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Pathogenesis of Lipid Disorders in Insulin Resistance: A Brief Review

Petter Bjornstad, M.D.[1,2] and **Robert H. Eckel, M.D.**[3]

[1]Department of Pediatrics, Division of Endocrinology, University of Colorado School of Medicine, Aurora, CO

[2]Department of Medicine, Division of Renal Diseases and Hypertension, University of Colorado School of Medicine, Aurora, CO

[3]Department of Medicine, Division of Endocrinology and Division of Cardiology, University of Colorado School of Medicine, Aurora, CO

Abstract

Purpose of the review: Insulin resistance (IR) is recognized to play an important role in the pathogenesis of dyslipidemia. This review summarizes the complex interplay between IR and dyslipidemia in people with and without diabetes.

Recent findings: IR impacts the metabolism of triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C) by several mechanisms. Trials with insulin sensitizing therapies, including biguanides and thiazolidinediones, have provided inconsistent results on lipid lowering in people with and without diabetes. In this review, we focus on the pathophysiological interplay between IR and dyslipidemia and recapitulate lipid and lipoprotein data from insulin sensitizing trials.

Conclusion: Further research elucidating the reciprocal relationship between IR and dyslipidemia is needed to better target these important risk factors for cardiovascular disease.

Address all correspondence to: Petter Bjornstad, M.D.Pediatric Endocrinology, University of Colorado School of Medicine, 13123 East 16th Ave ,Box B26, Aurora, CO 80045, Phone: (720) 777-4659; Fax: (720) 777-7301, petter.bjornstad@childrenscolorado.org. Co-author email: Robert.Eckel@ucdenver.edu

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Conflict of Interest

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Keywords

insulin resistance; dyslipidemia; hypertriglyceridemia

Introduction

Insulin resistance (IR) is an important metabolic component of obesity, metabolic syndrome, type 2 diabetes (T2DM) and even type 1 (T1DM) and is associated with elevated risk for micro- and macrovascular complications. Whereas hyperglycemia, hypertension, kidney disease and dyslipidemia are considered the traditional risk factors of cardiovascular disease (CVD) in diabetes, there is an increasingly recognized relationship between IR and CVD even in the absence of diabetes (1–3).

Despite the substantial link between IR and CVD, the mechanism underlying this relationship remains insufficiently understood. IR is associated with changes in lipid and lipoprotein metabolism which result in atherogenic dyslipidemia and has been proposed to contribute to an increased risk of CVD (4). Beyond changes in lipid and lipoprotein metabolism, IR is also associated with changes in mean particle size for lipoproteins. For example, nuclear magnetic resonance analysis has demonstrated larger mean particle size for VLDL and smaller size for LDL and HDL in IR individuals as compared to their insulin sensitive counterparts (5). Despite abundant data supporting strong relationships between IR and dyslipidemia, it remains unclear whether IR leads to dyslipidemia or vice versa. The sequence of this relationship is further complicated by the notion that clinical and metabolic phenotypes of IR may differ by diabetes status. For example, the clinical and metabolic features of IR in people with T1DM are quite different from those characteristics in obese people with T2DM and/or metabolic syndrome.

To better understand the relationship between IR and dyslipidemia, we must define the effects of IR on lipids, lipoproteins and related enzymes, and vice versa, i.e. whether dyslipidemia impacts insulin sensitivity or vice versa.

Pathogenesis of IR and lipid metabolism (Table 1)

i **VLDL and TG metabolism—**IR plays an important role in VLDL metabolism, including effects to increase hepatic VLDL triglyceride (TG) synthesis (6, 7). The increased VLDL TG synthesis is then variably linked to increased hepatic apo B-100 production (6–8). Collectively, this results in hypertriglyceridemia, variable increases in particle number reflected by VLDL apo B-100, and lower HDL-C concentrations (8). IR is also associated with increases in hepatic triglyceride lipase (HTGL) which may result in accelerated clearance of HDL and reductions in HDL-C (9). Furthermore, HTGL activity has recently been proposed to be an important regulator of insulin clearance (10). A major factor in the mechanism of both IR and increased VLDL-TG production is an accelerated rate of lipolysis of stored TG-derived free fatty acids (FFA) from adipose tissue with resultant increases in FFA flux to the liver (11). Moreover, although insulin is an important stimulator of adipose lipoprotein lipase (LPL) (12, 13), a pathway that reflects the provision of TG-rich lipoprotein (VLDL, chylomicron)-derived FFA for adipose tissue uptake and storage, there

is a shift to the right in the insulin (ATLPL) dose response curves in IR states (14). Accordingly, IR may reduce VLDL breakdown and consequently increase hypertriglyceridemia. Moreover, decreases in skeletal muscle LPL in T2DM may also contribute to reductions in TG-rich lipoprotein TG clearance (15). In fact, the LPL gene has been proposed to be a candidate gene for IR (16), and overexpression of LPL has been shown to increase whole-body insulin sensitivity in animal models (17). Low circulating adiponectin concentrations, which may also contribute to IR, are also associated with increased VLDL production and HDL catabolism (18, 19); however these effects may occur independent of IR (18–20).

The data reviewed in the preceding paragraph suggest that IR impacts TG metabolism in a major way, but there are also studies supporting the reciprocal, i.e. that lipid accumulation results in IR. For example, there is evidence linking hepatic TG accumulation with hepatic IR (21). Moreover, increased plasma FFA are associated with IR (22, 23) through intramyocellular and intrahepatic accumulation of TG and other metabolites (24). TG is not considered a signaling lipid, and thus it is thought to be more likely that diacylglycerol, the synthetic precursor of TG, ceramide, and other lipids are implicated in the pathogenesis of hepatic IR through several mechanisms including reduced insulin receptor tyrosine kinase activity, insulin receptor destabilization and reduced insulin-stimulated glycogen synthase activity (25–28). FFA may also mediate IR through pro-inflammatory effects (29, 30).

ii Chylomicron metabolism—Chylomicrons synthesized and released by the intestine, allow transport of diet-derived TG to other tissues in the postprandial state. Whereas VLDL contains apo B-100, apo B-48, a truncated form of the holoprotein, is the exclusive apo B in chylomicrons (31, 32). In the vasculature, chylomicrons are hydrolyzed by LPL releasing their fatty acids to peripheral cells. IR-related reduction in LPL activity also influences hydrolysis of chylomicron TGs (33). This is particularly evident if excessive hepatic VLDL saturates all available LPL binding sites in the endothelium (34, 35). Adults with T2DM who demonstrate a reduced level of ATLPL activity have an exaggerated postprandial chylomicron response (36). An additional consideration is the physiological role of glucagon-like peptides in chylomicron processing and postprandial chylomicron excursion (37).

iii HDL metabolism—Insulin has important effects on HDL metabolism, and low concentrations of HDL-C are commonly observed in IR states (35, 38). IR is thought to contribute to low HDL-C concentrations by several mechanisms. First, IR is associated with increased exchange of TG from chylomicrons and VLDL for cholesterol esters from HDL particles, thus reducing HDL-C, a process regulated by cholesteryl ester transfer protein (CETP) (39). Second, decreased LPL activity results in reduced hydrolysis of TG from chylomicrons and VLDL which may further limit the contribution of TG-rich lipoprotein-derived HDL particles (35, 38). Third, increased HTGL activity in IR states is associated with enhanced HDL clearance and therefore lower concentrations of HDL-C (35, 38). Fourth, low concentrations of HDL-C may also be due to reduced synthesis and secretion of apo A-I from liver and intestine (40).

iv LDL metabolism—Compared to VLDL metabolism, IR appears to have a more modest effect on LDL metabolism. Insulin is known to upregulate LDL receptor activity (41), and administration of insulin may increase the catabolism of LDL-C with a small reduction in LDL-C, as observed in people with T1DM (42). IR may also play an important role in the metabolism of the atherogenic small dense LDL particles (43), considered but unproven to be independent biomarkers for atherosclerosis (43, 44).

IR and dyslipidemia in obesity, T2DM and metabolic syndrome

Dyslipidemia in obese individuals with T2DM and/or metabolic syndrome is characterized by elevation of TG, reduction in HDL-C, increases in apo B-100, non-HDL-C and small dense LDL and HDL. In the European Group for the Study of Insulin Resistance (EGIR), insulin sensitivity quantified by hyperinsulinemic-euglycemic clamp technique strongly correlated with TG concentrations (45). In particular, hypertriglyceridemia and low HDL-C are characteristic of metabolic syndrome, and in fact the ratio of TG/HDL-C has been used as a surrogate of IR (46–48). Low HDL-C and hypertriglyceridemia are thought to occur in up to at least 1/3 of people with metabolic syndrome (49). It is also important to appreciate that early dyslipidemia may not be evident in the fasting state. For example, people with T2DM who have a normal fasting TG and optimal glycemic control experience a greater postprandial rise in VLDL, apo B-48, apo B-100, cholesterol and TG concentrations compared with their non-diabetic peers (50).

Youth-onset T2DM is increasing in prevalence and incidence worldwide and becoming a major public health burden (51). Further, youth-onset T2DM is considered a more aggressive disease than adult-onset T2DM with more rapid deterioration in β-cell function and a greater lifetime risk for comorbidities and complications independent of diabetes duration (52, 53). Furthermore, the recently completed Restoring Insulin Secretion (RISE) Study demonstrated that youth with impaired glucose tolerance or recently diagnosed T2DM, have lower insulin sensitivity and reduced insulin clearance compared with adults (54). Consistent with worse IR, dyslipidemia is also more prevalent in youth-onset T2DM. In fact, the prevalence of dyslipidemia was reported to be 82% in 1340 people with youth-onset T2DM, which included 41% with hypercholesterolemia, 53% hypertriglyceridemia, 59% low HDL-C and 65% high LDL-C (55).

Combined Hyperlipidemia

Combined hyperlipidemia is a disorder related to increases in total cholesterol and TG, and generally associated with IR. In the MESA study, the adjusted odds of combined hyperlipidemia was greater than 2-fold higher in participants with overweight and obesity compared with normal weight individuals and greater than 4-fold higher in quartiles 2 through 4 of IR compared to quartile 1 (56). Moreover, in 26 Japanese patients with apo E2/E2 and familial dysbetalipoproteinemia, mean total cholesterol was 256 mg/dl, TG 374 mg/dl and remnant cholesterol 49 mg/dL, respectively. Because patients with apo E2/E2 who manifest the familial dysbetalipoproteinemia lipid phenotype also have other etiologies of overproduction of VLDL and TG, it is not surprising that 54% of this cohrot had T2DM, 66% metabolic syndrome and 42% coronary heart disease (57).

IR and dyslipidemia in T1DM

Using gold-standard techniques, we and others have clearly demonstrated that IR is a prominent feature of T1DM in adolescents (58, 59) and adults (60) with T1DM. This IR in T1DM occurs irrespective of obesity and metabolic syndrome features (58, 61–63). Moreover, IR confers higher risk for a more atherogenic lipoprotein profile (64, 65) and micro- and macrovascular complications in T1DM youth (66) and adults (67, 68).

The classic diabetic dyslipidemia characterized by elevated TG, small dense LDL and low HDL-C (69), is seldom observed in modern cohorts of adults with T1DM. In fact, adults with T1DM have lipid values typically similar to or better than their non-diabetic peers, with lower total cholesterol, LDL-C, TG and even higher levels of HDL-C (70). However, data in youth with T1DM demonstrate higher prevalence of dyslipidemia (71). For example, the Diabetes-Patienten-Verlaufsdokumentation (DPV) registry reported hypercholesterolemia in 29% of youth with T1DM (72, 73), and T1DM Exchange data demonstrated elevated LDL-C in 28% of youth with T1DM with suboptimal glycemic control (74). The higher prevalence of dyslipidemia in youth compared to adults with T1DM is likely attributable to worse glycemic control, higher rates of obesity (75) and lower insulin sensitivity in adolescents (76, 77).

Despite having lipid concentrations comparable to adults without diabetes, people with T1DM are afflicted by increased risk of atherosclerotic CVD (ASCVD) (78–83), which is at least partially attributed to an increased atherogenic lipid profile, independent of LDL-C concentration (81, 84, 85). Possible mechanisms for the increased atherogenic lipid profile of T1DM include differences in lipoprotein particle size, lipoprotein subfraction cholesterol distribution, LDL-C oxidation, COX2 expression, inflammatory response to lipids and increased transvascular and macrophage lipid transport, in addition to variably greater concentrations of lipoprotein(a) (Lp(a)), apo B-100 and non-HDL-C in patients with T1DM (65, 86–89).

While people with T1DM and T2DM are at greater risk of ASCVD events and death from ASCVD compared to the general population, it is important to acknowledge that the pathophysiology underlying ASCVD may differ in T1DM vs T2DM. In fact, the atherosclerotic plaques in T1DM are thought to have different features than those found in T2DM, including softer, less lipid-laden and more concentric plaques associated with greater calcification and inflammation (90–95).

Insulin sensitizers and dyslipidemia

Insulin sensitizers are proposed to improve lipid and lipoprotein metabolism by several potential mechanisms including inhibition of both intestinal and hepatic sterol regulatory element-binding protein-1c (SREBP-1c), thereby decreasing the synthesis of TG-rich lipoproteins (96–100). While effects of metformin on lipid metabolism are generally modest, multiple mechanisms may contribute; these include metformin-mediated changes in the microbiome associated with reduced lipid absorption (101, 102), inhibition of bile acid absorption with resultant increases in LDL receptor-mediated LDL clearance (103, 104) and

reduced phosphorylation of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) via AMPK activation (105, 106).

i Insulin sensitizers and dyslipidemia in T1DM—There have been a few trials of insulin sensitizers in youth and adults with T1DM with lipid lowering as secondary outcomes. The REducing with MetfOrmin Vascular Adverse Lesions in T1DM (REMOVAL) study of adults with T1DM did not show reduction in LDL-C following 3 years of metformin therapy (107). A randomized controlled trial in youth with T1DM (8–18 years) by Anderson et al. found no significant effect of 12 months of metformin therapy on LDL-C, HDL-C, total cholesterol, TG or adiponectin (108). Another randomized control trial in overweight/obese youth with T1DM demonstrated no change in LDL-C, HDL-C VLDL-C, TG and total cholesterol with 26 weeks of metformin therapy in youth with T1DM (109, 110). Consistently with these data, we recently demonstrated in the Effects of MEtformin on CardiovasculaR Function in AdoLescents with Type 1 Diabetes (EMERALD) Study that 3 months of metformin therapy did not change LDL-C, HDL-C, TG and total cholesterol in youth with T1DM (111).

ii Insulin sensitizers and dyslipidemia in T2DM—The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, a multicenter randomized controlled trial in youth-onset T2DM did not report significant changes in total cholesterol, LDL-C, HDL-C or TG across 3 treatment arms: metformin, metformin + rosiglitazone or metformin and lifestyle (112). In contrast, in a more recent clinical trial in newly diagnosed adults with T2DM, participants were classified into two groups following 3 months of metformin therapy: responders (HbA1c reduction >= 1% from baseline) and non-responders. All participants received atorvastatin, gemfibrozil or atorvastatin and gemfibrozil daily. Responders experienced a greater decrease in LDL-C to HDL-C ratio, and total cholesterol to HDL-C ratio compared to non-responders, which may suggest that response to metformin therapy may influence therapeutic outcomes of atorvastatin on atherogenic lipid markers (113). Finally, a metabolic analysis in the population-based KORA cohort, demonstrated that metformin therapy was associated with lower concentrations of three acyl-alkyl PCs and LDL-C likely due to AMPK activation (114).

Conclusion

IR adversely affects lipid and lipoprotein metabolism and is strongly associated with dyslipidemia. The mechanisms by which IR influences lipid metabolism are complex and may depend on the disease state associated with the IR, i.e. obesity, metabolic syndrome, T2DM and T1DM. The relationship between IR and dyslipidemia is likely reciprocal and the direction of the causality remains incompletely defined. Data suggest that there are different phenotypes of IR in T1DM vs. T2DM, and an understanding of how these metabolic phenotypes influence lipid metabolism is needed to better target diabetic dyslipidemia and prevent ASCVD. Accordingly, carefully designed mechanistic human studies are needed to advance our understanding of how different phenotypes of IR impact dyslipidemia and ASCVD risk.

References:

Papers of particular interest, published recently, have been highlighted as:

• Of importance

24: Thorough mini-review on IR and dyslipidemia

51: Registry data reporting dyslipidemia in youth with T1DM

•• Of major importance:

13: One of the first studies using a hyperinsulinemic-euglycemic clamp to study metabolism of lipids and lipoproteins.

58 and 60: Translational studies demonstrating reduced insulin sensitivity in youth and adults with T1DM by hyperinsulinemic-euglycemic clamp technique

95: Randomized control trial with metformin in adults with T1DM demonstrating no effect on dyslipidemia

109: Randomized control trial with metformin in youth with T1DM demonstrating no effect on dyslipidemia

112: Randomized control trial with metformin, rosiglitazone and lifestyle changes in youth with T2DM demonstrating no effect on dyslipidemia

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Table 1

Impact of IR on Lipids and Lipoproteins

	Change in Lipids in IR	Proposed Mechanisms	Ref.
VLDL-C and TG	↑ VLDL-C and TG	↑ Hepatic VLDL TG synthesis ↑ HTGL ↓ LPL	(10-13)
Chylomicron	↑ Chylomicrons (especially postprandial)	↓ LPL	(30-34)
HDL-C	↓ HDL-C	↑ Exchange of TG from chylomicrons and VLDL for cholesterol esters from HDL particles ↑ HTGL ↓ LPL	(35-39)
LDL-C	↑ LDL-C	↓ LDL-receptor activity	(40-43)