REVIEW

Diabetes Management

The relationship of high-density lipoprotein cholesterol to new-onset diabetes: a review

Roderick C Deaño[1], Henry A Tran[1] & Peter M Okin*[,1]

Practice points

- Lower levels of high-density lipoprotein (HDL) cholesterol are associated with increased risk of incident cardiovascular events.
- Some population studies suggest an associated risk between low HDL cholesterol and the development of incident Type 2 diabetes.
- Statins slightly increase risk of development of incident Type 2 diabetes.
- Niacin worsens glycemic control.
- CETP inhibitors (torcetrapid and dalcetrapid) are effective agents for increasing HDL but have shown either increased risk or no benefit in regards to risk of death and incident cardiovascular events. They may have some small beneficial effects in regards to glycemic control.

SUMMARY Diabetes is an increasingly prevalent disease that has a well-known association with cardiovascular risk, a risk that may even exist in prediabetics. Lower levels of high-density lipoprotein cholesterol (HDL-C) have been associated with increased risk of incident cardiovascular events. Recent prospective studies have shown a potential temporal association between lower levels of HDL-C and development of incident Type 2 diabetes. This article will review the recent studies detailing potential causative association between low levels of HDL-C and incident Type 2 diabetes, examine the potential pathophysiology and mechanisms of such an association, and review associated treatment implications.

KEYWORDS
• apolipoprotein A-I • CEPT • diabetes • fibrates • HDL • HDL-C • niacin • pancreatic β cell • statin • Type 2 diabetes

Diabetes had an estimated prevalence of 6.4% in 2010, affecting 285 million adults worldwide, and expected to increase to 7.7%, affecting 439 million adults, by 2030 [1]. There is a well-known and strong association of diabetes with increased cardiovascular risk [2,3], an elevated risk that may even exist in prediabetics [4]. Lower levels of high-density lipoprotein (HDL) cholesterol (HDL-C) have been associated with increased risk of incident coronary heart disease [5–8]. By contrast, metabolic syndrome – a syndrome that generally includes a combination of low HDL-C, abdominal adiposity, high triglycerides, hypertension and impaired fasting glucose – is associated with increased risk of cardiovascular disease and Type 2 diabetes (T2DM) beyond that associated with each component risk factor, suggesting a synergistic effect on T2DM risk [9,10]. Indeed, one study demonstrated that HDL-C had an inverse relationship with calcium score and a stronger association in diabetic than nondiabetic patients [11]. The pathophysiology underlying these relationships may not be straightforward and studies suggest a self-perpetuating bidirectional relationship between risk factors such as HDL-C and impaired fasting glucose [12]. Multiple studies have shown that patients with T2DM have lower HDL-C

[1]Division of Cardiology, Department of Medicine, Weill Cornell Medical College, New York, NY, USA
*Author for correspondence: pokin@med.cornell.edu

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levels with functionally defective HDL particles (HDL-P) [2,13]. Furthermore, recent prospective studies have suggested a temporal association between decreased levels of HDL-C and development of incident diabetes [14]. This review will discuss recent studies detailing potential causative association between low levels of HDL-C and incident T2DM, examine the potential pathophysiology of such an association, and review associated treatment implications.

Relationship of low HDL-C to incident Type 2 diabetes

HDL exists in complex and dynamic relationships with the major lipoproteins such as VLDL, IDL and LDL. As a marker of heart disease, numerous epidemiologic studies have shown a robust inverse relationship between HDL-C and coronary heart disease (CHD). This is in contrast with triglyceride levels, which have not been shown to be independently predictive of CHD [15]. Similarly, there have been a number of recent studies suggesting a significant association between low HDL-C and the development of incident T2DM. A low level of HDL-C usually does not occur in serologic isolation and is often accompanied by hypertriglyceridemia [16–18]. Clinically, hypertriglyceridemia is often observed in patients with insulin resistance resulting in enhanced lipolysis and free fatty acid synthesis. Therefore, in analyzing the association of low HDL-C and incident diabetes, careful adjustment for coexistent hypertriglyceridemia is essential. This section will review some of the recent and relevant clinical studies that suggest an association between low levels of HDL-C and the development of incident T2DM.

• LIFE study

The LIFE study was designed to compare the effects of losartan versus atenolol-based antihypertensive therapy on cardiovascular morbidity and mortality [19]. Among the 7485 subjects without a history of diabetes who had baseline HDL-C levels and were followed for approximately 5 years, lower in-treatment HDL-C was strongly associated with increased risk of new-onset diabetes, and when treated as a time-varying covariate had better predictive power than baseline HDL-C for development of incident T2DM [20]. In multivariate Cox models that also adjusted for multiple other T2DM risk factors, the lowest quartile of in-treatment HDL-C (<1.22 mmol/l or 22 mg/dl) remained associated with an almost ninefold increased risk of new diabetes compared with those in the highest quartile of in-treatment HDL-C (>1.78 mmol/l or 32.1 mg/dl) [20].

• Prevend study

In this prospective study of 6820 non-diabetic Danish patients with a mean age of 49 years followed for 8 years, after multivariate analysis higher HDL-C was found to be associated with lower risk of development of T2DM with an odds ratio (OR) of 0.55 (0.47-0.64) for every 1 standard deviation (SD) increase in HDL-C [21]. Mean baseline HDL-C is this population was 1.34 mmol/l (or 24 mg/dl).

• ASCOT-BPLA

The ASCOT-BPLA trial was designed to evaluate the cardiovascular effects of different blood pressure regimens and randomized to either atenolol-based or amlodipine-based treatment [22]. In *post hoc* analysis of 14,120 nondiabetic patients, significant predictors of incident DM included elevated fasting glucose (HR: 5.8; 95% CI: 5.23–6.43), increased BMI (HR: 1.49; 95% CI: 1.38–1.62) as well as high triglyceride levels (HR: 1.12; 95% CI: 1.07–1.17) [22]. Variables that were found to be potentially protective against incident T2DM included amlodipine-based treatment (HR: 0.66; 95% CI: 0.59–0.74), increased HDL-C (HR: 0.72; 95% CI: 0.58–0.89) and aged greater than 55 years and alcohol use. Importantly, although higher fasting glucose levels were found to be the most powerful predictor of new diabetes, increased HDL-C levels remained associated with lower diabetes incidence after adjusting for confounders [22].

• Framingham Offspring Study

In a population sample that attended the fifth clinic examination of the Framingham Offspring study in the mid 1990's, 3140 predominantly Caucasian, nondiabetic subjects with a mean age of 54 years who had an oral glucose tolerance test were followed for an average of 7 years to determine predictors of new-onset T2DM [23]. The mean HDL-C in this population was 36.9 mg/dl at baseline. Predictors of T2DM included impaired fasting glucose, low HDL-C, obesity, triglyceride level, parental history of diabetes and high blood pressure [23]. Similar to ASCOT-BPLA [22], in their simple clinical model that they used to develop

a T2DM risk algorithm, impaired fasting glucose was the strongest predictor (OR: 7.25; 95% CI: 4.89–10.74), followed by low HDL-C (OR: 2.57; 95% CI: 1.75–3.77).

• San Antonio Heart Study

In a multinational population-based prospective study designed to study T2DM and cardiovascular disease among Mexican Americans and non-Hispanic whites living in San Antonio who were followed for approximately 8 years, 1734 overweight nondiabetic participants were identified [24]. Incident T2DM was associated with lower HDL-C (1.05 mm/l or 18.9 mg/dl in incident T2DM vs 1.24 mm/l or 22.3 mg/dl in nondiabetics; $p < 0.001$); however, multiple other variables were also associated with T2DM in univariate analyses, including age, ethnicity, family history of diabetes, impaired fasting glucose and metabolic syndrome [24]. Unfortunately, multivariate analysis was not performed to determine if the association of low HDL-C with incident T2DM was independent of other risk factors. Of note, analysis revealed Mexican–Americans to have an excess risk of development of impaired glucose tolerance and development of T2DM compared with non-Hispanic Whites [25].

• GEMS

In a prospective, multinational study of overweight subjects designed to study the genetics of metabolic syndrome, 715 subjects were identified who had low HDL-C (lowest 25th percentile) and elevated plasma triglyceride (upper 25th percentile) [26]. The mean HDL-C of this group was 0.95 mmol/l (or 17 mg/dl) versus 1.63 mmol/l (or 29.3 mg/dl) in the unrelated comparison controls with comparable BMIs recruited from the same centers. The study population with low HDL-C and elevated triglycerides had increased fasting glucose, lower insulin levels as well as higher levels of inflammatory markers such as CRP compared with overweight patients with normal HDL-C and triglyceride levels [26]. Notably, the subjects were not matched for many potential confounders and the study population was younger (mean age: 50 vs 55), more overweight with a higher BMI (28.7 vs 28.2) and waist circumference (98 vs 95 cm), more likely to be a smoker, on a β-blocker (23 vs 5%) and a statin (47 vs 2%), suggesting that this risk of developing diabetes could have been due to alternative factors [27,28].

• IRAS

In a multicenter, multiethnic prospective study initially designed to assess the relationship between insulin resistance and cardiovascular disease [29], 830 nondiabetic patients, mean age of approximately 55 years, were identified and followed for a mean of 5.2 years [30]. This study utilized nuclear magnetic resonance (NMR) spectroscopy to study lipid composition and found that via stepwise logistic regression models low HDL-C (OR: 1.64; 95% CI: 1.28–2.08) and high triglycerides were associated with development of incident T2DM. In addition, they also found that VLDL particle size and small HDL-P were associated with development of incident T2DM independent of metabolic covariables, suggesting that abnormalities in lipoprotein composition occur prior to the development of incident T2DM [30]. The analysis was consistent across the ethnic groups in the study: white, black and Hispanic [30].

• ARIC study

In this prospective study originally designed to study the etiology of atherosclerosis and cardiovascular disease [5], 7915 nondiabetic adults aged 45–64 years were examined to evaluate clinical predictors of incident T2DM [31]. A risk function utilizing logistic regression was developed to predict incident TD2M and found that including HDL-C and elevated triglycerides, in addition to waist, height, hypertension, family history of diabetes, ethnicity and age, improved the area under the receiving operative curve from 0.78 to 0.80 [31]. Unfortunately, the results of further multivariate analysis that demonstrate the association between low HDL-C and incident T2DM were not reported in the article.

Potential mechanisms for the association of T2DM with HDL-C

HDL-C is an integral part of the pathway that delivers cholesterol back to the liver and other steroidgenic organs via the efflux of cholesterol from cholesterol-loaded arterial macrophages [32,33]. However, recent literature has demonstrated that there are additional pleotropic effects of HDL-C that may be protective against the development of incident diabetes. Additionally, HDL-P have been shown to be functionally deficient in patients with T2DM, further suggesting additional interaction between low HDL-C and HDL-P function [13]. In this section, potential pathways between low HDL-C and development

of incident T2DM will be reviewed and include: decreased stimulation of pancreatic insulin secretion, effects on peripheral muscle glucose uptake and anti-inflammatory effects.

• Decreased stimulation of pancreatic β-cell insulin secretion

In mouse models, excessive accumulation of cholesterol (or lipotoxicity) in pancreatic cells demonstrated decreased pancreatic islet numbers and β-cell mass, decreased insulin content within the pancreatic islets and β cells and impaired glucose-stimulated insulin secretion [14,34,35]. One mouse model demonstrated a direct link between islet cholesterol levels and impaired glucose-stimulated insulin secretion with normal secretion restored by subsequent cholesterol depletion [35]. Additionally, the UK Prospective Diabetes Study found that the β-cell secretory function was approximately 50% decreased at the time of T2DM diagnosis [36,37].

In human studies, a recent double-blind placebo controlled crossover study in which 13 T2DM patients received both intravenous reconstituted HDL-C (rHDL-C) and placebo on separate days demonstrated that infusion of rHDL-C resulted in approximately a 1.4-fold increase in plasma HDL-C levels, a greater fall in plasma glucose, increased plasma insulin, as well as increased glucose uptake by the peripheral skeletal muscle [38]. Furthermore, a study in which apolipoprotein (apo) A-I or apo A-II proteins, the main apolipoprotein components of HDL-C, were incubated with primary pancreatic islets found increased β-cell insulin secretion [36].

Another study that was performed in both humans and rats demonstrated that HDL-P partially countered the adverse effects of proatherogenic oxidized LDL-cholesterol particles on β-cell function by preventing activation of the JNK pathway [39]. The JNK pathway, which is induced by oxidized LDL, is part of a larger mechanistic pathway that directly represses the production of insulin and induces β-cell apoptosis [39,40].

ABCA1 is a key transport protein that mediates the efflux of cholesterol from the pancreas [12,41]. One study demonstrated that mice with specific inactivation of ABCA1 in B cells had markedly impaired glucose tolerance and decreased insulin secretion, yet had normal insulin sensitivity [42]. Mice that lacked the ABCA1 receptor also had significantly higher levels of total cholesterol in the islet cells compared with those that had intact ABCA1 receptor, suggesting a functional role for cholesterol homeostasis in the pathogenesis of impaired glucose-mediated insulin secretion [42]. Another study in mice demonstrated that accumulation of cholesterol in islet cells due to loss of ABCA1 led to impaired insulin secretion via impaired exocytosis of insulin granules [43]. This defect was found to be reversible via acute cholesterol depletion, suggesting a potential therapeutic target [43].

In humans, a study in a Mexican population with a unique genetic polymorphism of the *ABCA1* gene that was associated with low HDL-C, obesity and T2DM demonstrated a significant decrease in cholesterol efflux compared with those with normal ABCA1 receptor – however, these were unpublished data and not subject to peer review [43]. In a study of 24 patients with T2DM with reduced expression of ABCA1 there was reduced cholesterol efflux in macrophages leading to increased cholesterol accumulation compared with controls without T2DM [43]. The increased cholesterol accumulation appeared to primarily be due to ABCA1 downregulation since upregulating the receptor via exogenous means reduced the intracellular cholesterol accumulation [44]. Additionally, heterozygous carriers of disruptive mutations in ABCA1 were also found to have impaired insulin secretion without insulin resistance, further demonstrating the importance of the ABCA1 receptor for normal β-cell function in humans [45].

Another HDL-mediated cholesterol transporter, ABCG1, was found to have complimentary roles with the ABCA1 transporter: mice with combined deficiency of both ABCG1 and ABCA1 had greater defects in β-cell function compared with deficiency of either transporter individually [46]. Loss of these transporters in macrophages also leads to increased inflammation via the increased expression of proinflammatory cytokines when challenged with free cholesterol or oxidized LDL [47].

• Peripheral skeletal muscle uptake

HDL-C enhances cellular uptake of cholesterol in the peripheral tissue by increasing plasma insulin via its effects on pancreatic β cells, and also by binding to surface receptors on skeletal muscle (ABCA1), activating the AMPK pathway, which directly promotes glucose intake into the

skeletal muscle [12]. This is an important finding considering that skeletal muscle accounts for the majority of glucose utilization in the body [12]. Furthermore, cellular studies have demonstrated skeletal muscle to be an important regulator of reverse cholesterol transport and HDL-C levels [48]. Skeletal muscle was also demonstrated to have similar reverse cholesterol transport receptors previously found in the liver, called liver X receptors (LXR) [48]. These receptors, when activated, increase reverse cholesterol transport. Inflammatory markers have been shown to inhibit LXR activity in macrophages thus inhibiting cholesterol uptake [49].

APoA-I is the main protein component of HDL-C and has been shown to directly activate the AMPK pathway leading to improved glucose uptake in muscle and decreased liver production [8,50]. As mentioned previously, a study in which rHDL-C was infused in 13 T2DM patients not only showed beneficial effects on the plasma insulin, HDL-C and glucose levels, but also demonstrated increased activation of the AMP-activated protein kinase pathway verified by peripheral muscle biopsy and increased peripheral glucose uptake by approximately 178% [38].

In a recent study of mice with overexpression of ApoA-I, not only did the mice with increased ApoA-I have elevated fasting glucose and higher Hgb A1C levels, but they also expressed decreased muscle glucose uptake and reduced muscle mitochondrial capacity [51,52]. Thus, in these mice there was evidence of impaired skeletal muscle mitochondrial function and cellular respiration with decreased HDL-C levels. This study, as nicely elucidated by the accompanying editorial, should spur interest in examining whether treatment to raise HDL-C levels may reduce the incidence of T2DM [51].

• Anti-inflammatory actions

Multiple studies in T2DM patients have shown increased features of inflammation (cytokines, immune cells and β-cell apoptosis) in pancreatic islets and increased number of macrophages [41,53,54]. Moreover, the ABCA1 receptor has also been shown to function as an anti-inflammatory receptor independent of cholesterol influx [55].

Fatty acids also seem to play a role in the relationship between inflammation and insulin resistance [56]. One study demonstrated that fatty acids induced inflammation via release of cytokines that can directly inhibit insulin signaling and contribute to insulin resistance [14,57]. As for a potential role of HDL-C, a study in mouse cells demonstrated adipocytes transfer cholesterol to HDL-C using the ABCA1 pathway [58] and that this pathway is downregulated with adipocyte inflammation, leading to lower levels of HDL-C [58].

Obesity, with its associated chronic inflammation and as part of the greater metabolic syndrome, may also play a role in conjunction with low HDL-C levels [49]. With the reduced anti-inflammatory function of the lower levels of HDL-C, the enhanced inflammatory state via inflammatory cytokines will inhibit insulin receptor substrates and lead to insulin resistance [49].

Furthermore, HDL-C isolated from healthy subjects was found to stimulate nitric oxide production, reduce endothelial oxidant stress and improve endothelium-dependent vasodilation compared with HDL-C from diabetic subjects [59]. The findings in diabetic subjects were improved when they were given niacin to boost HDL-C, suggesting a potential therapeutic option [59]. However, further studies have shown that higher niacin doses were associated with deleterious effects on glucose control and insulin resistance [60–62]

Treatment implications

Given the associations of low HDL-C with increased T2DM and mechanisms as described above, there could be therapeutic potential in raising HDL-C levels to reduce T2DM incidence among those at high risk. This section will review some of the current literature regarding the major HDL-C-raising medicine classes and the evidence on prevention of incident T2DM.

• Statins

Statins are HMG-CoA reductase inhibitors that lower LDL cholesterol levels, raise HDL-C levels and have other pleotrophic effects such as improvement of endothelial dysfunction, antioxidant effects and anti-inflammatory effects [63]. Given the mechanisms described previously, statins could be conceived to be beneficial in the prevention of incident of T2DM; however, studies examining the relationship of incident T2DM to stain therapy have mostly proved to have the opposite effect. An often cited, landmark meta-analysis of 13 studies involving 91,140 participants demonstrated a 9% increased risk of incident diabetes (OR: 1.09; 95% CI: 1.02–1.17) among patients randomized

to statin therapy, estimating one case of incident diabetes for every 255 nondiabetic patients treated for 4 years with an effect primarily seen in patients greater than 60 years of age with little statistical heterogeneity between trials and statins [64,65]. However, this was in contrast with the four to five cardiovascular events prevented for every 255 patients treated with statins for 4 years [66], thus estimating a benefit–risk ratio of 9:1 [65]. The vast majority of individual studies of this issue confirm the findings of this meta-analysis. However, some individual statin trials have been shown to be protective against the development of incident diabetes. For example, in WOSCOPS, a randomized double blind placebo controlled trial designed to test the clinical efficacy of 40 mg of pravastatin as primary prevention for coronary events with follow-up of 4.9 years, 5974 self-reported nondiabetics with nonelevated fasting glucose levels with mean age of 55 years were identified and used to prospectively study the effects of pravastatin therapy on the risk of developing diabetes [67]. Multivariate analysis demonstrated a 30% lower risk of incident diabetes for those on pravastatin (HR: 0.70; 95% CI: 0.50–0.99) [67]. Although mean HDL-C levels of the nondiabetics were 1.14 mmol/l (or 44 mg/dl) and 1.05 mmol/l (or 40.6 mg/dl) for those that developed incident diabetes, this difference was not statistically significant and HDL-C was not a significant predictor of incident T2DM (HR: 0.86; 95% CI: 0.67–1.11; p = 0.24) [67]. In a smaller study of 35 consecutive nondyslipidemic, nondiabetic patients with mean age of 55 years who were given 40 mg/day of fluvastatin and followed for 8 weeks, insulin sensitivity improved by measure of insulin resistance scores that utilized fasting glucose levels and immunoreactive insulin assays [68]. The HDL-C levels also improved from 45.9 to 50.4 mg/dl after treatment with fluvastatin (p < 0.0001) but there was no significant correlation between HDL-C and insulin resistance score (p = 0.736) [68]. However, this was a small study with no comparison group or placebo control.

• Fibrates

Fibrates are PPAR ligands that have HDL-C raising and triglyceride lowering effects [69]. By activating PPAR, they decrease fatty acid levels, increase adipogenesis, and improve insulin sensitivity via decreased peripheral muscle fatty acid uptake [70]. There have been some recent landmark trials, such as the ACCORD trial, that did not show any reduction of cardiovascular events with the addition of fibrates to a statin in patients with established diabetes, but unfortunately effects on insulin sensitivity or A1c levels were not reported in *post hoc* analyses [71]. In the BIP study, designed to investigate the safety and efficacy of administering bezafibrates to patients with coronary artery disease for secondary prevention, a *post hoc* subgroup analysis was performed on 303 nondiabetic patients with a mean age of 61 years with impaired fasting glucose (110–125 mg/dl) in which roughly half received 400 mg of bezafibrate once a day with a follow-up period of approximately 6 years [69]. At baseline, the mean HDL-C was approximately 34 mg/dl with no significant difference between the two groups, but the placebo group had a slightly higher BMI and lower prevalence of ACE-I utilization [62]. Over the follow-up period, bezafibrate therapy was associated with reduced fasting blood glucose levels, a lower incidence of new onset diabetes (42% in the bezafibrate group vs 54.4% in the placebo group; p = 0.04) and an increase in the mean time until onset of new T2DM (4.6 vs 3.8 years, p = 0.004). After multivariate analysis, bezafibrate treatment was an independent predictor of reduced risk of new diabetes (HR: 0.70; 95% CI: 0.49–0.99) [69].

• Niacin

Niacin (nicotinic acid), an effective HDL-C increasing medication via its effect on the liver and increased HDL-C biogenesis, has demonstrated some inhibition of atherosclerosis and has anti-inflammatory effects [60,72–74]. Thus, in theory, niacin would also seem promising as a potential therapy for those with low HDL-C and increased risk of incident T2DM. Quite the contrary, deleterious effects on glucose control and insulin resistance at higher levels of niacin have been noted in studies and previous guidelines from the National Lipid Association, American Heart Association and American Diabetic Association warn of such risk when initiating niacin [60]. In the NAUTILUS study, a multicenter open-label trial that enrolled 566 patients with dyslipidemia with mean HDL-C 0.85 mmol/l (32.9 mg/dl) in men and 0.95 mmol/l (36.7 mg/dl) in women, a mean age of 56 years, and 58% with T2DM at baseline, patients were given extended-release niacin with a target dose of 2000 mg daily and followed for 15 weeks [61]. After the 15-week period,

HBA1c increased by >0.2% in almost half the population and >1% in 9% of the population, and 6.4% also received intensified antidiabetic therapy. There were no comparison group in this study unfortunately and therefore risk assessments could not be performed. Similar findings were demonstrated in a randomized double blind placebo-controlled trial of 131 patients with hyperlipidemia with mean age of 54 years and HDL-C levels of approximately 45 mg/dl that were followed for 25 weeks and given extended-release niacin with goal dose of 3000 mg a day [61,62]. Finally, a meta-analysis of 30 trials with a total of 4749 subjects demonstrated 2.3% of patients receiving niacin developed hyperglycemia versus 0.4% in the control group, for a relative risk of 3.04 (95% CI: 1.28–7.21; p = 0.01) [60]. In sum, the literature points to increased glucose intolerance when patients are treated with niacin.

• Thiazolidinediones

As previously mentioned, Brunham *et al.* inactivated the ABCA-1 receptor in β cells which caused impaired glucose-sensitive insulin secretion and elevated pancreatic islets cholesterol levels. The addition of rosiglitazone restored normal glucose tolerance and lowered the free cholesterol level in pancreatic islet cells [42]. This class of medication is frequently used clinically to treat diabetes due to its insulin-sensitizing effects [75]. However, compounds within this class have differing effects on lipoproteins, independent of glycemic control. In a randomized, double blind multicenter trial of 735 patients with T2DM and dyslipidemia not treated with lipid-lowering agents, patients that were randomized to pioglitazone had greater increases in HDL-C (5.2 vs 2.4; p < 0.001), smaller increases in LDL and reduced triglyceride levels (versus an increase) compared with those that were randomized to rosiglitzone [76]. The patients in the pioglitazone group demonstrated a reduction in triglycerides versus an increase in the rosiglitazone group [76].

• CETP inhibitors

CETP is a glycoprotein that promotes transfer of cholesteryl esters from HDL to VLDL and LDL and other proatherogenic apoB proteins [77]. Deficiency of this protein is associated with increased levels of HDL-C and reduced coronary heart disease [77]. To determine if medications that reduce CETP would be beneficial in humans, the ILLUMINATE trial tested whether torcetrapib, a CETP inhibitor, could reduce major cardiovascular events. This trial was a randomized, double-blind study of 15,067 patients with a history of cardiovascular disease or diabetes, mean age of 81 years and a mean HDL-C level of approximately 49 mg/dl; patients were randomized to atorvastatin with placebo or atorvastatin plus torcetrapib [78]. Notably, torcetrapib effectively raised HDL-C: at 12 months HDL-C increased by 34.2 mg/dl in the torcetrapid group versus 0.5 mg/dl in the atorvastatin monotherapy arm (p < 0.001). The trial was terminated early due to increased risk of death and cardiac events in the torcetrapib arm. [78]. The etiology of the increased mortality with torcetrapib remains unclear, but was postulated by the authors to be either an off-target pharmacologic effect or possibly due to generation of dysfunctional or proatherogenic HDL-C [78]. Furthermore, in a subsequent *post hoc* analysis of the ILLUMINATE trial on the 6661 diabetic patients, the patients in the torcetrapib plus atorvastatin arm had lower plasma glucose (0.33 mmol/l lower; p < 0.0001) and insulin levels at 3 months and lower levels of mean A1c at 12 months compared with the atorvastatin plus placebo arm (7.16 vs 7.36%; p < 0.001) [79]. Another randomized, multicenter, placebo-controlled trial of a different CTEP inhibitor, dalcetrapib, was performed in 15,871 patients with a recent acute coronary syndrome [80]. The primary end point was a composite of death from coronary heart disease, a major nonfatal coronary event or ischemic stroke. The study stopped early due to futility after 71% of the projected prespecified primary end points had been reached, with no significant difference in the primary end point between treatment arms after a mean follow-up of 31 months. Dalcetrapid had a powerful effect on HDL-C, with 31–40% increases in HDL-C in the treatment arm versus 4–11% in the placebo arm, with minimal effects on LDL cholesterol levels and no effect on fasting plasma glucose or glycated hemoglobin. The authors postulated that the lack of cardiovascular benefit may have been due to high rates of optimal medical therapy (i.e., statins, β-blockers and antiplatelet therapy) for a secondary prevention cohort. They also postulated that HDL-C may be more effective in those without coronary artery disease and that the composition of HDL-C may be altered in the presence of coronary artery disease, potentially

mitigating any protective effects that might have been derived from directly raising HDL-C. In another small randomized, controlled placebo-controlled trial of 25 healthy subjects of whom ten received a daily dose of a CETP inhibitor and the others received placebo for a total of 14 days, beneficial changes on HDL-C levels (+0.55 mmol/l vs -0.10 mmol/l, placebo group; $p < 0.0001$), triglycerides (-0.06 mmol/l vs +0.9 mmol/l in placebo group; $p < 0.05$), and LDL-C (-0.86 mmol/l vs +0.03 mmol/l in placebo group; $p < 0.0001$) were demonstrated at 14 days. Furthermore, in murine pancreatic cells, the CETP group also showed a greater than twofold increase in postprandial insulin and C-peptide compared with the placebo group [81]. There are ongoing studies evaluating other CTEP inhibitors (anacetrapib and evacetrapib) [82]. It remains to be seen whether the discordance between positive increases in HDL-C and the negative clinical outcomes are a class effect or specific only to torcetrapib and dalcetrapid.

Conclusion

Population-based studies suggest a significant association between low HDL-C and an increased risk of developing diabetes. Although there have been no specific studies designed to test the hypothesis that raising HDL-C levels in patients with low HDL-C can reduce the risk of incident diabetes, the impact of various treatments on diabetes risk and glucose metabolism in these patients has been varied. Although results with statin therapy have been mixed, most studies and meta-analyses have demonstrated an increased risk of incident diabetes in patients treated with statins. Fibrates may have a protective effect, but this has only been demonstrated in a few small studies. Niacin can raise HDL-C modestly, but like statins it can slightly increase the risk of incident T2DM. CETP inhibitors have the largest effects on HDL-C, however, the increased mortality seen in the ILLUINATE trial raises significant safety concerns with regards to the use of these drugs.

Future perspective

Ultimately, there is an intriguing set of epidemiologic, experimental and animal data supporting a metabolic interplay between low HDL-C, hyperglycemia and incident T2DM. However, it remains an unproven proposition that increasing HDL-C can prevent the future development of incident T2DM. Until further clinical evidence can substantially support this hypothesis, low HDL-C continues to be a marker of T2DM risk rather than a target for therapy.

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References

Papers of special note have been highlighted as:
•• of considerable interest

1 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res. Clin. Pract.* 87(1), 4–14 (2010).

2 Kannel WB, Daniel L. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 241(19), 2035–2038 (1979).

3 Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263(21), 2893–2898 (1990).

4 Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of Type 2 Diabetes. *Diabetes Care* 25(7), 1129–1134 (2002).

5 Muntner P, Lee F, Astor BC. Association of high-density lipoprotein cholesterol with coronary heart disease risk across categories of low-density lipoprotein cholesterol: the atherosclerosis risk in communities study. *Am. J. Med. Sci.* 341(3), 173–180 (2011).

6 Koro CE, Bowlin SJ, Stump TE, Sprecher DL, Tierney WM. The independent correlation between high-density lipoprotein cholesterol and subsequent major adverse coronary events. *Am. Heart J.* 151(3), 755. e1–e755.e6 (2006).

7 Rahilly-Tierney C, Bowman TS, Djousse L, Sesso HD, Gaziano JM. Change in high-density lipoprotein cholesterol and incident coronary heart disease in apparently healthy male physicians. *Am. J. Cardiol.* 102, 1663–1667 (2008).

8 Assmann G, Nofer J-R. Atheroprotective effects of high-density lipoproteins. *Annu. Rev. Med.* 54, 321–341 (2003).

9 Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and Type 2 diabetes mellitus. *Circulation* 112(20), 3066–3072 (2005).

10 Gami AS, Witt BJ, Howard DE *et al.* Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J. Am. Coll. Cardiol.* 49(4), 403–414 (2007).

11 Martin SS, Qasim AN, Wolfe M *et al.* Comparison of high-density lipoprotein cholesterol to apolipoprotein A-I and A-II to predict coronary calcium and the effect of insulin resistance. *Am. J. Cardiol.* 107(3), 393–398 (2011).

12 Drew BG, Duffy SJ, Formosa MF *et al.* High-density lipoprotein modulates glucose metabolism in patients with Type 2 diabetes mellitus. *Circulation* 119(15), 2103–2111 (2009).

•• **Small study demonstrated that reconstiuted high-density lipoprotein (HDL) reduced plasma glucose in patients with Type 2 diabetes mellitus.**

13 Kontush A, Chapman MJ. Why is HDL functionally deficient in Type 2 diabetes? *Curr. Diab. Rep.* 8(1), 51–59 (2008).

14 Drew BG, Rye K-A, Duffy SJ, Barter P, Kingwell BA. The emerging role of HDL in glucose metabolism. *Nat. Rev. Endocrinol.* 8(4), 237–245 (2012).

15 Di Angelantonio E, Sarwar N, Perry P *et al.* Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 302(18), 1993–2000 (2009).

16 Ginsberg HN. Diabetic dyslipidemia: basic mechanisms underlying the common hypertriglyceridemia and low HDL cholesterol levels. *Diabetes* 45 Suppl. 3(10), S27–30 (1996).

17 Lamarche B, Rashid S, Lewis GF. HDL metabolism in hypertriglyceridemic states: an overview. *Clin. Chim. Acta.* 286(1–2), 145–161 (1999).

18 Rader DJ, Rosas S. Management of selected lipid abnormalities?: hypertriglyceridemia, low HDL cholesterol, lipoprotein(a), in thyroid and renal diseases, and post-transplantation. *Med. Clin. North Am.* 84(1), 43–61 (2000).

19 Dahlof B, Devereux RB, Kjeldsen SE, Beevers G, Al E. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359, 995–1003 (2002).

20 Okin PM, Hille DA, Wiik BP *et al.* In-treatment HDL cholesterol levels and development of new diabetes mellitus in hypertensive patients: the LIFE Study. *Diabet. Med.* 30(10), 1189–1197 (2013).

•• **Demonstrated that lower in-treatment HDL-cholesterol was strongly associated with increased risk of new onset diabetes, and had better predictive power than baseline HDL-cholesterol for development of incident Type 2 diabetes mellitus.**

21 Abbasi A, Corpeleijn E, Gansevoort RT *et al.* Role of HDL cholesterol and estimates of HDL particle composition in future development of Type 2 diabetes in the general population: the PREVEND study. *J. Clin. Endocrinol. Metab.* 98(8), E1352–E1359 (2013).

22 Gupta A, Dahlof B, Dobson J, Sever P, Wedel H, Poulter NR. Determinants of new-onset diabetes randomized in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm and the Relative Influence of Antihypertensive Medication. *Diabetes Care* 31(5) (2008).

23 Wilson P, Meigs J, Sullivan L, Fox CS, Nathan DM, Agostino RBD. Prediction of incident diabetes mellitus in middle-aged adults. *Arch. Intern. Med.* 167, 1068–1074 (2007).

24 Lorenzo C, Okoloise M, Williams K, Stern M, Haffner S. The metabolic syndrome as predictor of Type 2 diabetes: the San Antonio heart study. *Diabetes Care* 26(11), 3153–3159 (2003).

25 Lorenzo C, Lee R, Haffner SM. Impaired glucose tolerance and obesity as effect modifiers of ethnic disparities of the progression to diabetes: the San Antonio Heart Study. *Diabetes Care* 35(12), 2548–2552 (2012).

26 Barter P, McPherson YR, Song K *et al.* Serum insulin and inflammatory markers in overweight individuals with and without dyslipidemia. *J. Clin. Endocrinol. Metab.* 92(6), 2041–2045 (2007).

27 Cooper-DeHoff RM, Pacanowski MA, Pepine CJ. Cardiovascular therapies and associated glucose homeostasis: implications across the dysglycemia continuum. *J. Am. Coll. Cardiol.* 53(5 Suppl.), S28–34 (2009).

28 Deano R, Sorrentino M. Lipid effects of antihypertensive medications. *Curr. Atheroscler. Rep.* 14(1), 70–77 (2012).

29 Wagenknecht LE, Mayer EJ, Haffner S *et al.* The Insulin Resistance Atherosclerosis Study (IRAS): objectives, design and recruitment results. *Ann. Epidemiol.* 5(6), 464–472 (1995).

30 Festa A, Williams K, Hanley AJG *et al.* Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the Insulin Resistance Atherosclerosis Study. *Circulation* 111(25), 3465–3472 (2005).

31 Schmidt MI, Duncan BB, Bang H *et al.* Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 28(8), 2013–2018 (2005).

32 Scanu AM, Edelstein C. HDL: bridging past and present with a look at the future. *FASEB J.* 22(12), 4044–4054 (2008).

33 Davidson MH, Toth PP. High-density lipoprotein metabolism: potential therapeutic targets. *Am. J. Cardiol.* 100(11 A), 32N–40N (2007).

34 Ishikawa M, Iwasaki Y, Yatoh S *et al.* Cholesterol accumulation and diabetes in pancreatic beta-cell-specific SREBP-2 transgenic mice: a new model for lipotoxicity. *J. Lipid Res.* 49(12), 2524–2534 (2008).

35 Hao M, Head WS, Gunawardana SC, Hasty AH, Piston DW. A novel mechanism for pancreatic B-cell dysfunction. *Diabetes* 56(9), 2328–2338 (2007).

36 Fryirs M a, Barter PJ, Appavoo M *et al.* Effects of high-density lipoproteins on pancreatic beta-cell insulin secretion. *Arterioscler. Thromb. Vasc. Biol.* 30(8), 1642–1648 (2010).

37 U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of Type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 44(11), 1249–1258 (1995).

38 Patel S, Drew BG, Nakhla S *et al.* Reconstituted high-density lipoprotein increases plasma high-density lipoprotein anti-inflammatory properties and cholesterol efflux capacity in patients with Type 2 diabetes. *J. Am. Coll. Cardiol.* 53(11), 962–971 (2009).

39 Abderrahmani a, Niederhauser G, Favre D *et al.* Human high-density lipoprotein particles prevent activation of the JNK pathway induced by human oxidised low-density lipoprotein particles in pancreatic beta cells. *Diabetologia* 50(6), 1304–1314 (2007).

40 Bonny C, Oberson A, Negri S, Sauser C, Schorderet DF. Cell-permeable peptide inhibitors of JNK. *Diabetes* 50, 77–82 (2001).

41 Kruit JK, Brunham LR, Verchere CB, Hayden MR. HDL and LDL cholesterol significantly influence beta-cell function in Type 2 diabetes mellitus. *Curr. Opin. Lipidol.* 21(3), 178–185 (2010).

42 Brunham LR, Kruit JK, Pape TD *et al.* Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. *Nat. Med.* 13(3), 340–347 (2007).

43 Kruit JK, Wijesekara N, Fox JEM *et al.* Islet cholesterol accumulation due to loss of ABCA1 leads to impaired exocytosis of insulin granules. *Diabetes* 60(12), 3186–3196 (2011).

44 Mauldin JP, Nagelin MH, Wojcik AJ *et al.* Reduced expression of ATP-binding cassette transporter G1 increases cholesterol accumulation in macrophages of patients with

Type 2 diabetes mellitus. *Circulation* 117(21), 2785–2792 (2008).

45 Vergeer M, Brunham LR, Koetsveld J *et al.* Carriers of loss-of-function mutations in ABCA1 display pancreatic beta-cell dysfunction. *Diabetes Care* 33(4), 869–874 (2010).

46 Kruit JK, Wijesekara N, Westwell-Roper C *et al.* Loss of both ABCA1 and ABCG1 results in increased disturbances in islet sterol homeostasis, inflammation, and impaired β-cell function. *Diabetes* 61(3), 659–664 (2012).

47 Yvan-charvet L, Ranalletta M, Wang N *et al.* Combined deficiency of ABCA1 and ABCG1 promotes foam cell accumulation and accelerates atherosclerosis in mice. *J. Clin. Invest.* 117(12), 3900–3908 (2007).

48 Muscat GEO, Wagner BL, Hou J *et al.* Regulation of cholesterol homeostasis and lipid metabolism in skeletal muscle by liver X receptors. *J. Biol. Chem.* 277(43), 40722–40728 (2002).

49 Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes *J. Clin. Invest.* 115(5), 1111–1119 (2005).

50 Han R, Lai R, Ding Q *et al.* Apolipoprotein A-I stimulates AMP-activated protein kinase and improves glucose metabolism. *Diabetologia* 50(9), 1960–1968 (2007).

51 Mortensen SP, Boushel R. High-density lipoprotein: a new therapeutic target for glucose intolerance? *Circulation* 128(22), 4–10 (2013).

52 Lehti M, Donelan E, Abplanalp W *et al.* High-density lipoprotein maintains skeletal muscle function by modulating cellular respiration in mice. *Circulation* 128(22), 2364–2371 (2013).

53 Böni-Schnetzler M, Ehses JA, Faulenbach M, Donath MY. Insulitis in Type 2 diabetes *Diabetes Obes. Metab.* 10 (Suppl. 4), 201–204 (2008).

54 Ehses JA, Perren A, Eppler E *et al.* Increased number of islet-associated macrophages in Type 2 diabetes. *Diabetes* 56(9), 2356–2370 (2007).

55 Tang C, Liu Y, Kessler P *et al.* The macrophage cholesterol exporter ABCA1 functions as an anti-inflammatory receptor. *J. Biol. Chem.* 284(47), 32336–32343 (2009).

56 Poynten a M, Gan SK, Kriketos a D, Campbell L V, Chisholm DJ. Circulating fatty acids, non-high density lipoprotein cholesterol, and insulin-infused fat oxidation acutely influence whole body insulin sensitivity in nondiabetic men. *J. Clin. Endocrinol. Metab.* 90(2), 1035–1040 (2005).

57 Varma V, Yao-borengasser A, Rasouli N *et al.* Muscle inflammatory response and insulin resistance?: synergistic interaction between macrophages and fatty acids leads to impaired insulin action. *Am. J. Physiol. Endocrinol. Metab.* 296, 1300–1310 (2009).

58 Zhang Y, McGillicuddy FC, Hinkle CC *et al.* Adipocyte modulation of high-density lipoprotein cholesterol. *Circulation* 121(11), 1347–1355 (2010).

59 Sorrentino S a, Besler C, Rohrer L *et al.* Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with Type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* 121(1), 110–122 (2010).

60 Goldberg RB, Jacobson TA. Effects of niacin on glucose control in patients with dyslipidemia. *Mayo Clin. Proc.* 83(4), 470–478 (2008).

61 Vogt a, Kassner U, Hostalek U, Steinhagen-Thiessen E. Evaluation of the safety and tolerability of prolonged-release nicotinic acid in a usual care setting: the NAUTILUS study. *Curr. Med. Res. Opin.* 22(2), 417–425 (2006).

62 Goldberg a, Alagona P, Capuzzi DM *et al.* Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. *Am. J. Cardiol.* 85(9), 1100–1105 (2000).

63 Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 109(23 Suppl. 1), III39–III43 (2004).

64 Sattar N, Preiss D, Murray HM *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 375(9716), 735–742 (2010).

•• **Landmark meta-analysis study demonstrating that statin therapy is associated with a slightly increased risk of incident diabetes.**

65 Cannon CP. Balancing the benefits of statins versus a new risk-Diabetes. *Lancet* 375(9716), 700–701 (2010).

66 Yusuf S, Lonn E, Bosch J. Lipid lowering for primary prevention. *Lancet* 373(9670), 1152–1155 (2009).

67 Freeman DJ, Norrie J, Sattar N *et al.* Evidence for a protective treatment effect in the west of Scotland. *Circulation* 103, 357–362 (2001).

68 Sonmez A, Baykal Y, Kilic M *et al.* Fluvastatin improves insulin resistance in nondiabetic dyslipidemic patients. *Endocrine* 22(2), 151–154 (2003).

69 Tenenbaum A, Motro M, Fisman EZ *et al.* Peroxisome proliferator-activated receptor ligand bezafibrate for prevention of Type 2 diabetes mellitus in patients with coronary artery disease. *Circulation* 109(18), 2197–2202 (2004).

70 Tenenbaum A, Fisman EZ. Balanced pan-PPAR activator bezafibrate in combination with statin: comprehensive lipids control and diabetes prevention? *Cardiovasc. Diabetol.* 11(1), 140 (2012).

71 The ACCORD Study Group. Effects of combination lipid therapy in Type 2 diabetes mellitus. *N. Engl. J. Med.* 362(17), 1563–1574 (2010).

72 Zhang L-H, Kamanna VS, Ganji SH, Xiong X-M, Kashyap ML. Niacin increases HDL biogenesis by enhancing DR4-dependent transcription of ABCA1 and lipidation of apolipoprotein A-I in HepG2 cells. *J. Lipid Res.* 53(5), 941–950 (2012).

73 Digby JE, Martinez F, Jefferson A *et al.* Anti-inflammatory effects of nicotinic acid in human monocytes are mediated by GPR109A dependent mechanisms. *Arterioscler. Thromb. Vasc. Biol.* 32(3), 669–676 (2012).

74 Lukasova M, Malaval C, Gille A, Kero J, Offermanns S. Nicotinic acid inhibits progression of atherosclerosis in mice through its receptor GPR109A expressed by immune cells. *J. Clin. Invest.* 121(3), 1163–1173 (2011).

75 Libby P, Plutzky J. Inflammation in diabetes mellitus: role of peroxisome proliferator-activated receptor-alpha and peroxisome proliferator-activated receptor-gamma agonists. *Am. J. Cardiol.* 99(4A), 27B–40B (2007).

76 Goldberg RB, Kendall DM, Deeg M a *et al.* A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with Type 2 diabetes and dyslipidemia. *Diabetes Care* 28(7), 1547–1554 (2005).

77 Barter PJ. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 23(2), 160–167 (2003).

•• **Shows that although torcetrapib plus statin therapy had a marked increase in HDL compared with statin therpay alone, there was an an increased risk of mortality and morbidity in the torcetrapid plus statin therapy group.**

78 Barter P, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M. Effects of torcetrapib in patients at high risk for coronary events. *N. Engl. J. Med.* 357(21), 2109–2122 (2007).

79 Barter PJ, Rye K-A, Tardif J-C *et al.* Effect of torcetrapib on glucose, insulin, and

hemoglobin A1c in subjects in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial. *Circulation* 124(5), 555–562 (2011).

•• **Demonstrates that treatment with torcetrapib improves glycemic control in atorvastatin-treated patients with Type 2 diabetes mellitus.**

80 Schwartz GG, Olsson AG, Abt M *et al.* Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N. Engl. J. Med.* 367(22), 2089–2099 (2012).

•• **Demonstrates that in patients with recent acute coronary syndrome, dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent cardiovascular events.**

81 Siebel AL, Natoli AK, Yap FYT *et al.* Effects of high-density lipoprotein elevation with cholesteryl ester transfer protein inhibition on insulin secretion. *Circ. Res.* 113(2), 167–175 (2013).

82 Mohammadpour AH, Akhlaghi F. Future of cholesteryl ester transfer protein (CETP) inhibitors: a pharmacological perspective. *Clin. Pharmacokinet.* 52(8), 615–626 (2013).