New Aspects of Cellular Cholesterol Regulation on Blood Glucose Control—Review and Perspective on the Impact of Statin Medications on Metabolic Health

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Cholesterol is an essential component of cell membranes, and during the past several years, diabetes researchers have found that membrane cholesterol levels in adipocytes, skeletal muscle fibers and pancreatic beta cells influence insulin action and insulin secretion. Consequently, it is thought that dysregulated cell cholesterol homeostasis could represent a determinant of type 2 diabetes (T2D). Recent clinical findings compellingly add to this notion by finding increased T2D susceptibility in individuals with alterations in a variety of cholesterol metabolism genes. While it remains imperfectly understood how statins influence glucose metabolism, the fact that they display an influence on blood glucose levels and diabetes susceptibility seems to intensify the emerging importance of understanding cellular cholesterol in glucose metabolism. Taking this into account, this review first presents cell system and animal model findings that demonstrate the negative impact of cellular cholesterol accumulation or diminution on insulin action and insulin secretion. With this framework, a description of how changes in cholesterol metabolism genes are associated with T2D susceptibility will be presented. In addition, the connection between statins and T2D risk will be reviewed with expanded information on pitavastatin, a newer statin medication that displays actions favoring metabolic health.

Keywords

Cholesterol, dyslipidemia, glucose, insulin resistance, statins, type 2 diabetes

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In a series of recent studies, insulin-stimulated glucose disposal in animal models and human subjects was found to be inversely related to plasma membrane cholesterol content. Aberrantly increased plasma membrane cholesterol is seen uniformly in insulin-resistant mice, rats, swine, and humans, and normalization restores insulin responsivity.[1–4] Mechanistic studies in clonal cells, as well as in fat and skeletal muscle tissue demonstrate that excess plasma membrane cholesterol reduces cortical filamentous actin (F-actin), which is essential for glucose transporter type 4 (GLUT4) regulation by insulin. In addition to this negative consequence of excess plasma membrane cholesterol on insulin action, Llanos et al. found the ryanodine receptor calcium signals, which are important for GLUT4 regulation, are negatively affected by increased skeletal muscle membrane cholesterol.[4] Interestingly, exercise known to ward off diabetes development has recently been shown to prevent plasma membrane cholesterol accumulation, cortical actin filament loss, and insulin resistance in mice fed a western-style high-fat diet.[5] While F-actin and calcium signaling defects that manifest in cholesterol-laden plasma membrane seem to represent critical determinates of impaired GLUT4 regulation and glucose transport, the precise mechanisms of cellular cholesterol accumulation and insulin resistance remain elusive. In fact, Parpal et al. demonstrated that progressive cholesterol depletion of 3T3-L1 adipocytes with beta-cyclodextrin gradually destroyed plasma membrane caveolae structures and concomitantly diminished insulin-stimulated glucose transport, in effect making cells insulin-resistant.[6] The importance of this in metabolic health is that upsurges or plunges in plasma membrane cholesterol both

adversely affect insulin action. Interestingly, a set of pancreatic beta (β)-cell studies also demonstrate a strikingly similar damaging impact of too much or too little plasma membrane cholesterol on insulin secretion.

In 2007, Brunham et al. studied mice with a specific inactivation of *Abca1* in β cells.[7] *Abca1* encodes the adenosine 5'-triphosphate (ATP)-binding cassette transporter subfamily A member 1 (ABCA1) that mediates the rate-limiting step in high-density lipoprotein (HDL) biogenesis by effluxing cellular cholesterol to apolipoprotein A1 (ApoA1). Their deletion of β-cell ABCA1 increased cholesterol in these cells and impaired insulin secretion, suggesting that β-cell cholesterol accumulation may contribute to β-cell dysfunction. Subsequent investigation found that islets lacking the related cholesterol transporter ABCG1 also had impaired glucose-stimulated insulin secretion (GSIS).[8] Also, somewhat expectedly, it was found that losses of both ABCA1 and ABCG1 induced an exacerbated disturbance in β-cell function compared with loss of either transporter alone.[9] Another line of investigation revealed elevated islet cholesterol levels and impaired GSIS in ApoE-deficient mice.[10] Further experimental manipulation of β-cell cholesterol levels in this study demonstrated that excess membrane cholesterol impairs GSIS, whereas cholesterol normalization enhances GSIS.[10] Interestingly, in the context of what is seen in adipose tissue and skeletal muscle cells, it was also found that cholesterol-overloaded β cells exhibit diminished glucose-induced actin reorganization, membrane depolarization, and insulin secretion.[11] In terms of human β-cell health, infusion of reconstituted HDL in patients with T2D improves β-cell function, whereas carriers of loss-of-function mutations in ABCA1 have impaired β-cell function.[12] Of note, like extreme plunges in plasma membrane cholesterol negatively impacting insulin action, Tsuchiya et al. found that cholesterol composition of insulin secretory granule (SG) membrane is crucial for GSIS and SG formation.[13]

Together, these studies support the case that changes in cellular cholesterol metabolism may represent an etiological factor of T2D development. Next, we summarize genetic studies that come to the same conclusion. Also, new data suggesting how caloric excess may fuel cholesterol accumulation are highlighted. Finally, we present data and perspective on how statins may mechanistically influence glucose metabolism.

Cholesterol genes and diabetes

Several human genetic studies suggest a relationship between increased cellular cholesterol levels and alterations in glycemia. Ding et al. quantified the transcriptome and epigenome in monocytes from 1,264 participants in the Multi-Ethnic Study of Atherosclerosis, and found that alterations in a network of coexpressed cholesterol metabolism genes were associated with T2D.[14] This network included 11 genes related to sterol influx (↑*LDLR*, ↓*MYLIP*), synthesis (↑*SCD*, *FADS1*, *HMGCS1*, *FDFT1*, *SQLE*, *CYP51A1*, *SC4MOL*), and efflux (↓*ABCA1, ABCG1*), producing a molecular profile expected to increase intracellular cholesterol. Recent examination of multi-tissue transcriptomes and epigenomes suggest that these cholesterol metabolism genes are similarly altered in human adipose tissue.[15,16] Moreover, obesity-driven modifications in the epigenome predicted T2D, independent of conventional risk factors such as body mass index (BMI) and glycemia.[16] Many of the methylation sites responsive to obesity were involved in lipid and lipoprotein metabolism. Identified in this analysis was a strong relationship between the methylation of ABCG1 and T2D.[16] As expanded on below, genetic mutations resulting in diminished circulatory levels of both low-density and high-density lipoproteins are significantly associated with T2D.[17] Of interest is that these changes could have significant bearing on cellular cholesterol levels and thus possibly explain the increased T2D risk.

Low-density lipoprotein metabolism and type 2 diabetes

Low-density lipoprotein (LDL) receptors (LDLRs) mediate the cellular uptake of LDL-cholesterol (LDL-C) from the circulation. Myosin regulatory light chain-interacting protein (MYLIP) promotes LDLR degradation. Thus, increased *LDLR* gene expression and/or decreased *MYLIP* gene expression would favor diabetogenic LDLR-mediated cholesterol delivery to adipocytes, pancreatic β-cells, and skeletal muscle fibers. Consistent with this removal of LDL-C from the blood, lower circulating LDL-C levels have recently been found to be significantly associated with T2D susceptibility.[17] Interestingly, unlike ubiquitous MYLIP tissue expression, proprotein convertase subtilisin/kexin type 9 (PCSK9), which also promotes LDLR degradation, is produced predominantly in the liver. Therefore, PCSK9 inhibitors, unlike the genetic loss of MYLIP, would not be expected to increase cholesterol levels in non-hepatic cells. Whether PCSK9 inhibitors, however, increase T2D risk is not yet fully known.[18] Contrariwise to increased LDLRs and decreased LDL-C associating with T2D, loss-of-function mutations in the LDLR, as seen in familial hypercholesterolemia (FH), protects individuals from T2D risk.[19] In fact, the odds of developing T2D decreased linearly as the severity of FH increased,[19] or, from another prospective, as cellular ability to uptake cholesterol decreased.

High-density lipoprotein metabolism and type 2 diabetes

A significant association between genetically determined lower HDL-C and T2D has also been found.[17] Unlike the LDLs that deliver cholesterol to cells, HDLs remove cholesterol from cells. Many steps are involved in HDL metabolism and deserve an overview for discussion on HDL metabolism changes as a possible contributor to T2D. Briefly, HDLs originate from the liver, intestine, chylomicron (CM), and very-low-density lipoprotein (VLDL). The liver secretes lipid-poor ApoA1 called nascent or precursor HDL, the intestine directly synthesizes these particles, and lipoprotein lipase (LPL)-mediated lipolysis of CMs and VLDLs releases surface ApoA1 and phospholipids that also generate nascent HDLs. This later CM and VLDL-generated ApoA1 production is facilitated by phospholipid transfer protein (PLTP). These liver-, intestine-, CM-, and VLDL-derived nascent HDLs accept free cholesterol from cell membranes with excess cholesterol. This transfer of free cholesterol to HDLs is mediated by ABCA1, the class B, type 1 scavenger receptor (SR-B1), as well as other cell surface proteins (e.g., ABCG1). Following the transfer of free cholesterol to the surface of the nascent HDLs, the free cholesterol is esterified by lecithin: cholesterol acyltransferase (LCAT) and the formed cholesterol esters move away from the surface to a cholesterol ester-rich core forming a small, spherical, mature HDL particle (designated HDL_3). Through this same LCAT-mediated process HDL_3 accepts cellular free cholesterol, grows in size, and matures to a form designated as HDL_2. Cholesterol ester transfer protein (CETP) facilitates the transfer of cholesterol esters from HDL_2 to the lower density lipoproteins (VLDL, IDL, LDL) that transit to the liver for excretion. As the HDL_2 particles becomes devoid of cholesterol esters, hepatic lipase hydrolyzes triglycerides and phospholipids that the HDL_2 molecule accumulated and this reconverts HDL_2 to HDL_3. The regenerated HDL_3 cycles back through this pathway of accepting free cholesterol and transitioning to HDL_2 and then back to HDL_3.

Genetic mutations in several of the above mentioned HDL-regulatory system components tend to increase a carrier's risk for T2D. For example, Lara-Riegos et al. found T2D susceptibility in Mexican Mestizos was associated with a loss-of-function mutation in ABCA1;[20] however, genetic variation in ABCA1 was not found to predict T2D in other populations.[21] Moreover, mutation in genes for ApoA1, CETP, SR-B1, and Niemann-Pick disease, type C1 (NPC1) tend to increase a carrier's risk for T2D.[22–26] Loss-of-function mutations in ApoA1, CETP, and SR-B1 would negatively impact HDL functionality in accepting free cholesterol from cells with excess cholesterol. Efflux mutations in chromosome 9q31 in people with Tangier disease lead to defective ABCA1 transporters and many of these patients manifest impairments in insulin action and insulin secretion.[27] Similarly, a loss-of-function mutation in NPC1, a gene mutated in Niemann-Pick disease that disrupts intracellular cholesterol transport and accumulation in late endosomes and lysosomes, indirectly impedes ABCA1-mediated cholesterol efflux by sequestering this cholesterol transporter in the endosomal compartment.[28] A similar trapping of ABCA1 has been reported in insulin-resistant 3T3-L1 adipocytes with a cholesterol-laden plasma membrane where it was also found that endosomal membrane cholesterol was increased with ABCA1, away from its functional site of free cholesterol transfer to ApoA1.[29]

HMG-CoA reductase regulation and T2D

While genetic-related decelerations in HDL-mediated cellular cholesterol efflux and/or accelerations in LDL-mediated delivery as a basis of T2D warrants further investigation, emerging evidence also suggests diabetogenic increases in cellular cholesterol may arise from caloric excess associated increases in cholesterol biosynthesis. For example, a series of recent *in vitro* studies have found that excess glucose flux through the hexosamine biosynthesis pathway (HBP), a pathway known to impair insulin action in animals and humans, increases cellular membrane cholesterol. Mechanistically, HBP-mediated increases in *O*-linked *N*-acetylglucosamine modification of the transcription factor Sp1 triggers the transcriptional activation of HMG-CoA reductase (HMGR), the rate-limiting enzyme in cholesterol biosynthesis.[1,3,29,30] This HBP-induced cholesterolgenic transcriptional response increases plasma membrane cholesterol reducing cortical F-actin and insulin-stimulated GLUT4-mediated glucose transport, as well as increases endosomal membrane cholesterol that sequesters ABCA1 and thus, suppresses cholesterol efflux capacity of the insulin resistant cells.[1,3,29,30] Strikingly, inhibition of the HBP, or Sp1 binding to DNA, blocked membrane cholesterol accumulation, F-actin loss, and the dysregulation in both GLUT4-mediated glucose transport and ABCA1/ApoA1-mediated cholesterol efflux.[1,3,29,30] Although it is not known whether excess cholesterol content measured in insulin-resistant animal and human muscles results from increased HBP activity, this pathway is documented to cause insulin resistance in animal models and human subjects, and is increased in skeletal muscle of patients with T2D.[31] Considering that an increase in HBP activity, which normally accounts for 2% of total glucose flux, to 4–6% impairs insulin action, aberrant cholesterol biosynthesis could represent an imperfectly understood mechanism of HBP-mediated insulin resistance.[32] Also, considering that at the level of the pancreatic β-cell, there is evidence that hyperglycemia itself can lead to many of the defects in insulin secretion that are observed in T2D,[32] future studies of the role of this pathway in cholesterol accumulation/toxicity in adipocytes, pancreatic β cells, and skeletal muscle *in vivo* are clearly indicated.

Challenges, opportunities, and lessons from statin therapy

Despite the unequivocal importance of cholesterol-lowering therapy in preventing cardiovascular disease, there is a modest risk of T2D with statin therapy. With this risk, a significant challenge and value exist in untangling the relationship between statins and glucose metabolism. Interestingly, in the context of this review, nearly two decades of randomized control trials and meta-analyses suggest that the risk of T2D is not the same among statins. Furthermore, recent network meta-analyses,[33] as well as a Delphi study that ascertained the opinion of primary care physicians and specialists with experience in treating dyslipidemia,[34] have ranked different statins in order of diabetogenicity, with atorvastatin, simvastatin, and rosuvastatin being the most diabetogenic; lovastatin and fluvastatin having an intermediate risk; and pravastatin and pitavastatin having the lowest diabetogenicity. In fact, basic and clinical data suggest that these least diabetogenic statins, especially pitavastatin, may even exhibit a positive effect on glucose metabolism.[35–43] Intricately layered with our full understanding of why and how statins negatively or positively impact glycemic health is an array of factors including patient characteristics and integrative control mechanisms of cholesterol regulation. It is also now recognized that high-potency, high-dose, and long-treatment durations add to the diabetogenicity of statins, however, pitavastatin, a fully synthetic and high-potency statin,[44] is a notable exception that displays many cellular cholesterol homeostatic antidiabetic attributes, which will be reviewed below.

It is first important to note, however, that the diabetogenicity associated with statins as a class corresponds with studies that have found loss-of-function mutations in the *HMGR* gene to increase T2D risk.[45] Cholesterol biosynthesis pathway intermediates, reduced with HMGR inhibition, are essential for signaling and transport processes that mediate insulin-stimulated GLUT4 translocation and glucose-stimulated insulin secretory granule trafficking. Brault et al. has recently reviewed studies demonstrating the impact statins have on pathways mediated by intermediates of the cholesterol synthesis pathway.[46] This discussion focuses on the potential of statins to directly impact the delicate balance of cellular cholesterol. For example, studies introduced earlier by Parpal et al. and Tsuchiya et al. document the necessity of cellular cholesterol for insulin signaling and insulin secretory granule formation.[6,13] Reduced cholesterol synthesis could decrease cellular cholesterol causing cells to respond in a similar manner.

Intuitively, we would expect reduced membrane cholesterol to result from HMGR inhibition by statins. However, there is little *in vivo* documentation of statin effects on membrane cholesterol content. It is also noteworthy that inhibition of cholesterol biosynthesis causes a cascade of compensatory responses intended to maintain a functional level of membrane cholesterol and cholesterol biosynthetic intermediates. There is a possibility that compensation increases cellular cholesterol by turning up cholesterol influx and decreasing efflux. For example, like the upregulation of LDLRs that occurs in the liver with HMGR inhibition by statins, muscle LDLRs and LDL-C uptake are increased in mice treated with high doses of simvastatin.[47] It has also been found that skeletal muscle LDL-C uptake is increased in statin-treated mice overexpressing LPL in skeletal muscle.[47] These data suggest that LPL (the primary enzyme for intravascular hydrolysis of triglyceride [TG]), could also be an important mediator of skeletal muscle cholesterol uptake by increasing the availability of LDLC from VLDL/IDL conversion. Notably, statins increase LPL serum mass and activity in T2D.[48–50]

Perhaps these findings offer an alternative explanation as to why statins increase, albeit modestly, the risk of T2D.[33,51–55] Interestingly, LPL activity was not increased in guinea pigs treated with pitavastatin,[56] consistent with its neutral effect on blood glucose or T2D risk, however, increased mRNA/protein expression levels of LPL have been reported in 3T3-L1 adipocytes and L6 myotubes treated with pitavastatin, suggesting that this statin may have this capacity.[48,57]

Another facet of HMGR inhibition is cellular compensatory mechanisms which appear to be mediated by increased transcription of SREBPs and two associated microRNAs (miR), miR-33a and miR-33b.[58,59] In response to statins, SREBPs and miR-33a/b increase HMGR and LDLR, and decrease ABCA1, ABCG1, NPC1, and AMPK.[58,59] These metabolic changes are advantageous for reducing circulating blood cholesterol, although an exaggerated response in adipocytes, pancreatic β-cells, or skeletal muscle fibers could have deleterious consequences on glucose regulation. While these possible adverse side-effects of HMGR inhibition could explain the greater diabetogenicity of atorvastatin, simvastatin, and rosuvastatin that generally promote, especially at high-doses, an increased risk of T2D development,[53,55,60] these statins have also been shown to improve insulin sensitivity in some populations with diabetes.[61–69] Similarly, although the preponderance of studies with pravastatin suggest that this statin reduces T2D risk, a significant relative increase in diabetes incidence has been observed in elderly patients.[70] Two recent meta-analyses of large randomized, controlled trials found that either being older (average age >60 years) or being treated with intensive-dose statin therapy leads to a higher incidence of new-onset diabetes.[53,55]

A start to understanding how statins could have beneficial, neutral, or adverse effects on glucose metabolism could be a close examination of pitavastatin's qualities which make this statin neutral to, or protective of, glucose disturbances, and T2D. Pitavastatin was demonstrated to have neutral effects on glucose homeostasis in patients with metabolic syndrome in the CAPTAIN and PREVAIL US trials, independent of its efficacy in reducing atherogenic lipoprotein levels.[71] In a comparison of pitavastatin and atorvastatin in Japanese patients with hypercholesterolemia (the CHIBA study; NCT02193698), waist circumference, body weight, and body mass index were all significantly correlated with percent reduction of non-HDL-C in the atorvastatin group, whereas pitavastatin showed consistent reduction of non-HDL-C, regardless of body size.[72] In addition, in a prospective randomized controlled trial of 1,260 patients with impaired glucose tolerance, the J-PREDICT study (NCT00301392), pitavastatin was shown to have a neutral effect and possibly even a protective effect against the development of diabetes.[73] Meta-analysis of the largest contemporary dataset involving 4,815 participants that assessed the impact of pitavastatin on glycemia and the risk of diabetes found that pitavastatin did not adversely affect glucose metabolism or the development of diabetes in comparison with placebo.[74] This was also determined in a recent network analysis that found pitavastatin to be the least diabetogenic. This analysis included 29 trials in which 163,039 participants had been randomized; among these, 141,863 were non-diabetic patients. While statins, as a class, significantly increased the likelihood of developing diabetes by 12% (pooled odds ratio [OR] 1.12, 95% confidence interval [CI] 1.05–1.21, I^2 36%, p=0.002), the OR of pitavastatin was the lowest (OR 0.74, 95% CI 0.31–1.77); whereas the highest risk was associated with atorvastatin 80 mg (OR 1.34, 95%CI 1.14–1.57). Several other trials also support limited, if any, adverse effects of pitavastatin in patients with metabolic syndrome (CHIBA[72] and CAPTAIN/PREVAIL-US trials;[71] NCT01256476), or in those with impaired glucose tolerance (J-PREDICT; NCT00301392).[73]

Unlike other statin drugs, pitavastatin has been demonstrated to consistently produce significantly greater HDL-C elevations that are maintained, or increased, over time.[41,74–77] This action may counterbalance any unwanted upregulation of LDLRs in skeletal muscle by augmenting ABCA1/ApoA1-mediated cholesterol efflux. This key process in restoring cellular cholesterol balance may also be enhanced by increased ApoA1 generation. Maejima et al. found that pitavastatin efficiently increases ApoA1 in culture medium of HepG2 cells by promoting ApoA1 production through inhibition of HMGR, suppression of Rho activity, and by protecting ApoA1 from catabolism through ABCA1 induction and lipidation of ApoA1.[78] Interestingly, endothelial lipase (EL), a relatively recent addition to the triglyceride lipase gene family, is a major determinant of HDL-C metabolism. This lipase participates in HDL-C metabolism by promoting the turnover of HDL-C components and increasing the catabolism of ApoA1. A recent study by Kojima et al. found that pitavastatin suppressed basal and stimulated EL expression in cultured endothelial cells and mouse tissues.[79] Furthermore, in that study plasma EL concentrations in human subjects were found to be negatively associated with plasma HDL-C levels in patients with cardiovascular diseases, and pitavastatin treatment reduced plasma EL levels and increased HDL-C levels in patients with hypercholesterolaemia.[79] Whether other statins have this capacity to concomitantly increase key components of the reverse cholesterol transport pathway to ameliorate cellular cholesterol toxicity is unknown, yet perhaps this explains the unique relationship between pitavastatin and glucose.

Pitavastatin also has several other pharmacological features that translate into a broad range of anti-diabetic actions. For example, altered adipokine levels (↓adiponectin, ↑resistin) and inflammatory factors (↑TNFα, ↑IL-6), as well as oxidative stress, mitochondrial dysfunction and ER stress are implicated in obesity-associated insulin resistance via their disruptive actions on insulin signaling.[80] Note that the loss of insulin signaling induced by these obesity-associated changes may manifest later in T2D development, as an emerging view is that the onset of insulin resistance is not associated with defective insulin signaling.[3,81,82] Regardless, pitavastatin administration has been found to significantly decrease human serum resistin levels.[83] This effect of lowering resistin was also measured in a human breast cancer cell line.[84] In that study, pitavastatin inhibited the proliferation and suppressed the nuclear expression of NF-κB p65 induced by TNF-α, an inflammatory pathway that contributes to insulin resistance.[80] Several clinical studies have also found that pitavastatin possesses an adiponectin-increasing effect in hyperlipidemic patients with and without T2D.[85–90] Adiponectin is a protein with antiatherosclerotic, anti-inflammatory, and antidiabetogenic properties exerted on liver, skeletal muscle, adipose tissue and pancreatic β-cells.[90] Mechanistically, adiponectin stimulates AMPK, a kinase that suppresses energy-consuming pathways such as hexosamine and cholesterol biosynthesis.[91–93] We have found that AMPK stimulation improves GLUT4-mediated glucose transport and ABCA1/ApoA1-mediated cholesterol efflux from insulin-resistant 3T3-L1 adipocytes via lowering membrane cholesterol levels.[2,29,94]

Future directions

The studies cited point to crucially important aspects of cellular cholesterol regulation on blood glucose control. Mechanistically, cell data suggest that the HBP may funnel excess glucose into cholesterol

biosynthesis, however, whether this occurs *in vivo* is not known. An interesting perspective regarding this occurring in adipose tissue is that membrane cholesterol accumulation would permit cell enlargement and, over time, perhaps hypertrophic obesity. Interestingly, this cholesterol-laden membrane would also have defects in insulin-regulation of glucose transport, yet perhaps not in lipid storage. At the same time, this HBP-mediated transcriptional cholesterolgenic response in skeletal muscle also impairs glucose transport regulation by insulin and in a tissue responsible for the majority of blood glucose disposal. Whether an early aspect of pancreatic β-cell failure also results from HBP-mediated cholesterol biosynthesis/accumulation is not known. An interesting possibility is that obesity, insulin resistance, and pancreatic β-cell failure arise simultaneously from a defect in cholesterol regulation. This scenario could explain how body mass appears to impact statin diabetogenicity. For example, an observation made in the Women's Health Initiative (WHI) study was that there was a greater risk for statin-induced new-onset diabetes in females with a BMI lower than 25.0 kg/m^2 compared with those with a BMI of 30.0 kg/m^2 or higher.[95] Although the WHI study was an observational study, it suggests, somewhat counterintuitively, that a leaner phenotype may be associated with a greater risk, and this may be relevant in the context of the HBP/cholesterol response model. For instance, given that a patient's BMI likely reflects his/her eating/lifestyle habits, a BMI lower than 25.0 kg/m^2 would likely be associated with normal cellular HBP activity and a cellular cholesterol status that may be vulnerable to statin therapy for reasons already detailed. Similarly, Daido et al. found that pitavastatin administration decreased fasting blood glucose levels in a subgroup of Japanese patients with a BMI of 25 kg/m^2 or higher.[41] This factor was not found to differ before and after administration of pitavastatin in overall analysis of all the subjects. Therefore, a precise cellular and molecular understanding of cholesterol-glucose interactions as they relate to metabolic health needs to be evaluated in the setting of a range of BMIs. Moreover, a clinical consideration is that lifestyle and many pharmacological interventions apparently mediate improvement in glucose regulation via increasing AMPK activity.

Conclusions

Mechanistically, research summarized in this review suggests that caloric excess modifies nutrient sensing pathways to favor cellular cholesterol accumulation. The accumulation of cellular cholesterol in turn alters muscle, adipose, and β-cell homeostasis, promoting insulin resistance and pancreatic β-cell failure. The human genetics studies cited clearly demonstrate that obesity drives epigenome and transcriptome changes in cholesterol metabolism, which significantly predispose people to T2D. Statins as a class, like caloric excess, modify cholesterol pathways in a manner that has the potential to drive cellular cholesterol accumulation. On the other hand, pitavastatin seems unique in this regard as it favorably engages pathways that not only lower blood cholesterol, but also excess cellular cholesterol. ❑

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