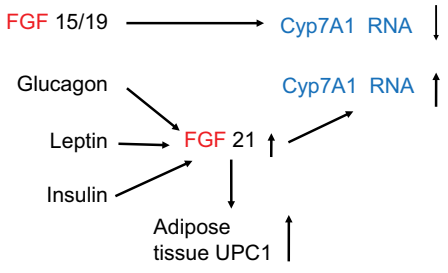

Figure 3 FGF 15/19 and FGF 21 have opposing effects on bile acid synthesis through their effect on Cyp7A1.
Note: Glucagon, leptin, and insulin increase FGF 21, which increases adipose tissue UCP1. Cyp7A1 is also termed cholesterol 7a-hydroxylase.
Abbreviation: FGF, fibroblast growth factor.

Serine/threonine protein kinase (STK25)

The networks controlling fat deposition and insulin responsiveness are very complex and attract much attention. The enzyme STK25 has been shown to influence intramyocellular lipid accumulation, impair skeletal muscle mitochondrial function and sarcomeric ultrastructure, and induce perimysial and endomysial fibrosis, thereby reducing endurance exercise capacity and muscle insulin sensitivity.[69] The same group had previously shown that STK25 regulates lipid partitioning in human liver cells by controlling triglyceride synthesis as well as lipolytic activity and, thereby, NEFA release from lipid droplets for β-oxidation and triglyceride secretion.[70]

Forkhead transcription factors

FoxO1 plays an important role in orchestrating fuel metabolism and influences glucose, fat, and bile metabolic pathways through its effect on mitochondrial function and adipocyte differentiation.[71–75] FoxO1 alters mitochondrial biogenesis, morphology, and function in the liver of insulin-resistant mice, while genetic ablation of FoxO1 significantly normalizes mitochondria and metabolism.[73,76] In the adipocyte, silencing of FoxO1 inhibits cell differentiation and lipid accumulation, with changes in expression of mitochondrial respiration chain proteins.[71,73,74] FoxO1 has been shown to control lipid droplet growth and adipose autophagy.[77–81] Inhibition of autophagy leads to browning of white adipose tissue, which is characteristic of increased expression of uncoupling protein 1 (UCP1).[78–81] UCP1 uncouples mitochondrial respiration from adenosine triphosphate (ATP) production/oxidative phosphorylation, dissipating energy as heat.[82,83] Liu et al[84] have recently shown that FoxO1 interacts with transcription factor EB (Tfeb), a key regulator of autophagosomes and lysosomes, and mediates the expression of UCP1, UCP2, and UCP3. However, the study[84] showed that inhibition of FoxO1 suppressed Tfeb and autophagy, attenuated UCP2 and UCP3, but increased UCP1 expression (Figure 4). The enzyme protein deglycase (DJ-1) is involved in multiple physiological processes. Wu et al[85] have recently shown that this protein is involved in maintaining energy balance and glucose homeostasis, regulating brown adipose tissue (BAT) activity. They showed that DJ-1-deficient mice had reduced body mass, increased energy expenditure, and improved insulin sensitivity. DJ-1 has been shown to inhibit FoxO1-dependent UCP1 expression in BAT. FoxO1 has also been shown to downregulate apoA1 gene activity in HepG2 cells under oxidative stress induced by hydrogen peroxide.[86] ApoA1 forms HDL particles and has an antioxidant function.

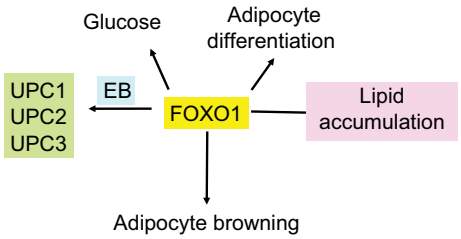

Figure 4 Effect of FoxO1 on adipocyte differentiation and mitochondrial function.
Notes: FoxO is a regulator of glucose metabolism, lipid accumulation, and adipocyte differentiation. It also increases adipocyte browning and interacts with Tfeb to regulate UCPs 1, 2, and 3.
Abbreviation: Tfeb, transcription factor EB.

Leptin is an important metabolic regulator. Leptin injections have been shown to increase plasma FGF21 in vivo in Wistar rats and in vitro using human-derived hepatocarcinoma HepG2 cells, mediated by STAT 3 activation.[68] FoxO1, FoxO3, and FoxO4 have been shown to be involved in muscle proteasomal and autophagy–lysosomal degradation. Diabetes strongly affects protein metabolism, muscle wasting being a very significant finding in uncontrolled diabetes. Insulin and IGF-1 enhance muscle protein synthesis through their receptors.[87] O'Neill et al[88] have shown that both IGF-1 and the insulin receptor are involved in muscle proteostasis, the insulin receptor being more important than IGF-1. They found that muscle-specific deletion of FoxO1, FoxO3, and FoxO4 in double knockout of both insulin receptor and IGF-1 in mice completely rescued the muscle mass without changing the proteasomal activity.

FoxO1, rapamycin, and perilipin (PLIN)

Muscle is an important tissue for whole-body glucose homeostasis.[89,90] Target of rapamycin (TOR) C2 is found in the insulin signaling pathway and is responsible for regulating muscle glucose metabolism.[91–93] Acute inhibition of mTOR complexes increases lipid utilization, probably due to the effect of mTOR C2.[91] PLIN 3 is a regulator of lipid storage.[94–96] Knockdown of PLIN 3 in the liver of high-fat-diet-fed mice improves hepatic steatosis along with glucose homeostasis.[97] PLIN 3 overexpression has been shown to increase muscle triglyceride.[98] FoxO1 is a regulator of PLIN 1. AMPK modulates FoxO1 transcriptional activity.[99] A FoxO1 antagonist has been shown to suppress autophagy and lipid droplet growth in adipocytes.[77]

Fibroblast activation protein (FAP)

FAP is a serine protease, and it has been shown to regulate the degradation of FGF 21[100] Sánchez-Garrido et al[101] have shown that inhibition of FAP using a known FAP inhibitor, talabostat, enhances levels of FGF21 in obese mice, reducing body weight, food consumption, and adiposity while increasing energy expenditure, glucose tolerance, and insulin sensitivity, as well as lowering cholesterol levels. The metabolic effect of FAP inhibition was markedly reduced in lean animals.[101]

Peroxisome proliferator-activated receptor (PPAR)

Insulin resistance in skeletal muscle plays a major role in obesity and type 2 diabetes.[27] The PPAR superfamily of transcription factors includes the isoforms PPAR-alpha, which modifies insulin resistance in the liver; PPAR-γ, which regulates genes involved in fatty acid metabolism, inflammation, and macrophage homeostasis;[102] and PPAR delta, which has been implicated in obesity-associated insulin resistance.[103] It is highly expressed in muscle compared to PPAR alpha and gamma. A high-fructose diet-induced obesity results in insulin resistance in mice with hyperinsulinemia, hyperleptinemia, hyperlipidemia, and hypoadiponectinemia. The diet has been shown to impair insulin and AMPK signaling pathways and reduce glucose transporter type 4(GLUT-4) and GLUT-5 expressions. The study showed that a PPAR delta agonist GW0742 had no effect on control mice, but in the high-fructose-diet animals, it increased the expression of PPAR delta and significantly attenuated all the effects of the diet on the phosphorylation of insulin receptor substrate-1 (IRS-1), protein kinase B (PKB) or AKT, and glycogen synthase kinase 3 beta (GSK-3B). The agonist reduced skeletal muscle triglyceride and increased muscle glucose uptake. The drug increased phosphorylation of both AMPK and acetyl Co-A carboxylase (ACC) and increased protein expression of carnitine palmitoyl transferase-1 (CPT-1), all suggesting an increase in fatty acid oxidation. There was a dramatic increase of FGF-21 production in the muscle.[104]

DAG transferase

Hypertriglyceridemia is a major finding in uncontrolled diabetes. Indeed, many years ago,[105] Shafrir and Gutman[105] showed that as glucose intolerance increased from normal to diabetes through prediabetes, free fatty acids became much more markedly abnormal and preceded the glucose shift from normal to diabetes. Free fatty acids are converted to DAG through diglyceride acyltransferase (DGAT)-1 and then to triacylglycerol through DGAT2. The other major pathway of triglyceride synthesis is the glycerol phosphate pathway. In both pathways, fatty acyl-CoA and DAG are converted jointly to form triglyceride, catalyzed by DGAT. A novel DGAT1

inhibitor has been shown in mice to improve insulin resistance in adipose tissue, as well as systemic glucose metabolism, through a reduction in body weight.[106]

Triglyceride and cholesterol absorption in diabetes

Excess calories are first stored as triglyceride in adipose tissue to be released as fuel through the fatty acid cycle when carbohydrate is in short supply. Lipoprotein lipase (LpL) is suppressed by insulin, and therefore in insulin deficiency states, lipolysis increases even in a high-glucose environment. FoxA2 has been shown in the liver to regulate the *LpL* gene; thus, FoxA2 may be another important regulator of lipid and glucose metabolic pathways.[107] Dietary fat is solubilized by bile acids in the intestine and, apart from the short-chain fatty acids, is absorbed by the lymphatic system passing to the liver. Triglyceride absorption is unregulated, so that fecal fat remains in very small quantities even in very-high-fat diets. Fatty acids stimulate synthesis of apoB100, which is edited to apoB48 in the intestine.[108] ApoB48 is the solubilizing protein by which triglycerides and cholesterol are carried to the liver and then around in the circulation in the postprandial state. Although triglyceride absorption is unregulated, cholesterol absorption is tightly regulated. NPC1L1 is the regulating transporter protein in the first step in cholesterol absorption in the intestine. NPC1L1 mRNA is upregulated in diabetes.[109] It has been shown that in a high-glucose environment, cholesterol absorption is increased.[110]

The dimer proteins ABCG 5/8 act together in the intestine to excrete excess cholesterol back into the lumen. These genes are downregulated in diabetes.[109] Genetic variants in ABCs G5/8 have been shown to protect against myocardial infarction (MI) but also to increase the risk of symptomatic gallstone disease, demonstrating the interdependence between bile acid and cholesterol metabolic pathways.[111] The final step in the absorption process is the attachment of the triglyceride and cholesterol onto apoB48 through MTP. MTP is upregulated in diabetes, and this is reflected in higher levels of apoB48 in serum (Figure 5).[112] These particles are thought to be particularly atherogenic because of their large size and rapid turnover, so even though their cholesterol quantity per particle is low, the total carrying power of these particles is large; therefore, they are inherently atherogenic since the particles lodge in atheromatous plaques.[113]

The postprandial apoB48-containing particles and the VLDL apoB100 triglyceride-rich particles gather various apoproteins in the circulation. For example, apoC1 inhibits its clearance of triglyceride by LpL. High levels of white adipose tissue apoC1 secretion has been shown to delay clearance of postprandial chylomicrons in overweight and obese subjects.[114] ApoC11 is an obligatory cofactor for LpL. Recently, deficient cholesterol esterification has been found to occur in an apoC11-deficient zebrafish, which mimics the familial chylomicronemia syndrome in human patients, with a defect in apoC2 or LpL genes.[115] ApoC111 inhibits the delipidation of triglyceride from the particle by inhibiting the action of LpL, thus delaying the clearance of the particle from the circulation.[116] The Bruneck Study[117] was designed to examine the importance of various apolipoproteins in the genesis of cardiovascular events over a 10-year period. The study found that apoC11, apoC111, and apoE were the apolipoproteins most significantly associated with incident

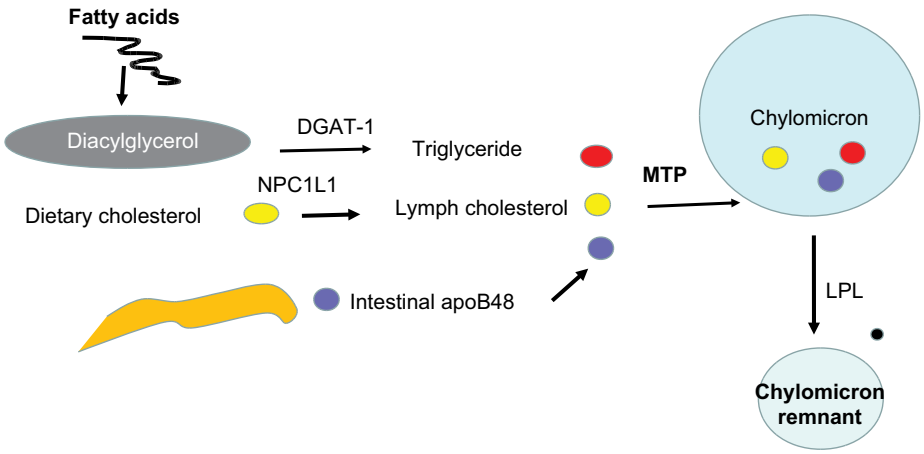

Figure 5 Cholesterol absorption and chylomicron assembly and breakdown.
Notes: Diacylglycerol is formed from free fatty acids under the influence of DGAT-1. Dietary cholesterol uptake from the intestine into the lymph is regulated by NPC1L1. ApoB48 is synthesized in the intestine. Triglyceride, cholesterol, and apoB48 are combined under the influence of MTP to form the chylomicron. In the circulation, the chylomicron is delipidated by LPL and cleared by the liver.
Abbreviations: DGAT, diglyceride acyltransferase; LPL, lipoprotein lipase.

CVD. These associations were independent of HDL and non-HDL cholesterol and extended to stroke and MI. Interestingly, these three apolipoproteins, apoC1, apoC11, and apoE, were implicated in de novo lipogenesis, glucose metabolism, complement activation, blood coagulation, and inflammation, through the lipidomic and proteomic profiles determined in the study.[118] In the liver, NPC1L1 plays a part in the transport of cholesterol to the canaliculi, wherein the VLDL particle is assembled. The ABCs G5/8 play an important part in regulating the amount of cholesterol diverted to the bile for excretion. AUP1 is an endoplasmic reticulum-associated protein. Very recently, it has been shown to be involved in the regulation of apoB100, hepatic lipid droplet metabolism in the liver, and intracellular lipidation of VLDL particles.[119] Its role in the intestine is so far unknown.

Diabetes disturbs the synthesis and metabolism of triglyceride-rich lipoprotein particles, increasing their atherogenicity. The specific role of triglycerides in atherogenesis has been difficult to tease out as the lipoprotein cascade is so interdependent and changes in the chylomicron influence VLDL assembly in the liver through the increase in delivery of both triglyceride and cholesterol to the liver.[120] The increase in triglyceride content of the VLDL particle translates to an LDL particle with an increase in fatty acids. LDL atherogenicity is dependent at least in part on its oxidizability. The more the number of fatty acids with more-than-one double bond, the easier it is to oxidize, and it is the oxidized LDL that is taken up in an unregulated way by the macrophage, the hallmark of the atheromatous plaque.[120] Small dense LDL particles are particularly associated with atheromatous risk and these particles arise from triglyceride-rich VLDL particles. An analysis of lipoprotein subfractions in 920 patients with and without type 2 diabetes confirmed the increase in concentration and size of smaller LDL particles.[121]

Free radical production is increased in the hyperglycemic state, so the diabetes environment increases the oxidation of LDL. In this context, delays in treatment intensification with oral antidiabetic drugs have been shown to increase the risk of major cardiovascular events.[122]

Diabetes dyslipidemia, atherosclerosis, and HDL

The hallmark of diabetes dyslipidemia is high triglycerides with low HDL.[123,124] The interdependence of triglycerides and HDL has made it very difficult to separate the risk of atherosclerosis from one or the other. Until recently, HDL has come out on top and the triglyceride-rich lipoproteins have been undervalued as risk factors for accelerated atherosclerosis. Epidemiological studies in the 1970s established the strong inverse relationship between low HDL levels and coronary heart disease.[125,126] More recently, the focus has been on the quality of HDL since functionality has been shown to be of major importance in predicting atherogenic risk.[127,128] Hermans et al[128] have suggested that the ratio of HDL-C/apoA1 might be a better way to predict angiopathic risk. Sun et al[129] have shown that HDL from people with type 2 diabetes had the ability to stimulate secretion of tumor necrosis factor (TNF)-a, an inflammatory cytokine, in incubated human peripheral blood mononuclear cells to a greater extent as compared to HDL from control subjects. They showed that HDL from the patients with coronary artery disease (CAD) had a greater capacity to stimulate TNF-a as compared to HDL from the type 2 diabetic subjects who did not have coronary heart disease. The proinflammatory ability of HDL was a significant predictor for the presence of CAD in patients with diabetes. HDL particle number, rather than cholesterol content, may be a better predictor of atherogenicity. A multiethnic study[130] of atherosclerosis has examined this in patients with the metabolic syndrome and diabetes**.** Tehrani et al[130] found that HDL particle number in diabetes predicted coronary heart disease (CHD) and CVD. In those with metabolic syndrome, only LDL particle number was positively associated with CVD.

A retrospective study[131] among >47,000 patients attending Italian diabetic centers investigated >15,000 patients with no evidence of renal disease. A 4-year follow up demonstrated that low HDL and high triglyceride levels were independent risk factors for the development of diabetic kidney disease over 4 years.[131] Poor glycemic control in type 2 diabetes enhances functional and compositional alterations of small dense HDL3.[132] Gomez Rosso et al[132] showed that defective functionality of small dense HDL particles was present in patients with type 2 diabetes mellitus with poor glycemic control. The HDL had also diminished its antioxidant ability. One of the benefits of lifestyle intervention is the increase in HDL and, in particular, large HDL. It has recently been shown that lifestyle intervention can offset unfavorable genetic loading for most lipid traits, including the size of HDL.[133] The understanding of functionality of HDL may become clearer following the description of the use of atomic force microscopy to examine the organization of apoA1.[134]

Conclusion

The dysregulation of metabolism when relative or absolute insulin deficiency appears has been more clearly defined in the past few years. The interplay between the bile, cholesterol,

and carbohydrate metabolic pathways and the genes involved have opened up new possibilities of treatments to ameliorate the atherogenic potential of diabetic dyslipidemia. Overfeeding leads to obesity and insulin resistance. Hyperinsulinemia progresses to a relative, and then absolute, deficiency of insulin. It is difficult to dissect the metabolic disturbances that occur at each stage of the disease process. Dyslipidemia potentiates the disease process through oxidation of LDL, which further damages the β-cell. The abnormal HDL and the deficiency of its antioxidant functions in the defense of the β-cell have made for exciting speculations on treatments that might slow or stop β-cell destruction. Calorie excess, together with inadequate exercise, remains central to type 2 diabetes and diabetic dyslipidemia. Bariatric surgery and starvation both have shown how calorie restriction can ameliorate the metabolic dysfunction of type 2 diabetes, which includes dyslipidemia.

The most obvious lipid defect in uncontrolled diabetes is the elevated level of triglycerides. A consequence is the lowering of HDL. The triglyceride-rich lipoproteins have again come into fashion as important atherogenic particles. Although these particles carry much less cholesterol than LDL per particle, their actual load is similar to LDL if one takes into account their rapid half-life. LDL has a half-life of days rather than minutes in the case of chylomicrons. The influence of insulin on regulation of the apoB48-containing chylomicron in the intestine through a complex series of steps has helped to understand how dysregulation occurs in diabetes.

Disclosure

The authors report no conflicts of interest in this work.

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