Chapter 3
Links Between Glucose and Lipoproteins

Alicia J. Jenkins

Introduction

While hyperglycemia is the hallmark of diabetes mellitus, there are many associated abnormalities of lipoprotein metabolism, including quantitative and qualitative changes in lipoprotein classes and subclasses. There are also multiple associations between hyperglycemia and its treatment and lipoproteins and vice versa, which may also impact complication susceptibility.

Lipoprotein Functions

The primary function of lipoproteins is the transportation of fatty acids, triglycerides, and cholesterol from the gut to the liver (via chylomicrons and chylomicron remnants) and from the liver to the periphery (via Very Low Density Lipoproteins (VLDL), VLDL remnants, and Low Density Lipoprotein (LDL)) to target cells where it is used for cellular structures, such as cell membranes, for energy use or storage (e.g., in adipocytes) and for cellular functions, such as steroid hormone synthesis. Reverse cholesterol transport, enacted predominantly by High Density Lipoprotein (HDL), in particular the smaller, denser, lipid poor protein-rich HDL particles, removes excess cholesterol from peripheral tissues, delivering it to the liver, from where it is redistributed to other tissues or removed via the gallbladder and intestine [1, 2]. HDL is also involved in defenses against viruses and toxins [1,

A. J. Jenkins (✉)
NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia

Diabetes and Vascular Medicine, Baker Heart and Diabetes Institute, Melbourne, VIC, Australia
e-mail: alicia.jenkins@sydney.edu.au

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3]. The physiologic role of the proatherogenic and pro-thrombotic lipoprotein lipoprotein(a) is not yet fully elucidated, and people without Lp(a) are healthy. It has been speculated that with its pro-thrombotic and lipid delivery capability it may be a means of assisting with blood clotting and with wound repair [4]. As reviewed in other chapters in this book, lipoproteins have many roles in cell survival, thrombosis, inflammation, oxidative stress, defense against infection, vascular dysfunction, atherosclerosis, and in modulating insulin section and action, hence glycemia. Lipoproteins act via many receptors, cell signaling and molecular pathways [1–4].

As well as the same general roles of lipoproteins in the non-diabetic population, in people with diabetes quantitative and qualitative changes in lipoproteins also impact the development and progression of the macrovascular and microvascular complications of diabetes, including cardiovascular disease, diabetic retinopathy, kidney disease, and neuropathy [1]. Relationships between lipoproteins and these chronic complications are discussed in more detail in other chapters in this book. Effects are mediated directly by lipoprotein effects and indirectly by lipoprotein effects on glycemia and other pleiotropic effects.

Contributors to Lipoprotein Levels in Diabetes

There are many factors contributing to lipoprotein levels in people with diabetes, including *glycemia* [2], which are summarized in Table 3.1. Many factors, such as adiposity, physical fitness, and diet, impact both lipoproteins and glycemia, hence quantifying the exact contributions of glycemia on lipoproteins can be challenging in free-living people with diabetes, especially as changes in lipoproteins and in some glycemia measures, such as HbA1c, fructosamine, and 1,5-anhydroglucitol [5] take weeks to months.

HbA1c levels are usually, but not always, correlated with fasting triglyceride levels and inversely with HDL-cholesterol (HDL-C) levels. Worsening hyperglycemia is usually associated with increasing total triglyceride, VLDL and ApoB levels, and with lowering of HDL-cholesterol (HDL-C) and ApoA1 levels. Hyperglycemia is usually associated with similar or somewhat elevated Low Density Lipoprotein Cholesterol (LDL-C) levels than in normoglycemic people, with a shift toward more pathogenic small, dense, lipid poor, protein-rich LDL particles. This pattern of "diabetic dyslipidemia," is common in people with Type 2 diabetes, and also in people with Type 1 diabetes in the setting of poor glucose control, obesity, and/or renal impairment. In people with Type 1 diabetes with good metabolic control, a healthy body mass index (BMI) and normal kidney function traditional lipid levels are similar to that of non-diabetic subjects, often with lower triglyceride and higher HDL-C levels due to the activating effects of supraphysiologic insulin levels on lipoprotein lipase (LPL). Lipoprotein(a) levels are usually higher with poor glucose control in people with Type 1 diabetes, but not with Type 2 diabetes, in which levels

Table 3.1 Contributors to lipoprotein levels and composition in diabetes

Diabetes related
Hyperglycemia
Insulin levels
Insulin resistance
Glucose variability
Lifestyle
Poor diet
Adiposity
Physical inactivity/high sedentary time
Smoking
Stress
Diabetes complications and comorbidities
Renal disease
Liver disease, e.g., non-alcoholic fatty liver disease
Inflammation
Others, e.g., hypothyroidism
Genetics
Drugs
Examples
For glucose control
For lipid control
Diuretics
Beta blockers
Sex steroids
For infections, e.g., HIV

may even be lower than in the non-diabetic population, perhaps related to other, e.g., genetic effects [1–4]. Lp(a) is discussed in more detail herein in the book chapter by Drs' K. and G. Kostner.

As for people without diabetes, lipid levels in people with diabetes are impacted by *lifestyle factors*, such as diet quality, alcohol intake, obesity, physical activity or inactivity, and smoking. These effects are discussed in another chapter in this book, by Dr. Peter Clifton.

Insulin levels and insulin resistance also modulate lipoprotein levels and metabolism, with peripheral insulin resistance being associated with diabetic dyslipidemia (usually defined as high triglycerides and low HDL-C levels). In people with Type 1 diabetes endogenous insulin production is low, though even very low level residual insulin production, reflected by detectable C-peptide using high sensitivity assays, is associated with better glycemic control, including less hypoglycemia and lower glucose variability, and lower risk of micro- and macrovascular complications [6, 7]. In people with Type 1 diabetes, their essential for life exogenous insulin therapy is injected into their subcutaneous tissue rather than via the portal system,

hence circulating insulin levels are supraphysiologic, which can induce insulin resistance, which can also exacerbated by obesity, growth spurts, puberty, and intercurrent illnesses [8].

Renal disease also changes lipoproteins. Even very early kidney disease, such as low level albuminuria (microalbuminuria) and normal or high (hyper-filtering) glomerular filtration rates (GFR), is associated with dyslipidemia and elevated lipoprotein(a) levels. More severe kidney disease with proteinuria and/or GFR loss are associated with worsening lipoprotein profiles (higher triglycerides, VLDL and apolipoprotein B (ApoB), and lower HDL and ApoA1 and a shift to small dense LDL subclasses). With proteinuria, ApoA1 levels can be lost via urine, contributing to HDL-lowering and altering lipoprotein metabolism (discussed in the chapter by Dr. Per-Henrik Groop et al.). Renal dysfunction is also associated with increases in Lp(a) levels, and higher Lp(a) levels may be a risk factor for diabetic nephropathy as well as cardiovascular disease [1, 9–11].

Similarly *liver disease*, such as due to alcohol excess, obesity, and hypertriglyceridemia or non-alcoholic fatty liver disease (NAFLD) which can also be due to poor glucose control (in both Type 1 and Type 2 diabetes) also promote dyslipidemia [1, 2, 12].

Common comorbidities such as *hypothyroidism* can also aggravate dyslipidemia and, until treated, can reduce benefit and tolerance of some lipid lowering drugs, such as increasing the risk of myalgia and elevated creatinine kinase levels from statin or fibrate drug classes [13, 14].

Genetics can impact lipoprotein metabolism in both people with and without diabetes. There are many polygenic and some monogenic conditions which modulate lipoprotein and lipid levels, which may even modulate Type 2 diabetes risk. For example, heterozygous (autosomal dominant) familial hypercholesterolemia (FH), which causes very high LDL-C levels, is associated with lower risk of Type 2 diabetes than in people without FH [15]. Lp(a) levels and genes modulating Lp(a) levels may also be associated with Type 2 diabetes risk [16].

Drugs. In general, all oral and injectable agents for glucose control in people with diabetes impact lipid levels, mostly by improving glycemia, though there may also be other glucose independent effects.

In general, people with and without diabetes respond similarly to lipid drugs regarding effects on lipid levels and cardiovascular risk reduction, as discussed in other chapters herein.

Other drugs such as hormone therapies (such as the oral contraceptive pill, hormone replacement therapy, testosterone, corticosteroids, thiazide diuretics, and some anti-retroviral drugs for HIV) can affect lipoproteins [2].

Thus, as well as glucose and insulin levels and insulin resistance, there are many aspects of the diabetes milieu, including inherited and acquired factors that can impact lipoprotein levels, composition, and function in diabetes. Lipoproteins can also impact glucose levels in people with diabetes, and this may even begin prior to diabetes onset [1–3]. The effects of glucose levels on lipoproteins will now be briefly overviewed. More details are found in other chapters in this book.

Table 3.2 Effects of glycemia on lipoproteins and lipoprotein metabolism

Altered lipid levels and metabolism
Altered lipoprotein size, density, and composition
Non-enzymatic glycation, which alters metabolism and cellular handling
Impact on lipoprotein oxidation and glyco-oxidation
Altered immunogenicity
Altered lipoprotein function

Effects of Glycemia on Lipoproteins and Lipids

There are multiple effects of glucose on lipoproteins and lipoprotein metabolism, summarized in Table 3.2, and discussed briefly below. This area is also expanded upon in other book chapters herein.

Hyperglycemia and high free fatty acid levels (both of which occur with suboptimal insulinization and/or marked insulin resistance) increase hepatic VLDL production and reduce VLDL clearance rates via reduced activity of vascular endothelial lipoprotein lipase (LPL) activity and by non-enzymatic glycation of apolipoproteins. Hyperglycemia also reduces the rate of HDL production and impairs HDL maturation, partly related to increased non-enzymatic glycation of HDL which increases HDL turnover rates [1–3]. Insulin resistance, common in people with Type 2 diabetes and present in some with Type 1 diabetes [8, 17], is associated with an increase in the ratio of ApoCIII/ApoCII, which reduces LPL activity the function of which is to enhance triglyceride transfer from triglyceride-rich lipoproteins to HDL, which are more rapidly removed by hepatic lipase. The rate of LDL clearance is also slowed by non-enzymatic glycation of LDL [18–20]. The level of non-enzymatic glycation of apolipoproteins in lipoproteins is influenced by both ambient glucose levels, the duration of lipoprotein exposure, lipoprotein subclasses [20], and other lipoproteins, such as HDL [21]. Hence, fasting triglycerides and HDL-C levels are often correlated with concurrent HbA1c levels (positive for triglycerides and negatively for HDL-C) and will usually improve somewhat with better glucose control.

Lipoprotein glycation may also promote lipoprotein oxidation and glycoxidation, which require research laboratory assays for their quantification. As well as altering lipoprotein turnover, these changes can sometimes also adversely impact cellular interactions with receptors, immunogenicity and cellular responses, including worsening the pathogenicity of lipoproteins, such as by promoting foam cell formation and reducing HDL's vasoprotective actions [18–26]. Examples include HDL glycation reducing HDL-associated paraoxonase activity, and its anti-oxidant and anti-inflammatory efficacy [27]. Increased glycation of lipoproteins enhances their immunogenicity, and the resultant lipoprotein and antibody immune complexes can increase foam cell formation, promoting the macrovascular and microvascular complications of diabetes [24, 26]. These changes are discussed in more detail elsewhere in this book, including in chapters on lipoprotein glycation and lipoprotein immune complexes.

Effects of Lipoproteins on Glycemia and Insulin

HDL Effects on Glucose Metabolism

HDL can lower glucose by both insulin-dependent and insulin-independent methods, with HDL effects in the pancreas, liver, skeletal muscle, adipose tissue, and myocardium. HDL can protect against cellular apoptosis, including that of insulin producing pancreatic beta cells, and HDL and ApoA1 can also promote pancreatic islet cell release of insulin. In the liver, HDL activates (phosphorylates) AMPK, increases expression of insulin receptors, and suppresses enzymes for gluconeogenesis. In skeletal muscle, HDL and ApoA1 can also activate AMPK, increasing glucose uptake. In adipose tissue, it enhances adiponectin, an insulin sensitizer. In the myocardium, HDL can decrease glycogen content, which is greatly increased in the hearts of people and animals with diabetes relative to non-diabetic subjects, and that glycogen overload may contribute to diabetic cardiomyopathy [3, 28].

In basic science experiments, HDL has been shown to inhibit endoplasmic reticulum stress-induced apoptosis of pancreatic β-cells [29]. In a double-blind, placebo controlled cross-over study in 13 adults with Type 2 diabetes, a single intravenous infusion of rHDL transiently increased their HDL levels and reduced their blood glucose levels and increased insulin levels [30]. Large scale clinical trials of CETP inhibitors which substantially increase HDL-C and ApoA-1 levels also support HDL roles in glycemia. In the "Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events" (ILLUMINATE) trial, the CETP inhibitor, torcetrapib, improved glycemic control in statin-treated patients with Type 2 diabetes [31]. Another CETP inhibitor trial, the "Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib" in Patients at a High Risk for Vascular Outcomes' (ACCELERATE) trial, glycemia was also improved in Type 2 diabetes participants [32].

Hypertriglyceridemia

High triglycerides can induce insulin resistance and hyperglycemia. The body's level of insulin resistance has been positively correlated with the level of skeletal muscle triglycerides, which usually correlated with circulating triglyceride and free fatty acid levels [33, 34]. The intravenous infusion of lipids can worse insulin resistance and inflammation, even in lean non-diabetic subjects [35]. Lowering triglyceride levels such as in people with severe hypertriglyceridemia can also improve insulin sensitivity and glycemia. Some lipid drugs in development, such as a monoclonal antibody targeting ANGPTL3, lowered triglyceride levels by about two-thirds, LDL-C levels by one-third, and also reduced hepatic fat and improved insulin resistance in early phase human trials [36].

Severe hyperglycemia, often associated with inherited forms of hypertriglyceridemia and an environmental trigger, such as obesity or drugs such as the pill or thiazides, can trigger acute pancreatitis, which can lead to destruction of both the endocrine and exocrine pancreas, inducing insulin requiring diabetes and need for digestive enzyme replacement [2, 37].

Associations Between Lipid Levels and Diabetes Onset

Type 2 Diabetes

HDL: Evidence is mixed as to whether low HDL levels are a risk factor for Type 2 diabetes. Many observational studies in humans support inverse associations between HDL-C levels, HDL particle numbers, and apoA1 levels even years before the development of Type 2 diabetes [38–42]. In the PREVEND study, both lower HDL-C and HDL-C/ApoA1 were independent predictors of Type 2 diabetes onset [38] and in the Diabetes Presentation Program (DPP) on-study rises in HDL-C were associated with lower rates of progression from pre-diabetes to Type 2 diabetes in the control, intensive lifestyle and metformin arms [43].

Lipid variability has also been associated with increased risk of Type 2 diabetes [44]. In 45,911 Chinese patients with three TG and HDL-C measures during 2006–2011, average real variability (ARV) was calculated and participants subdivided into tertiles of TG/HDL-ARV. There were 3724 cases of incident diabetes during follow-up. The 7-year cumulative incidences of diabetes in TG/HDL-ARV tertiles 1, 2, and 3 were 6.13%, 8.09%, and 11.77%, respectively. Results remained significant after adjustment for mean TG/HDL-C ratio, TG/HDL-C ratio change slope, fasting plasma glucose variability (ARV), and other traditional risk factors for diabetes. The HR for new-onset diabetes was 1.38 (1.25–1.50) for the highest tertile, with risk of diabetes increasing by 4% per 1 standard deviation (SD) increase in TG/HDL-C ratio variability [44].

HDL-related genetics: In contrast, a very large Mendelian randomization study in the general population ($n = 47{,}627$) evaluating genes associated with HDL levels does not support associations between low HDL levels and subsequent Type 2 diabetes [45].

ApoCIII: High levels of serum apoCIII, an inhibitor of LPL, which leads to elevated triglycerides, and the ratio apoCIII/apoA1, have also been found to be independent predictors of subsequent Type 2 diabetes [46].

Lipoprotein(a): While higher levels of Lp(a) are associated with increased risk of cardiovascular disease, some studies support that high levels of Lp(a) are associated with lower risk of Type 2 diabetes [47]. In a prospective study of 26,746 healthy US women (mean age 54.6 years), baseline Lp(a) concentrations were related to incident type 2 diabetes ($n = 1670$) over a 13-year follow-up. Analyses were adjusted for risk factors including age, ethnicity, smoking, hormone use, family history, blood pressure, CRP, BMI, HbA1c, and lipids. Baseline Lp(a)

levels were inversely associated with incident diabetes, with fully adjusted hazard ratios (HRs) and 95% CIs for quintiles 2–5 versus quintile 1: 0.87 (0.75–1.01), 0.80 (0.68–0.93), 0.88 (0.76–1.02), and 0.78 (0.67–0.91); p for trend 0.002. Results were confirmed in a study in 9652 Danish men and women with prevalent diabetes ($n = 419$) [47].

Type 1 Diabetes

Lipids have also been implicated in the development of Type 1 diabetes in humans. While the clinical onset of Type 1 diabetes is quite acute, often with symptoms (polyuria, polydipsia, weight loss) for only days to weeks pre-diagnosis, autoantibodies to insulin producing cells in the pancreatic islets of Langerhans are usually present for many years pre-diagnosis. The AMORIS cohort followed 591,239 people in Sweden from 1985–1996 up until 2012, during which time 1122 people developed Type 1 diabetes. Levels of triglycerides and ApoB/ApoA1 were positively associated with Type 1 diabetes risk, and higher ApoA1 levels were associated with lower Type 1 diabetes incidence. Even 15 years pre-diagnosis triglycerides, uric acid (which can reflect insulin resistance) [48], and glycemia (reflected by glucose and fructosamine levels) were higher in subsequent Type 1 diabetes cases vs. non-cases [48]. These changes may relate to lipotoxicity and glucotoxicity effects on islets, which are relevant to the pathogenesis of both Type 1 and Type 2 diabetes.

HDL and Glycemic Progression in Type 2 Diabetes

There are associations between HDL levels, insulin resistance, and the progression of Type 2 diabetes to need for pharmacologic glucose control [49, 50]. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial in adults with Type 2 diabetes HDL-C and HDL-C/ApoA1 at baseline predicted glycemic progression in adults with Type 2 diabetes over a median of 5 years follow-up. To be eligible for the FIELD trial, people had to have Type 2 diabetes with a lipid profile that did not merit lipid lowering drugs by treatment standards then. Total cholesterol levels had to be 3.0–6.5 mmol/L, triglycerides ≥1.0 mmol/L, HDL-C <1.5 mmol/L, or TG/HDL-C ratio ≥4.0. People with severe hypertriglyceridemia or with marked renal or liver dysfunction were excluded from the trial, reducing the generalizability of results.

In the FIELD trial, HDL-C levels did not correlate significantly with concurrent HbA1c levels, but in the 13,900 subjects screened, with a wider range of HDL-C levels than those 9795 who progressed to the trial, HDL-C correlated weakly with HbA1c levels ($r = -0.030$, $p < 0.001$). For the 9795 participants, HbA1c was not correlated with HDL-C, ApoA1, or HDL-C/ApoA1; but these three HDL-related measures were weakly correlated with HOMA-IR and HOMA-B (all $p < 0.001$) and HOMA-B adjusted for HOMA-IR correlated weakly with ApoA-1 ($r = -0.041$, $p < 0.001$) [50].

At baseline 2698 of the 9795 participants had their glycemia managed by lifestyle measures alone: mean age 62 years, 38% female, mean known diabetes duration 2 years, fasting triglycerides 1.68 mmol/L, HDL 1.11 mmol/L, Apo-A1 1.3 g/L, and HDL-C/Apo A1 0.33. On age and sex-adjusted analyses, HDL-C, ApoA1, and HDL-C/ApoA1 levels did not correlate significantly with concurrent HbA1c levels. However, in these 2608 subjects, baseline HDL-related measures were significantly inversely correlated with insulin resistance: HOMA-IR (HDL-C, $r = -0.245$; ApoA1, $r = -0.169$; and HDL-C/ApoA1 $r = -0.254$, all $p < 0.05$). Only ApoA1 significantly, albeit weakly, correlated with HOMA-Beta ($r = -0.063$, $p < 0.05$). Thus, HDL levels were more strongly associated with measures of insulin resistance and secretion than with concurrent glycemia, however baseline HDL-related measures were strongly associated with progression to need for glucose control drugs [50].

In the FIELD trial glucose management was not part of the trial and was left to the usual treating doctors, with national guidelines recommending up-titration of glucose management at HbA1c levels over 7% (53 mmol/mol). Of the 2608 subjects on lifestyle measures for glucose control at baseline 1520 subjects (58%) progressed to needing oral glucose drugs and/or insulin injections. At the time of the FIELD trial, this was usually sulfonylureas, metformin, and insulin. Incretin based drugs and SGLT2 inhibitors were not routinely available. Even so glucose management was up-titrated (by the usual care doctors, not the trialists) during the FIELD trial at a mean HbA1c of 7.1% (54 mmol/mol) and achieved a mean HbA1c level of about 7% (53 mmol/mol) during the (median 5-years) trial. There was no significant difference in changes in HbA1c or drug up-titration by fenofibrate or placebo allocation in the FIELD trial. Higher HDL-C and higher HDL-C/ApoA1 levels, but not ApoA1 levels, at baseline were associated with significantly longer periods of glucose management by lifestyle only measures. Comparing the first vs. fourth quartile of HDL-C/ApoA1 and of HDL-C levels, there were a mean of 24- and 13-months delay, respectively, in need for glucose control drugs (HR 1.51, $p < 0.01$ for HDL-C/ApoA1 and HR 1.26, $p = 0.02$ for HDL-C). Analyses were adjusted for age and sex. There were no significant differences by fenofibrate or placebo allocation [50]. Significance was retained for HDL-C and HDL-C/ApoA1 retarding need for glucose control drugs even when adjusted for HOMA-IR, BMI and HbA1c, WHR, renal function, liver function test, smoking and alcohol use, exercise, female menopause status, and statin or RAAS drug use. Significance of HDL alone but not that of HDL/ApoA1 as a predictor of glycemic progression was lost when adjusted for baseline triglycerides. As HDL-C/ApoA1 reflects smaller HDL particles, we speculate that smaller HDL particles may be particularly relevant to protection against the glycemic progression of Type 2 diabetes [50].

Glucose and Lipid Variability and Diabetes Complications

Associations between glycemia and traditional lipid levels are recognized with higher HbA1c levels usually being associated with higher triglycerides and lower HDL-C levels and with more adverse VLDL, LDL, and HDL subclass profiles.

Correlations usually positive between HbA1c and calculated or measured LDL-C levels are less strong than between HbA1c and triglycerides and LDL, but associations with a shift to more pathogenic small dense LDL are recognized [1–3]. More recently, variations in glucose and in traditional lipid levels [51–56] have been associated with chronic complications and with mortality, though there are relatively fewer studies of lipid variability and diabetes complications than of glucose variability. As a number of measures of glycemia and its variability are now available and they cover different time frames, we now briefly review glycemia measures which have been or could be related to lipids and lipid variability and to health outcomes in clinical studies.

Aspects of Glycemia

Longer term measures: There are several aspects of glucose metabolism to consider, summarized in Table 3.3. Most measured in clinical practice are *HbA1c* levels, a longer term measure of non-enzymatic glycation of hemoglobin which reflects mean blood glucose levels over the previous 2–3 months. Higher HbA1c levels are exponentially associated with increased risk of microvascular complications of diabetes (retinopathy, nephropathy, and neuropathy) and also with risk of macrovascular complications (cardiovascular, cerebrovascular, and peripheral vascular disease) [52].

Intermediate-term measures of glycemia are fructosamine, glycated albumin, and 1,5 anhydroglucitol reflect mean glucose levels over shorter time frames than

Table 3.3 Clinical and research measures of glucose metabolism

Hyperglycemia: Glucose (by blood test or interstitial fluid Continuous Glucose Monitor (CGM) time above range (TAR), HbA1c, fructosamine, 1,5 anhydroglucitol, glycated albumin)
Hypoglycemia: Glucose (by blood test or interstitial fluid CGM time below range (TBR))
Glucose variability
HbA1c CV or SD
Blood glucose CV or SD
Continuous Glucose Monitor (CGM)-based glucose CV, or MAGE or CONGA
Insulin or C-peptide levels
Insulin sensitivity/insulin resistance
Hyperinsulinemic, euglycemic clamp studies
Estimated glucose disposal rate (eGDR)
Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)
HOMA-beta (both HOMA-IR and HOMA-beta are calculated from fasting insulin and glucose levels in non-insulin treated subjects)
Insulin secretion in response to oral or intravenous glucose
Pancreatic islet beta cell mass
Markers of pancreatic islet cell death, e.g., microRNA signatures
Adipokines, e.g., adiponectin, an insulin sensitizer
Glycogen stores, e.g., in heart, liver, or skeletal muscle

HbA1c. *Fructosamine*, which is widely available for clinical use, and *glycated albumin*, a research tool, are non-enzymatically glycated plasma proteins which reflect mean blood glucose over about 2 weeks. Plasma or serum *1,5 anhydroglucitol* (1,5AG) levels, which are used clinically in some countries and as a research tool in others, reflects levels of a naturally occurring metabolically inert monosaccharide present in almost all foods, that competes with glucose for reabsorption in the kidneys. Blood levels fall with glycosuria, which usually occurs with blood glucose levels over 10 mmol/L (180 mg/dL) and reflects glucose control over the previous 2 weeks. Unlike HbA1c, fructosamine, and glycated albumin levels, 1,5-AG levels more accurately reflect glucose variability and post-prandial glucose levels [5].

Short-term measures of glycemia are reflected by changes in glucose levels of days to a week or two. Increasingly commonly used *Continuous Glucose Monitoring* (CGM) systems enable the measurement of interstitial fluid glucose levels every five to 15 min for six to 14–180 days, depending on which commercial system is used. Many CGM systems can alarm to alert the wearer and sometimes a carer to high or low glucose levels, and some when linked with a compatible insulin pump can increase or decrease insulin delivery [57]. International consensus groups now recommend glucose targets for CGM metrics for clinical and research use with glucose CV recommended to be <36% [58].

Hypoglycemia: While links between hyperglycemia and chronic diabetes complications are well-recognized, hypoglycemia has also been associated with increased risk of vascular complications. Hypoglycemia can prolong the cardiac QT interval and induce cardiac arrhythmias, which can cause sudden cardiac death [59]. An episode of hypoglycemia can also cause vascular endothelial dysfunction, inflammation, and oxidative stress which can last for several days [60]. CGM are reliable systems to detect low glucose levels [57].

Glucose variability has also been associated with increased vascular dysfunction, inflammation, oxidative stress, and risk of macrovascular and microvascular complications and of mortality [52, 54]. While relevant data are available in many existent and planned trials, there are few reports of the role of lipids and lipid variability in the pathogenesis of diabetes complications and of their mitigation by therapeutic interventions. Most of those available to date are positive.

Lipids and Lipid Variability in Diabetes and Effects on Chronic Complications

Both lipid and HbA1c levels have been associated with chronic diabetes complications and mortality, often with non-linear (U or J-shaped associations between HbA1c and lipids and complications) [61–63]. The time course, magnitude, and causes of variations in lipid levels are not as well-studied as those in glycemia. Associations between lipid variability, chronic complications, mortality, and other modulators are less well-studied. It is yet unclear as to the links between lipid and

glucose variability on the development of events, such as microvascular complications, macrovascular events, and mortality.

In most, but not all, major cohort studies variability in lipid levels has been associated with chronic diabetes complications and with death. Similar to HbA1c, in a very large (n = 25,186) study of Asians with diabetes, there was heterogeneity in the associations of HDL-C variability with adverse outcomes. Some studies report higher risk of adverse events with greater HDL-C variability, while others do not find statistically significant associations [64–68]. Factors contributing to variations in findings may be differences in study size, study duration, laboratory measures, the number of lipid measures, underlying genetics, and interactions by lifestyle factors such as smoking, diet, and statistical analyses, including whether adjustment for mean levels is performed and whether the standard deviation (SD) or coefficient of variability (CV) is used. Standardization of variability measures between studies can assist with meta-analyses and the use of lipid variability measures in clinical practice.

In the Italian AMD Annals database, 7560 Type 2 diabetic patients with at least five measures of traditional lipid levels (total cholesterol, triglycerides, LDL-C, HDL-C), HbA1c, systolic and diastolic blood pressure, and uric acid over 3-years were followed for up to 5-years. The impact of risk factor variability on the risk of diabetic kidney disease was assessed. Lipid variability was not significantly associated with risk of developing albuminuria in 4231 subjects, but prediction was strong when considering variability in both HDL-C and HbA1c (HR = 1.47; 95% CI 1.17–1.84). Variability in HDL-C and in LDL-C significantly predicted loss of eGFR to <60 mL/min/1.73^2 [69].

In a large Asian study of 25,186 people with Type 1 diabetes or insulin-treated Type 2 diabetes (mean age 63 years, 50% male) attending Hong Kong public hospitals during 2009, the variability of total cholesterol, LDL-C, HDL-C and triglycerides and HbA1c was related to all-cause mortality (primary endpoint) and to (secondary outcomes) diabetes complications. Lipid and HbA1c variability were significant predictors of all-cause mortality, and for incident cardiovascular, cerebrovascular, peripheral vascular disease, heart failure, and atrial fibrillation ($p < 0.05$). There were also significant correlations between lipid variability, like HbA1c, and the baseline blood neutrophil-lymphocyte ratio (reflecting inflammation) [56].

Another large multicenter study in Asia found similar results for mortality and also for non-fatal CVD [70]. In a retrospective cohort study of 125,047 Type 2 diabetes patients aged 45–84 years, managed in primary care during 2009–2012 variability (SD) of LDL-C, TC/HDL-C, and TG (in mmol/L) was related to a composite endpoint of CVD events (n = 19,913) and death (n = 15,329) over a median follow-up of 77.5 months, including 0.8 million person-years. Positive linear relationships between lipid variability and the clinical endpoint (CVD and death) were identified. Each unit increase in the variability of LDL-C, TC/HDL-C, and TG was associated with increased risk of CVD or death: LDL-C, 27% (HR: 1.27 [95% CI: 1.20–1.34]); TC/HDL-C, 31% (HR: 1.31 [95% CI: 1.25–1.38]); and TG 9% (HR: 1.09 [95% CI: 1.04–1.15]). Age-specific effects for 45–54 y.o. subjects were found for LDL

variability (HR: 1.70 [95% CI: 1.42–2.02]) with a 53% increased risk for the composite endpoint than those aged 75–84 y.o. (HR: 1.11 [95% CI: 1.01–1.23]). Similar age effects were observed for TC/HDL-C and TG variability [70].

Lipid variability has also been demonstrated to be a risk factor for kidney disease in people with Type 2 diabetes [71]. LDL-C, TC/HDL-C, and TG variability were evaluated in a retrospective cohort study of 105,552 Type 2 diabetes patients aged 45–84 with normal urine albumin to creatinine ratio and eGFR >60 mL/min/1.73m^2 who attended Hong Kong public primary care clinics during 2008–2012. Variabilities of LDL-C, total cholesterol to HDL-C ratio, and triglyceride were determined using the standard deviation of the respective parameter obtained from a mixed effects model to minimize regression dilution bias. The associations between LDL-C, TC/HDL-C, and TG variability and incident kidney disease, ≥30% reduction in estimated glomerular filtration rate (eGFR) since baseline, and end-stage renal disease (ESRD: eGFR <15 mL/min/1.73 m^2) were evaluated with a median follow-up of 66.5 months (0.5 million person-years in total), during which 49,653 new-onset kidney disease cases, 29,358 with renal function decline, and 1765 with ESRD developed. There were no associations with TGs, but positive linear associations with LDL-C and TC/HDL-C were found. Each mmol/L increase in LDL-C variability was associated with 20% (HR 1.20 [95% CI 1.15–1.25]), 38% (HR 1.37 [95% CI 1.30–1.45]), and 108% (HR 2.08 [95% CI 1.74–2.50]) higher risk in incident kidney disease, renal function decline, and ESRD, respectively. Similarly, each unit increase in TC/HDL-C was associated with 35% (HR 1.15 [95% CI 1.10–1.20]), 33% (HR 1.33 [95% CI 1.26–1.40]), and 75% (HR 1.75 [95% CI 1.46–2.09]) heightened risk in incident kidney disease, eGFR loss, and ESRD, respectively.

Such data for diabetic retinopathy, and for Type 1 diabetes and for other ethnic groups are of interest. Potential medicators of lipid variability may be alternations in glycemia, in diet, exercise, smoking, and use of lipid modulating drugs. The effects of interventions that reduce lipid variability on clinical events including the development and progression of microvascular and macrovascular complications and of mortality are merited. As lipotoxicity, as well as glucotoxicity, is implicated in the progression of Type 2 diabetes, the effects of lipid variability on the need for pharmacologic agents for glucose control in people with Type 2 diabetes are merited.

While the underlying mechanisms linking lipid variability are unclear, hypotheses include increased oxidative stress and inflammation, and that large fluctuations in LDL and HDL can induce plaque instability and proatherogenic substances.

Lipid Drugs and Effects on Glycemia

Some lipid drugs have been associated with changes in glycemia, with divergent effects, predominantly between classes, summarized in Table 3.4. Both direct and indirect effects may be involved. Effects on glycemia and may differ between non-diabetic and diabetic subjects and between humans and animals.

Table 3.4 Effects of lipid drug classes on glycemia

Drug class	Example(s)	Effects on glycemia
Predominantly LDL-lowering drugs		
Statins	Atorvastatin Rosuvastatin Pravastatin Simvastatin Pitavastatin	May worsen glucose and HbA1c ↑ Risk of new-onset diabetes (NOD)
Bempedoic acid		No worsening of glycemia or NOD May improve glycemia
PCSK9 inhibitors	Evolucmab	No change or perhaps mild worsening of glycemia. No NOD
Ezetimibe		No change or mild improvement
Resins	Cholestyramine Colesevelam Colestimide	Moderate improvements in glucose and HbA1c, with no risk of hypoglycemia Colesevelam approved by FDA for glucose (and lipid) lowering in T2D
Predominantly TG-lowering drugs		
Fibrates	Fenofibrate Pemafibrate Bezafibrate	No substantial effect of PPARα agonists (e.g., fenofibrate) Fibrates with PPAR alpha and gamma activity (e.g., bezafibrate) improve glucose and HbA1c
Omega-3 fatty acids	Omacor	Inconsistent results due to different sources, types, and doses
Fish oils		Overall—no major benefit or harm re glycemia and diabetes
Niacin/nicotinic acid		Worsens glucose and HbA1c, more so in diabetes subjects Less marked with low dose, slow titration, and slow-release preparations Reversible with cessation
Predominantly HDL-elevating drugs (currently research only)		
rHDL	Lower glucose, increase insulin	
CETP inhibitors	Lower glucose and HbA1c	

LDL-Lowering Drugs

The effect of *statins* on glycemia is most well-studied. While HMG CoA reductase inhibitors (statins) have major primary and secondary cardioprotective effects in diabetes [72], this class has been associated with mild elevations in glucose (in non-diabetic and diabetic subjects) and HbA1c and increased risk (by about 9%) of new-onset (Type 2) diabetes, (NOD) [73–78]. Most statins are thought not to worsen insulin sensitivity, and pravastatin may even improve insulin sensitivity in non-diabetic subjects [74]. The risk of NOD is higher with older age, higher statin doses, more potent statins, greater (>50%) LDL-C reductions, longer statin use and the presence of pre-diabetes or the metabolic syndrome. Mechanisms may relate to HMGCoA reductase inhibition, direct drug effects, and altered intracellular lipids, which decrease insulin sensitivity and/or beta cell function [79]. While new-onset diabetes would increase the risk of diabetes complications and of CVD, the overall cardiovascular and death risk-benefit ratio for most people being offered statin therapy is deemed favorable [79].

Bempedoic acid is the first drug in a relatively new drug class of lipid lowering drugs, the adenosine triphosphate-citrate lyase (ACL) inhibitors, which blocks hepatic cholesterol production at a different site than HMG CoA reductase inhibitors. In a meta-analysis of 11 trials ($n = 4391$ general population subjects), the drug significantly reduced LDL-C (median 22.9%, 95% CI 27.3–18.5), CRP (median 24.7%, 95% CI 32.1–17.3), composite cardiovascular events (RR 0.75, 95% CI 0.56–0.99) and significantly reduced rates of NOD or worsening of glucose levels (RR 0.65, 95% CI 0.44–0.96) [80]. Another meta-analysis of five bempedoic acid trials with at least 4-weeks follow-up and 2419 bempedoic acid treated subjects and 1210 control arm subjects specifically addressed glycemia and NOD and was confirmatory. Bempedoic acid allocation was associated with a significant reduction in new-onset or worsening diabetes [Odds Ratio: 0.66, 95% CI: 0.48–0.90; $I2$: 0%]. It is speculated that the drug may reduce gluconeogenesis [81].

PCSK9-inhibitors. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors given by subcutaneous injections every 2–4 weeks are even more potent LDL-C lowering drugs than statins, with similar efficacy for lipid and cardiovascular benefit in people with and without diabetes. In a recent meta-analysis (38 trials, $n = 68{,}123$ subjects), there was no significant effect on glucose control reflected by fasting glucose, HbA1c or NOD [82]. Longer term follow-up will be of interest.

Ezetimibe, a once daily selective inhibitor of cholesterol absorption from the intestine, acts predominantly via inhibition of the Niemann-Pick C1-Like 1 transporter on the brush border of enterocytes. In animal studies, ezetimibe has improved glucose tolerance, insulin sensitivity, and insulin production and may also have incretin effects. In humans, ezetimibe effects range from no changes in glycemia or insulin sensitivity [83] to small (about 0.3%) HbA1c reductions (even with concomitant statins) and lower fasting insulin levels, with no significant difference in glucose levels [79].

Resins/bile acid sequestrants. While often not as potent or as well-tolerated as other LDL-lowering drugs, and sometimes increasing triglyceride levels, this drug class has been associated with small to modest reductions in glucose and HbA1c levels, including in adults with existent Type 2 diabetes. In a meta-analysis of bile acid sequestrants in adults with Type 2 diabetes in 17 trials, with 2950 subjects randomized to colesevelam or colestimide or to placebo resin allocation were associated with statistically and clinically significant lower HbA1c % levels (mean difference 0.55%, 95% CI 0.64–0.46%) [84]. Indeed, in 2012 the USA FDA approved colesevelam for use in Type 2 diabetes patients as an adjunct to improve glycemia. Suggested mechanisms related to the resin effects on removing bile acids which also interact with various membrane and nuclear receptors [79, 84].

Triglyceride Lowering Drugs

PPAR subtypes alpha, gamma, and beta/delta exist. Fenofibrate is a PPAR alpha agonist. Despite lowering triglycerides and free fatty acids, in the fenofibrate based FIELD, ACCORD and DAIS trials, there were no significant changes in glycemia in their Type 2 diabetes participants [79]. However, as discussed above, in the

FIELD trial, higher HDL and HDL/ApoA1 levels were associated with retarding the need for glucose lowering drugs in adults with Type 2 diabetes [50], but there was no difference between those allocated fenofibrate or placebo.

PPAR gamma activation increases glucose uptake by skeletal muscle and decreases hepatic glucose production, hence as expected, fibrates with PPAR gamma activity, such as bezafibrate (which activates all three PPAR subtypes) have been associated with improvements in glycemia and insulin sensitivity [79]. In a Japanese study 6-months of bezafibrate was associated with lower glucose and HbA1c (% units) reductions of 0.47% in all subjects and by 0.76% in those with baseline HbA1c levels >7% (53 mmol/mol), with HbA1c reductions correlating with triglyceride reductions [85].

Fish oils: Results vary depending on whether fish oils are taken by diet or supplement, and the dose, duration of treatment, and type of fish oils. A Cochrane systematic review of 23 randomized controlled trials of *n*−3 PUFA supplements in people with Type 2 diabetes found no significant changes in fasting glucose, fasting insulin, or HbA1c levels [86]. Several meta-analyses report no significant deterioration in glucose or HbA1c levels in people with Type 2 diabetes [86]. Similarly, no effects on insulin sensitivity were identified in a systematic review of *n*−3 PUFA in diabetic and non-diabetic subjects [87].

Niacin and nicotinic acid: In human studies, this drug class worsens glucose control (reflected by glucose and HbA1c levels) likely by worsening insulin resistance. Lower doses and slow-release preparations are usually less adverse [79]. In a meta-analysis of 11 trials with 26,340 non-diabetic participants, 1371 were assigned niacin and 646 were assigned control tablets, with a mean of 3.6 years follow-up. Niacin was associated with a RR of 1.34 (95% CIs 1.21–1.49) for new-onset diabetes, with limited heterogeneity between trials ($I2 = 0.0\%$, $p = 0.87$). The number needed to treat for 5 years to develop one additional case of diabetes was 43 (95% CI 30–70). Results were similar whether subjects also received a statin or laropiprant [88].

Marked HDL-C Elevating Drugs (Research Only)

IV infusion of rHDL on humans with Type 2 diabetes has been associated with improved glucose levels, which may relate to HDL, including its components apoA1 and apoAII, promoting insulin secretion and activating AMPK in skeletal muscle [89].

While not in clinical use, CETP inhibitors, which markedly elevate HDL levels, have been shown to significantly lower glucose and HbA1c levels, likely by enhanced beta cell insulin secretion [79]. In the ILLUMINATE trial, HbA1c (in % units) was reduced by 0.33% after 3-months treatment with the CETP inhibitor torcetrapib and atorvastatin in people with Type 2 diabetes [90]. There was no increase in new-onset Type 2 diabetes.

Future Directions

Other studies of interest include analyses of existent and future trials regarding effects of lipid levels, lipid variability, and lipid drugs on various measures of glycemia, insulin levels, and insulin sensitivity. Relevant subgroups include non-diabetic subjects, those with pre-diabetes, Type 1 diabetes, and Type 2 diabetes. Lipid drug mechanisms of action, potency, and duration of therapy should be considered. The reversibility of any adverse glycemic effects is of interest. The understanding of underlying mechanisms of action and the development of clinically effective drugs that improve both lipids, glycemia and reduce vascular events and mortality rates are desirable.

Conclusions

Abnormalities in lipoproteins and of glycemia and insulin sensitivity often co-exist. There are complex bidirectional relationships between lipoproteins and glucose, some of which are favorable and others adverse. Treatment of glucose levels usually improves lipoprotein levels, but the treatment of lipid levels, particularly with drugs, has variable effects of glucose metabolism depending on drug types. Some drugs are beneficial for both lipids and glycemia. Relatively new concepts are the relationship between lipid and glucose variability and adverse clinical outcomes. Very few studies have evaluated both, nor evaluated the causes of lipid variability and the consequences of its treatment. Consideration of the bidirectional relationships between lipoproteins and glycemia is important in both clinical practice and in research. Drugs that favorably modulate both lipoproteins and glycemia are desirable.

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