Role of High-Density Lipoproteins in Cholesterol Homeostasis and Glycemic Control

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Numerous human epidemiological studies have established unequivocally that a high plasma high-density lipoprotein cholesterol (HDL-C) level is inversely associated with the risk of developing atherosclerotic cardiovascular disease.[1] This has led to the hypothesis that increasing HDL-C levels may reduce the risk of having a cardiovascular event. However, most therapies that increase plasma HDL-C levels have not reduced cardiovascular events when tested in large-scale clinical outcome trials. Despite these discouraging results, there has been an upside suggesting that interventions that increase HDL-C levels are associated with significantly improved glycemic control in people with type 2 diabetes mellitus (T2DM).[2–4] When this association is considered in light of outcomes from preclinical studies and small randomized clinical trials in which HDL-C levels were increased in patients with T2DM, as well as in vitro studies that have provided an insight into the molecular basis of the clinical findings, it follows that modulating the individual constituents of HDLs, which may or may not include increasing HDL-C levels, may be a potential therapeutic target for improving glycemic control in patients with diabetes mellitus.

This review outlines what is known about the antidiabetic properties of HDLs and the main HDL apolipoprotein, apoA-I. Insights into the mechanistic basis of these properties, and how they are regulated by intracellular and plasma cholesterol levels, is also discussed in the context of the 2 main forms of diabetes mellitus: T2DM, in which insulin resistance leads to pancreatic β-cell compensation and increased insulin secretion that eventually culminates in β-cell exhaustion and complete loss of function; and type 1 diabetes mellitus (T1DM), which is characterized by selective autoimmune β-cell destruction.

Regulation of Glycemic Control by HDLs and apoA-I: Clinical Aspects

An association between a low plasma HDL-C level and an increased risk of developing diabetes mellitus has been reported in several human population studies.[4–8] Evidence of an inverse association between HDLs, apoA-I, and insulin resistance was obtained from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial in which the homoeostasis model assessment of insulin resistance was used to monitor insulin resistance of patients with T2DM.[9] In a smaller study of subjects with impaired glucose tolerance, apoA-I was further identified as an independent risk factor for glucose tolerance and was also found to be inversely associated with the homoeostasis model assessment of insulin resistance.[10] However, this relationship has not been recapitulated in large genome-wide association studies,[11,12] or in a recent Mendelian randomization study in which it was concluded that the association between genetically determined low HDL-C levels and incident diabetes mellitus is not causal.[13]

Despite the negative outcome from the aforementioned Mendelian randomization study, evidence from randomized, placebo controlled clinical trials have indicated that acutely increasing HDL-C and apoA-I levels with a single infusion of reconstituted HDLs (rHDLs) consisting of apoA-I complexed with phosphatidylcholine,[2] or chronically increasing HDL-C and apoA-I levels by inhibiting activity of CETP (cholesteryl ester transfer protein),[3] improves glycemic control in people with T2DM. While the results from these studies are consistent with the observed improvement in glycemic control in these patients being attributable to increased pancreatic β-cell function and improved insulin sensitivity, they do not provide an insight into whether this benefit is causally related to the increase in HDL and apoA-I levels, nor do they provide an insight into the extent to which HDL-C and apoA-I levels, or other HDL components, must be increased before glycemic

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control is improved. Nevertheless, support for the notion that increasing HDL-C and apoA-I levels may be directly responsible for improving glycemic control in patients with T2DM has emerged from these in vivo studies, as well as from in vitro studies.

Much less is known about the relationship of HDL-C and apoA-I levels with glycemic control in patients with T1DM. Although plasma HDL-C levels tend to be either normal or elevated in patients with T1DM,[14] the evidence that these individuals are at increased risk of developing cardiovascular disease at an early age is compelling.[15–17] This suggests that the cardioprotective functions of HDLs may be impaired in patients with T1DM, especially in those with poor glycemic control in whom persistently elevated blood glucose levels can lead to the generation of reactive α-oxoaldehydes that nonenzymatically glycate HDL apolipoproteins and impair their cardioprotective and antidiabetic functions.[18]

Support for this hypothesis has been obtained from a small, prospective study of children with T1DM and a case control study of young adults with T1DM, in which cholesterol efflux capacity and HDL–apoA-I exchange, a surrogate marker of cholesterol efflux capacity, were both significantly impaired.[19,20] Impaired cholesterol efflux, and a reduction in the antioxidant and anti-inflammatory capacity of HDLs from adult patients with T1DM has also been reported in small cross-sectional studies.[21–23] The ability of HDLs to improve endothelial function and increase nitric oxide production is also impaired in patients with T1DM.[24] Collectively, these studies indicate that at least some of the cardioprotective functions of HDLs are lost in people with T1DM. This is also consistent with the outcome of a recent preclinical study in which macrophage-to-feces reverse cholesterol transport was decreased in mouse models of T1DM.[25] Whether the antidiabetic functions of HDLs and apoA-I are also impaired in patients with T1DM is not known, but this is something that is clearly worthy of investigation.

HDLs, apoA-I, and Insulin Sensitivity

In vitro studies have established that HDLs and lipid-free apoA-I improve glycemic control by increasing glucose uptake in skeletal muscle and decreasing insulin resistance. Incubation of primary human skeletal myotubes with conditioned media from cholesterol-loaded THP-1 cells, or primary human monocyte-derived macrophages, reduces insulin-dependent glucose uptake, and this can be reversed by preincubating the cholesterol-loaded macrophages with HDLs isolated from the plasma of normal healthy subjects.[26]

Lipid-free apoA-I also improves insulin-dependent and insulin-independent glucose uptake in primary human skeletal muscle cells by increasing phosphorylation of the insulin receptor, insulin receptor substrate-1, phosphoinositide-3-K, Akt and Akt substrate of 160 kDa (Figure 1).[27] Activation of this signal transduction pathway by HDLs and apoA-I culminates in the translocation of glucose transporter type 4 to the cell surface and increased uptake of glucose into the cells.[27] Activation of this pathway is also dependent on expression of the ATP-binding cassette transporter A1 (ABCA1), which effluxes cellular cholesterol to lipid-free/lipid-poor apoA-I in the extracellular space,[28–31] and scavenger receptor class B type 1, which selectively removes cholesteryl esters from HDLs and mediates the bidirectional exchange of unesterified cholesterol between cell membranes and HDLs in the extracellular space.[32–34] While it could be argued that the involvement of ABCA1 and scavenger receptor class B type 1 in the apoA-I–mediated uptake of glucose into skeletal muscle cells is due to apoA-I effluxing cholesterol from the cells, this was found not to be the case.[27]

Further insights into the capacity of HDLs and apoA-I to improve insulin sensitivity have been obtained from incubations of skeletal muscle cells from patients with T2DM with HDLs and apoA-I (Figure 1). This activates adenosine monophosphate–activated protein kinase (AMPK), an energy-sensing enzyme that increases ATP production and glucose uptake into skeletal muscle.[2,35] Incubation of skeletal muscle cells with HDLs and apoA-I also activates glycogen synthase kinase-3, which promotes glycogen synthesis in response to insulin (Figure 1).[36,37]

Long term infusions of rHDLs into *db/db* mice, a widely used animal model of T2DM, have further been shown to reduce plasma glucose levels and increase phosphorylation of glycogen synthase kinase-3 and AMPK in skeletal muscle.[37] Evidence that this improvement in glycemia is a reflection of increased insulin sensitivity was obtained in a subsequent study in which administration of apoA-I to *db/db* mice improved glucose tolerance by increasing glucose uptake into skeletal muscle.[38]

ApoA-I treatment also activates AMPK and acetyl-coenzyme A in apoA-I–deficient mice, in isolated skeletal muscle from wild-type mice, and in C2C12 myocytes.[35] These results have been recapitulated in incubations of L6 myotubes with rHDLs in a study that additionally established the C-terminal domain of apoA-I as a key determinant of increased glucose uptake, AMPK phosphorylation and glucose transporter type 4 translocation to the plasma membrane.[39] It should also be noted that these events are independent of Akt phosphorylation.[39] Additional mechanistic insights into these observations have been obtained in a study showing that myocytes internalize apoA-I in a clathrin-dependent endocytosis process.[35] Although the fate of the internalized apoA-I was not elucidated in that study, the results raise the possibility that apoA-I may have a previously unrecognized role in metabolic

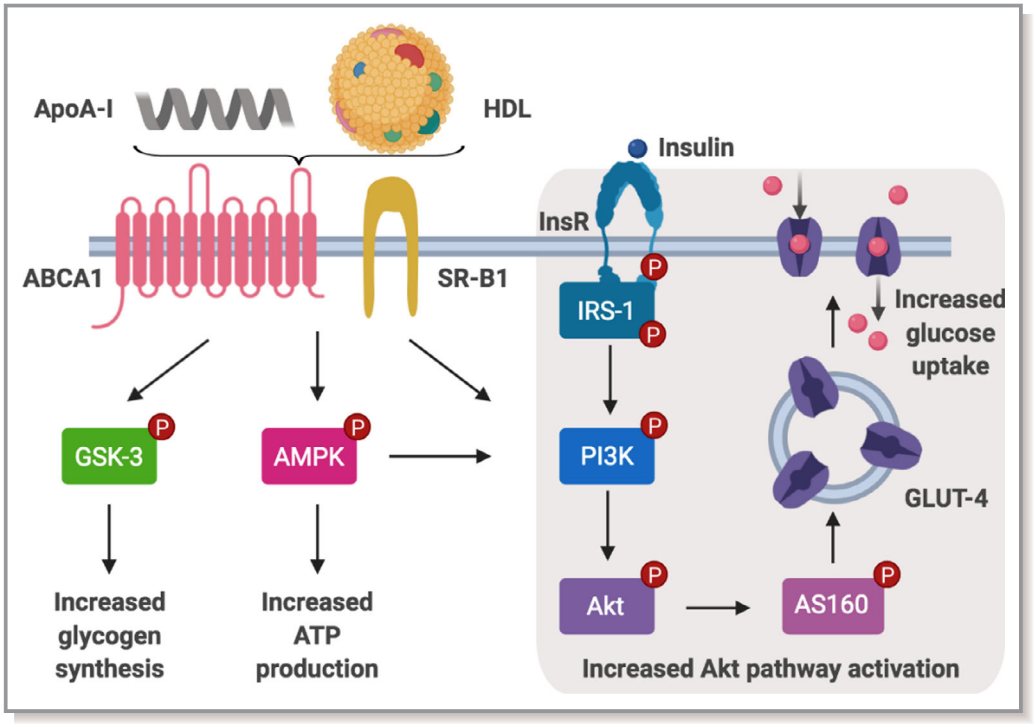


Figure 1. HDL and apoA-I improve insulin sensitivity and glucose uptake in skeletal muscle. ApoA-I and HDLs activate GSK-3 and AMPK. They also increase glucose uptake via increased insulin-mediated activation of the PI3K/Akt pathway resulting in increased GLUT4 translocation to the cell surface. ABCA1 indicates ATP-binding cassette transporter A1; AMPK, adenosine monophosphate-activated protein kinase; apoA-I, apolipoprotein A-I; AS160, Akt substrate of 160 kDa; GLUT4, glucose transporter type 4; GSK-3, glycogen synthase kinase-3; HDL, high-density lipoprotein; InsR, insulin receptor; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide-3-K; SR-B1, scavenger receptor class B type 1.

processes in tissue beds that play key roles in the regulation of glycemic control.

A number of the aforementioned in vitro results have been recapitulated in vivo. For example, treatment of high-fat–fed, insulin-resistant mice with lipid-free apoA-I reduces glucose intolerance, increases insulin sensitivity and improves hepatic glucose metabolism.[40] Treatment with lipid-free apoA-I also reduces systemic inflammation and attenuates hepatic inflammation by inhibiting activation of nuclear factor-κB.[40] These results have been further confirmed in an in vitro study in which the tumor necrosis factor-α–induced nuclear translocation of nuclear factor-κB in the human hepatoma HuH-7 cell line was inhibited by incubation with apoA-I–containing rHDLs.[40]

Systemic and adipose tissue inflammation are also associated with insulin resistance,[41] and therapeutic approaches that reduce inflammation can potentially improve insulin sensitivity.[42] Incubation of 3T3-L1 adipocytes with HDLs and apoA-I has been shown to inhibit the proinflammatory signal transduction pathways that are activated by lipopolysaccharide[43] and palmitate.[44] Inflammatory markers and macrophage accumulation in adipose tissue of mice transgenic for human apoA-I are also significantly reduced relative to what has been reported for wild-type mice.[44]

Lipid-free apoA-I infusions also increase insulin sensitivity and reduce systemic inflammation in rats with pregnancy-induced insulin resistance.[45] In that study, the improvement in insulin sensitivity was attributed specifically to enhanced glucose uptake by white and brown adipose tissue as well as skeletal muscle, while the reduction in systemic inflammation was associated with decreased adipose tissue macrophage content and proinflammatory cytokine production.[45] These observations, which raise the possibility that interventions that increase plasma apoA-I levels may reduce pregnancy-mediated inflammation and insulin resistance in humans, have important implications for patients at risk of developing gestational diabetes mellitus, the incidence of which is increasing more rapidly than any other form of diabetes mellitus.[46]

HDLs, apoA-I, and β-Cell Function

Although development of insulin resistance leading to a compensatory increase in β-cell mass and insulin secretory capacity is a key process in the initiation of T2DM, disease progression is driven by β-cell exhaustion that leads to a

reduction in β-cell mass and function. β-cell loss in T2DM has been attributed to apoptosis and dedifferentiation into cells that are no longer able to secrete insulin, or express the transcription factors that are essential for maintaining β-cell identity and survival.[47–51] This makes interventions that improve β-cell function and promote β-cell survival highly attractive as therapeutic options for patients with T2DM, as well as for patients who have T1DM with progressive autoimmune-mediated β-cell loss. The key caveat for the regeneration of new β cells and the conservation of β cells that have escaped autoimmune destruction in patients with T1DM is that newly regenerated β cells and surviving β cells remain susceptible to autoimmune attack. This suggests that such approaches may need to be implemented in combination with an immune-based therapy to ensure long-term efficacy and extended β-cell survival.

Emerging evidence that apoA-I may improve β-cell survival and potentially has the capacity to regenerate new β cells, has come from studies in which treatment with apoA-I improves glucose tolerance and insulin secretion in high-fat–fed mice,[52,53] and in mice with conditional deletion of both ABCA1 and ATP-binding cassette transporter G1(ABCG1) in β cells.[54] ABCG1 is a transporter that effluxes cellular cholesterol to HDLs.[55,56]

Some mechanistic insights into these observations have been obtained from studies of the Min6 and Ins-1E clonal β-cell lines.[57,58] Incubation of Min6 cells with HDLs isolated from normal human plasma, apoA-I–containing rHDLs or lipid-free apoA-I increases transcription of the *Ins1* and *Ins2* genes, modestly increases insulin secretion under basal conditions and significantly increases glucose-stimulated insulin secretion (GSIS).[58] It is particularly noteworthy that apoA-I increases insulin secretion in Min6 and Ins-1E cells without altering intracellular cholesterol levels and that it also increases transcription of the gene encoding for Pdx1, a transcription factor that is essential for maintaining β-cell identity and survival.[57,58] Importantly, treatment with apoA-I has recently been shown to increase GSIS in islets from mice in which ABCA1 and ABCG1 are conditionally deleted in β cells.[59] The islet cholesterol levels in these mice were approximately double that of control mice, and their GSIS was impaired.[59] While it is reasonable to assume that apoA-I increased GSIS in islets in these mice by acting as an acceptor of the excess cholesterol that effluxed from their β cells, this was not the case, with apoA-I treatment having no effect on islet cholesterol levels in these animals.[54] The mechanistic basis of this unexpected observation is not known and is currently under investigation.

In direct contrast to the in vitro and in vivo results outlined above, HDLs isolated from normal subjects that had been treated for 2 weeks with a CETP inhibitor increased cholesterol efflux and insulin secretion in cholesterol-loaded Min6 cells.[60] The reasons for this discrepant cholesterol efflux result are not entirely clear but may be related to the short duration of CETP inhibitor treatment, which only modestly increased HDL-C and apoA-I levels, and the fact that the Min6 cells were cholesterol loaded by incubation with oxidized low-density lipoproteins (LDLs).[60] The cholesterol that accumulates in the islets of mice with conditional β-cell deletion of ABCA1 and ABCG1 is, by contrast, produced intracellularly and is unlikely to contain significant amounts of oxysterols. In the case of cells that have been cholesterol loaded with oxidized LDLs, oxysterols comprise up to 50% of the total cellular cholesterol.[61]

Although apoA-I increases GSIS by a mechanism independent of ABCA1-mediated cholesterol efflux,[54,58,59] there is compelling evidence that a direct interaction of apoA-I with ABCA1 on the β-cell surface is responsible for increasing GSIS and transcription of the *Ins1* and *Ins2* genes in Ins-1E cells (Figure 2).[57] This interaction activates a trimeric G-protein subunit (Figure 2A), which stimulates a transmembrane adenylate cyclase and increases intracellular cAMP levels (Figure 2B). This activates PKA (protein kinase A) (Figure 2C), which phosphorylates and excludes the transcription factor, FoxO1 (forkhead box protein O1) from the Ins-1E nucleus (Figure 2D), leading to derepression of insulin gene transcription (Figure 2E).[57]

Activated PKA also inactivates K^+ channels, opens voltage-gated Ca^{2+} channels (Figure 2F), and phosphorylates proteins in the insulin granule surface, leading to an increased Ca^{2+} response and enhanced secretion of insulin granules from the β-cell surface (Figure 2G).[62,63] These results offer a potential explanation for the observation that a single rHDL infusion can improve β-cell function and increase plasma insulin levels in patients with T2DM.[2]

It is possible that apoA-I may also improve β-cell function by regulating intracellular cholesterol trafficking. Internalization of apoA-I has been reported in endothelial cells,[64] skeletal muscle cells,[35] and adipocytes.[65,66] Internalization of apoA-I by β cells has not been reported. Exploration of this possibility would provide insights into whether apoA-I is able to increase insulin secretion by acting intracellularly as an acceptor of excess cholesterol from insulin granule membranes in islets with elevated cholesterol levels and impaired GSIS.

The HDL-associated antioxidant enzyme paraoxonase-1 (PON1) can also increase insulin secretion in both mouse and cell models.[67] PON1 knockout mice develop more severe diabetes mellitus when challenged with streptozocin, which selectively destroys β cells, than wild-type mice. Conversely, streptozotocin-treated mice transgenic for human PON1 develop less severe diabetes mellitus than control mice.[68] Pretreatment with recombinant PON1 before streptozocin administration also protects mice from β-cell loss, improves

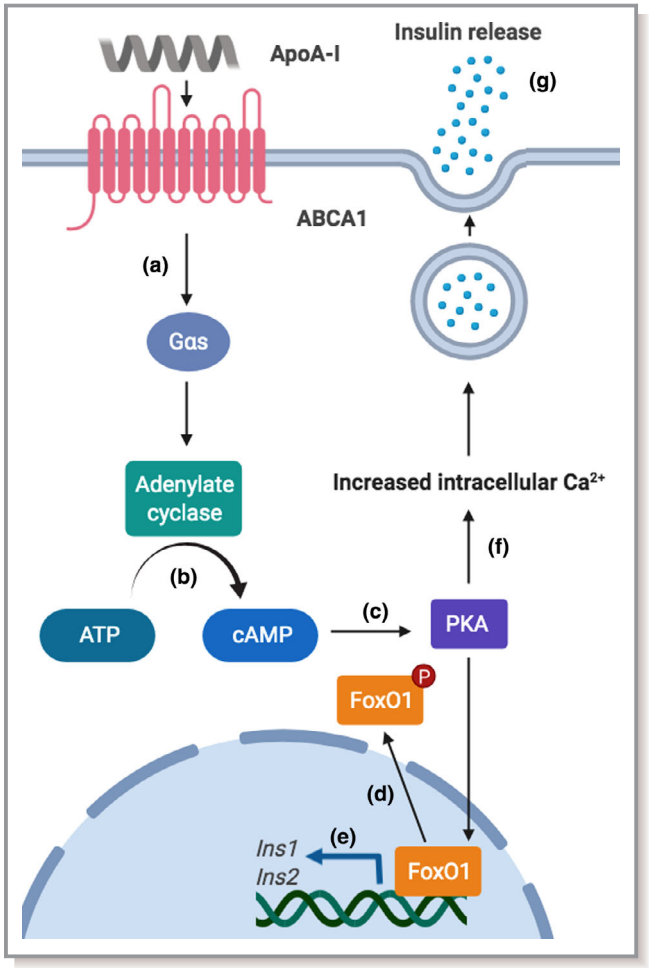


Figure 2. Insulin synthesis and secretion is increased in apoA-I treated pancreatic β cells via a PKA-FoxO1 dependent mechanism. Interaction between apoA-I and ABCA1 at the cell surface results in (**A**) activation of the $G\alpha_s$ subunit of the heterotrimeric G protein and (**B**) activation of adenylate cyclase which converts ATP to cAMP. Elevated cAMP levels activate PKA (**C**), which translocates to the nucleus, where it phosphorylates and excludes FoxO1 (**D**), resulting in derepression of insulin gene transcription (**E**). Activated PKA also increases intracellular calcium levels (**F**), and increases insulin secretion. ABCA1 indicates ATP-binding cassette transporter A1; apoA-I, apolipoprotein A-I; FoxO1, forkhead box protein O1; PKA, protein kinase A.

glucose tolerance, and increases serum insulin levels.[67] These results have been recapitulated in vitro by showing that incubation of the βTC3 cell line with recombinant PON1 increases GSIS and reduces oxidative stress.[67] HDLs from wild-type mice also increase insulin secretion in βTC3 cells under both basal and high-glucose conditions to a greater extent than HDLs from PON1 knockout mice.[67]

HDLs also play a pivotal role in maintaining β-cell survival and protecting against apoptosis. HDLs antagonize the ability of LDLs and very-low-density lipoproteins to induce β-cell apoptosis in isolated rat islets[69] and βTC3 cells.[70] Isolated human HDLs also prevent oxidized LDLs from reducing insulin and preproinsulin mRNA levels in Min6 cells[71,72] and protect human and murine islets against interleukin-1β– and glucose-induced apoptosis.[71,72] Isolated HDLs additionally protect against apoptosis-induced endoplasmic reticulum (ER) stress in cultured β cells, as well as in human and rat islets.[73] In that study, incubation with HDLs restored ER morphology and improved protein folding and export.[73] However, in a subsequent study of Min6 cells, HDLs reduced apoptosis by preserving ER morphology but had no effect on protein folding, or the export capacity of the ER.[74] This discrepancy may have been attributable to different ER stressors being used in the incubations, which raises the possibility that more than a single mechanism may be responsible for the antiapoptotic effects of HDLs.

Cholesterol Homeostasis and β-Cell Function

The progressive reduction in β-cell function and eventual β-cell loss in patients with T2DM has been attributed to glucotoxicity and elevated free fatty acid levels in association with increased oxidative stress,[75] ER stress,[76] mitochondrial dysfunction,[77] and an elevated inflammatory response, leading to infiltration of inflammatory cells into islets.[78] In recent years, mounting evidence has indicated that dysregulation of cholesterol homeostasis in β cells also impairs insulin secretion in response to a glucose challenge and can accelerate the progression of T2DM.[59,79–81] Elevated cholesterol levels in β cells additionally have the capacity to cause oxidative stress and apoptosis,[82] as well as ER stress[83] and mitochondrial dysfunction.[84]

These results are to be expected given that cholesterol homeostasis is a critically important determinant of cell function. Cellular cholesterol is synthesized endogenously or acquired from LDLs that are removed from the circulation via the LDL receptor. Because most peripheral cells lack the necessary machinery for cholesterol catabolism, there is also a need for a mechanism to remove excess cholesterol from cells, a requirement that is fulfilled by ABCA1, which exports cellular cholesterol to lipid-free/lipid-poor apoA-I, and ABCG1, which exports cellular cholesterol to HDLs. Cholesterol also regulates the fluidity and permeability of cell membranes, and it is a key component of the lipid rafts that are located in the outer leaflet of cell membranes and regulate signal transduction pathways.[85]

Insulin secretory granules are the major site of excess cholesterol accumulation in β cells. This impairs insulin granule maturation, disrupts the insulin secretory machinery,[86] and impairs the ability of insulin granules to fuse with the plasma membrane.[87] Elevated intracellular β-cell cholesterol levels can thus reduce insulin secretion by impairing the exocytosis of insulin granules[88] and increasing neuronal NO synthase dimerization.[79] Direct evidence that cholesterol

accumulation causes β-cell dysfunction emerged from a study by Hao et al,[79] who found that GSIS was impaired in cholesterol-loaded β cells, and normalized by incubation with methyl-β-cyclodextrin, which acts as a sink and depletes cells of cholesterol. Transgenic mice with selective overexpression of the transcription factor sterol regulatory element-binding protein-2 in β cells have normal plasma cholesterol levels but increased islet cholesterol levels attributable to increased transcription of genes encoding for proteins that are rate limiting for cholesterol biosynthesis, including 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, and the LDL receptor.[81] These mice also have impaired GSIS and are glucose intolerant.[81]

On the other hand, lowering β-cell cholesterol levels by inhibiting squalene epoxidase, one of the rate-limiting enzymes in the cholesterol biosynthesis pathway, impairs insulin secretion by reducing activation of voltage-dependent Ca^{2+} channels.[89,90] Chronic inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase also reduces intracellular cholesterol levels in Ins-1E cells and impairs insulin secretion by disrupting the structural organization of the plasma membrane.[90]

Regulation of β-Cell Function by ABCA1 and ABCG1

Evidence that ABCA1 has a role in β-cell function in humans comes from studies of patients with Tangier disease that have loss-of-function mutations in the gene encoding for ABCA1. These mutations cause cholesterol to accumulate in all cell types, including β cells, where they reduce the first phase of insulin secretion in response to a glucose challenge.[91,92] It is additionally noteworthy that insulin sensitivity is normal in people with loss-of-function mutations in ABCA1, which indicates that loss of β-cell function is likely responsible for the impaired glycemic control that has been reported in these individuals.[92,93]

Significant insights into the functional role of ABCA1 and ABCG1 in β cells have been obtained from studies of various mouse models (Figure 3). Mice in which the *Abca1* gene is deleted only in β cells have increased islet cholesterol levels and are glucose intolerant.[80] They also have impaired GSIS but normal insulin sensitivity.[80] These animals additionally exhibit a compensatory upregulation of ABCG1 in β cells, which minimizes the perturbation of β-cell cholesterol homeostasis caused by the loss of ABCA1.[80] These results are consistent with β-cell dysfunction being directly responsible for the glucose intolerance that has been reported in these animals. This is also consistent with what has been reported in patients with Tangier disease but distinct from what occurs in patients with T1DM and T2DM, where glucose intolerance is driven by autoimmune β-cell destruction and β-cell loss subsequent to long-term insulin resistance, respectively. However, T2DM in the absence of insulin resistance has also been reported in a small number of subjects that are genetically predisposed toward development of the disease.[94–96]

Mice with global ABCG1 deficiency are also glucose intolerant and have impaired GSIS but normal insulin sensitivity (Figure 3).[97] The mechanistic basis of this phenotype is distinct from what has been reported for mice with conditional deletion of the *Abca1* gene in β cells. Islets isolated from ABCG1 knockout mice have normal cholesterol levels but perturbed cholesterol trafficking that depletes cholesterol from insulin granules. This alters insulin granule morphology and impairs their ability to interact with the insulin secretory machinery, which is a prerequisite for insulin secretion.[97,98]

When ABCG1 knockout mice are crossed with mice in which the *Abca1* gene is conditionally deleted in β cells, the offspring develop a phenotype that is more pronounced than that reported for either ABCG1 knockout mice or mice with conditional β-cell deletion of the *Abca1* gene (Figure 3).[99] In addition to displaying increased islet macrophage infiltration and interleukin-1β levels, these mice also have more pronounced glucose intolerance, greater cholesterol accumulation in islets, and more severely impaired GSIS than ABCG1 knockout mice or mice with conditional β-cell ABCA1 deletion.[99]

Mice in which the *Abca1* and *Abcg1* genes are both conditionally deleted in β cells have a phenotype that is more complex than what has been reported for the aforementioned models (Figure 3).[59] In addition to resembling mice with conditional deletion of ABCA1 in β cells by virtue of having elevated islet cholesterol levels, impaired insulin secretion, and normal insulin sensitivity, mice in which ABCA1 and ABCG1 are both conditionally deleted in β cells also have increased adipose tissue mass, reduced skeletal muscle mass and systemic inflammation.[59] When taken together, these studies collectively indicate that cholesterol homeostasis and cholesterol efflux, together with ABCA1 and ABCG1, all play critically important roles in β-cell function that, if perturbed, can lead to adverse metabolic effects.

Various mechanisms have been proposed to explain β-cell loss and dysfunction in islets with elevated cholesterol levels. Oxidative stress leading to mitochondrial dysfunction and apoptosis has been reported in Min6 cells with increased cholesterol levels.[81,82,84,100–102] Increased cholesterol levels in Ins1 and βTC-6 cells also increase ER stress,[83] and activate nuclear factor-κB in Min6 cells, leading to the production of proinflammatory cytokines.[101,102]

Cholesterol-loaded β cells in wild-type mice and ABCA1 knockout mice also have impaired voltage-gated Ca^{2+}

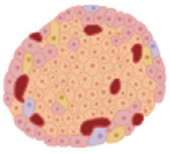
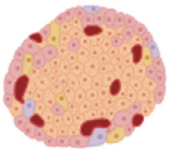
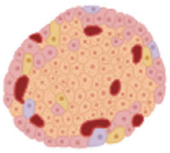
Model	Phenotype	Ref
 β-cell specific ABCA1$^{-/-}$	Increased islet cholesterol Glucose intolerant Impaired GSIS	80
 Global ABCG1$^{-/-}$	Normal islet cholesterol Perturbed cholesterol trafficking Glucose intolerant Impaired GSIS	97
  β-cell specific ABCA1$^{-/-}$ X Global ABCG1$^{-/-}$	Glucose intolerant Impaired GSIS Macrophage infiltration in islets	99
 β-cell specific ABCA1$^{-/-}$ ABCG1$^{-/-}$	Glucose intolerant Impaired GSIS Increased adipose tissue Reduced skeletal muscle mass Systemic inflammation	59

Figure 3. Summary of mouse models used to study the impact of deletion of ABCA1 and/or ABCG1 on β-cell function. ABCA1 indicates ATP-binding cassette transporter A1; ABCG1 indicates ATP-binding cassette transporter G1.

channel activity, which reduces glucose-stimulated Ca^{2+} influx and insulin secretion.[88,103] In the case of mice with conditional β-cell deletion of ABCA1, the reduction in GSIS is also associated with ultrastructural changes in the Golgi apparatus, impaired insulin biosynthesis and processing, altered fusion of insulin granules with the plasma membrane, and changes in the organization of proteins that regulate the insulin secretory machinery in the β-cell membrane.[88]

Cholesterol Homeostasis and Glucose Disposal in Skeletal Muscle and Adipose Tissue

Caveolae that contain cholesterol, sphingolipids, and caveolin localize to the plasma membrane, where they play a critically important role in the binding of insulin to the insulin receptor and activation of the downstream intracellular insulin signal transduction pathways that mediate glucose uptake by skeletal muscle (Figure 1).[104,105] Caveolae function is highly dependent on plasma membrane cholesterol levels. Disrupting cholesterol homeostasis by depleting cells of cholesterol with β-cyclodextrin inhibits insulin-dependent glucose uptake.[105] Conversely, increasing cholesterol levels by inducing the hexosamine biosynthesis pathway in 3T3-L1 adipocytes disrupts the structural organization of the plasma membrane and results in insulin resistance.[106]

Accumulation of cholesterol in the plasma membrane can also cause insulin resistance in skeletal muscle by decreasing translocation of glucose transporter type 4 to the cell surface.[107] This deleterious effect can be reversed by treatment with methyl β-cyclodextrin, which acts as an acceptor of the excess cholesterol.[107,108]

Table. Role of HDL and apoA-I in Glycemic Control, Insulin Sensitivity and β-Cell Function

Topic	Outcome	Reference
Association of HDL-C and apoA-I levels with glycemic control		
Subjects with T2DM	Serum HDL-C, apoA-I, and HDL-C/apoA-I levels are inversely associated with insulin resistance by HOMA-IR	9
Subjects with impaired glucose tolerance	ApoA-I level is an independent risk factor for glucose tolerance	10
HDL and apoA-I in glucose disposal/insulin sensitivity		
Primary human skeletal muscle cells	ApoA-I improves insulin-dependent and -independent glucose uptake	27
C2C12 skeletal muscle cells	ApoA-I increases glucose uptake by phosphorylation of AMPK	35
High-fat–fed C57BL/6 mice	ApoA-I improves insulin sensitivity by reducing systemic and hepatic inflammation	40
db/db mice	Long-term HDL infusion improves glucose tolerance by activating GSK-3 and AMPK in skeletal muscle	37
Pregnant female Wistar rats	ApoA-I infusions increase insulin sensitivity, reduces systemic inflammation and protects against pregnancy-induced insulin resistance	45
Subjects with T2DM	A single rHDL infusion reduces plasma glucose levels by increasing insulin secretion and promoting glucose uptake in skeletal muscle	2
HDL and apoA-I in β-cell function		
Min6 insulinoma cells	HDLs isolated from normal human plasma, rHDLs, and apoA-I increase *Ins1* and *Ins2* gene transcription and GSIS	58
Ins-1E insulinoma cells	ApoA-I increases *Pdx1* gene transcription and GSIS	57
βTC3 insulinoma cells	Incubation with HDL protects βTC3 cells against LDL-induced apoptosis	70
C57BL/6 mice	ApoA-I infusions increase insulin secretion and improve glucose tolerance	52
High-fat–fed C57BL/6 mice	Short-term apoA-I treatment increases GSIS and improves glucose clearance independent of insulin secretion	53
Mice with conditional deletion of ABCA1 and ABCG1 in β cells	ApoA-I infusions increase GSIS in islets isolated from mice with elevated islet cholesterol levels	54
Healthy subjects and Min6 cells	CETP inhibition increases plasma HDL-C, apoA-I, and insulin levels in normal human subjects. Plasma from these subjects also increases GSIS in Min6 cells pretreated with oxidized LDLs	60
Isolated human islets	HDL protects human islets against oxidized LDL-induced apoptosis	71
Isolated human and mouse islets	HDL protects human and mouse islets from interleukin-1β– and glucose-induced apoptosis	72

AMPK indicates adenosine monophosphate-activated protein kinase; apoA-I, apolipoprotein A-I; CETP, cholesteryl ester transfer protein; GSIS, glucose-stimulated insulin secretion; GSK, glycogen synthase kinase-3; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; rHDL, reconstituted HDL.

Therapeutic Approaches for Improving Glycemic Control With HDLs and apoA-I

Emerging evidence indicates that therapies, such as CETP inhibitors and rHDL infusions, that increase plasma HDL-C and apoA-I levels have the capacity to slow diabetes mellitus progression, reduce incident diabetes mellitus, and improve glycemic control in patients with established disease.[2,3,109] However, as these agents were developed to reduce cardiovascular events in at-risk populations and the outcomes of the clinical trials in which they have been investigated have mostly been negative, the likelihood of any of them being repurposed as a therapy for improving glycemic control in patients with diabetes mellitus is low.

Other HDL-raising approaches that could be implemented but are likely to improve glycemic control less effectively than CETP inhibition or rHDL infusions include lifestyle interventions such as reducing weight, increasing exercise, and quitting smoking.[110–112] One year of intensive lifestyle intervention that includes calorie restriction and increased physical activity has been reported to improve glycemic control, reduce the use of antidiabetic medications, and increase HDL levels.[113] While such interventions may slow disease progression, most likely by improving insulin sensitivity, they fail to address the decline in β-cell function that drives diabetes mellitus progression. There is thus a major, unmet need to develop new therapies that

specifically target the restoration and preservation of β-cell function in people with prediabetes mellitus or diabetes mellitus.

Cyclodextrins, which accept the excess cell cholesterol that effluxes from cholesterol-loaded cells may fulfill this need to some extent.[114] Cyclodextrin derivatives have shown promising results for treating cardiovascular and neurodegenerative diseases, including atherosclerosis and Niemann-Pick type C disease.[115–120] Methyl-β-cyclodextrin treatment improves glucose tolerance and normalizes fasting glucose levels in mice with diet-induced obesity.[121] It also increases basal and insulin-stimulated glucose uptake in skeletal muscle,[121] and partially restores insulin secretory capacity in isolated islets from apoE-deficient mice and *ob/ob* mice.[79] As both of these mouse strains have elevated islet cholesterol levels, it follows that this approach may be useful for improving glycemic control in humans with Tangier disease and possibly familial hypercholesterolemia.

Other potential HDL-targeted options for improving glycemic control include infusion of delipidated HDLs,[122] rHDLs,[2,123–127] and apoA-I mimetic peptides. The apoA-I mimetic peptide L-4F has been shown to reduce adiposity and improve glucose tolerance and insulin sensitivity in *ob/ob* mice by increasing plasma adiponectin levels, reducing systemic inflammation and phosphorylating AMPK and the insulin receptor.[128,129] The apoA-I mimetic peptide RG54 also increases glucose uptake in C2C12 myotubes and enhances GSIS in Ins-1E cells.[130] Although considerable effort will be required to develop clinically effective apoA-I mimetic peptides, they are clearly potential candidates for improving glycemic control, increasing insulin sensitivity, and preventing β-cell loss in all forms of diabetes mellitus.

Conclusions

Emerging evidence (summarized in Table) indicates that HDL- and apoA-I–targeted therapies are a potential option for conserving residual β-cell function and improving insulin sensitivity in patients who are progressing toward, or have already developed, T1DM and T2DM. The recent failures of HDL-raising agents in cardiovascular clinical outcome trials highlight the need to develop novel and innovative HDL-targeted approaches to achieve these goals. Elucidating the mechanism(s) underlying the antidiabetic functions of HDLs and apoA-I will also provide opportunities to identify and develop new HDL-targeted therapies for diabetes mellitus. Achievement of these goals could be particularly advantageous for patients with T1DM for whom treatment options are currently limited to insulin replacement therapy, and for patients with T2DM that are refractory to currently available therapies.

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