



# Role of the Gut in Diabetic Dyslipidemia

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Type 2 diabetes (T2D) is associated with increased risk of cardiovascular disease (CVD). In insulin resistant states such as the metabolic syndrome, overproduction and impaired clearance of liver-derived very-low-density lipoproteins and gut-derived chylomicrons (CMs) contribute to hypertriglyceridemia and elevated atherogenic remnant lipoproteins. Although ingested fat is the major stimulus of CM secretion, intestinal lipid handling and ultimately CM secretory rate is determined by numerous additional regulatory inputs including nutrients, hormones and neural signals that fine tune CM secretion during fasted and fed states. Insulin resistance and T2D represent perturbed metabolic states in which intestinal sensitivity to key regulatory hormones such as insulin, leptin and glucagon-like peptide-1 (GLP-1) may be altered, contributing to increased CM secretion. In this review, we describe the evidence from human and animal models demonstrating increased CM secretion in insulin resistance and T2D and discuss the molecular mechanisms underlying these effects. Several novel compounds are in various stages of preclinical and clinical investigation to modulate intestinal CM synthesis and secretion. Their efficacy, safety and therapeutic utility are discussed. Similarly, the effects of currently approved lipid modulating therapies such as statins, ezetimibe, fibrates, and PCSK9 inhibitors on intestinal CM production are discussed. The intricacies of intestinal CM production are an active area of research that may yield novel therapies to prevent atherosclerotic CVD in insulin resistance and T2D.

**Keywords:** intestine, chylomicron, Enteroendocrine, lipoprotein, diabetes

## INTRODUCTION

Atherogenic dyslipidemia is characterized by hypertriglyceridemia, elevated small, dense LDL particles, reduced HDL, elevated remnant lipoproteins and postprandial hyperlipidemia (1). This complex of lipid abnormalities is associated with underlying insulin resistance (IR) and has an increased prevalence in type 2 diabetes (T2D). The exaggerated postprandial lipemia in individuals with T2D or IR is attributed to elevated liver- and intestine- derived triglyceride-rich lipoproteins (TRL) due to decreased lipoprotein clearance and/or increased secretion. Intestinally-derived chylomicron (CM) particles can be quantified by the presence of an apolipoprotein B48 (apoB48) singularly present on each particle. ApoB48 is detected in atherosclerotic plaque demonstrating that CM remnants can penetrate the endothelium and contribute to lesion formation (2).

Dysregulation of TRL clearance from the circulation has been extensively reviewed elsewhere (3) and will not be the focus of this review. However, it is important to note that postprandial accumulation of lipoproteins and lipoprotein remnants is largely influenced by clearance capacity (4). CMs and liver-derived very-low-density lipoproteins (VLDL) compete for delipidation by

lipoprotein lipase (LPL) and for subsequent saturable hepatic remnant removal (5, 6). In IR, lipoprotein clearance is diminished, in part due to decreased LPL activity, altered lipoprotein composition, reduced hepatic clearance and remnant removal or increased TRL pool size resulting in more competition for clearance (7). In addition, insulin mediated activation of LDLR-related protein-1 which is involved in CM remnant clearance is blunted in insulin-resistant mice (8). Although clearance is an important factor to consider in diabetic dyslipidemia, this review will focus on our current understanding of CM production by the gut in IR states and T2D. We will discuss how existing therapeutic strategies targeting dyslipidemia influence CM secretion and the potential utility of novel therapeutics to specifically reduce CM production. We acknowledge that few studies have examined intestinal lipoprotein secretion in diabetic animal models and humans; therefore at the present time we extrapolate from healthy and insulin resistant animal models and humans, with the understanding that our knowledge of intestinal lipoprotein secretion in diabetes is far from complete and will undoubtedly require revision as our knowledge expands.

## PHYSIOLOGICAL INTESTINAL LIPID HANDLING AND CM SECRETION

To understand the role of the intestine in diabetic dyslipidemia, we will briefly review normal lipid processing by the gut, which has been extensively reviewed elsewhere (9, 10). Dietary triglycerides (TGs) are hydrolyzed to monoacylglycerol (MAG) and fatty acids (FAs) in the intestinal lumen. Several putative FA transporters have been identified including CD36/FAT. FA binding proteins (FABP) such as I-FABP and L-FABP are involved in intracellular FA transport (9).

Re-esterification occurs primarily by the monoacylglycerol pathway through sequential esterification by monoacylglycerol acyltransferase (MGAT) and diacylglycerol acyltransferase (DGAT) between the leaflets of the endoplasmic reticulum (ER) membrane (11). This pathway contributes the majority of TG for CM synthesis while *de novo* lipogenesis (DNL) and the glycerol phosphate pathway are additional contributors. TGs enter the ER lumen to fuse with lipid-poor apoB48-containing particles to form prechylomicrons, which also contain cholesteryl esters and acquire apolipoprotein AIV (apoAIV) (12). This

**Abbreviations:** CM, chylomicron; CVD, cardiovascular disease; DGAT, diacylglycerol acyltransferase; DNL, *de novo* lipogenesis; ER, endoplasmic reticulum; FA, fatty acid; FABP, fatty acid binding protein; FAT/CD36, fatty acid translocase/cluster of differentiation 36; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; HoFH, homozygous familial hypercholesterolemia; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance; LPL, lipoprotein lipase; MAG, monoacylglycerol; MAPK, mitogen-activated protein kinase; MGAT, monoacylglycerol acyltransferase; MTP, microsomal triglyceride transfer protein; NPC1L1, Niemann-Pick C1-like 1 protein; PCSK9, proprotein convertase subtilisin/kexin type; PPAR $\alpha$ , peroxisome proliferator-activated receptor alpha; SGLT, Sodium-glucose co-transporter; SNARE, soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptors; SREBP, sterol regulatory element binding protein; T2D, type 2 diabetes; TG, triglyceride; TRL, triglyceride-rich lipoprotein; VLDL, very-low density lipoprotein.

lipidation process is mediated by microsomal triglyceride transfer protein (MTP). Prechylomicrons are transported to the Golgi in prechylomicron transport vesicles with fusion occurring at the Golgi facilitated by various SNARE proteins. Mature CMs are subsequently exocytosed at the basolateral membrane, each containing a single apoB48 along with apoAI and apoAIV. During active lipid absorption the basement membrane underlying enterocytes may become leaky to facilitate movement of CMs into the lamina propria (13, 14). Large porous junctions in lacteals allow CMs to enter the lymphatic vasculature for eventual delivery to the circulation. Rather than serving as a passive conduit, lacteals and lymphatic ducts are gaining attention as active regulatory sites in CM transport (15). As CMs circulate, interactions with other lipoproteins facilitate the exchange of apolipoproteins allowing CM particles to acquire apoE, apoC2, and apoC3, which regulate hepatic CM removal and delipidation by LPL (16).

Although the absorption of dietary TG is highly efficient, not all TGs are immediately released from enterocytes. Following re-esterification at the ER, a portion of TGs bud off the ER membrane into the cytosolic space to form cytosolic lipid droplets (CLDs), which serve as transient lipid storage pools within enterocytes. CLDs and other enteral lipid stores are evident in human intestinal tissue for many hours after a meal and can be mobilized by a number of stimuli (17–19). Several factors including dietary macronutrient load, circulating FA, glucose, insulin, and gut hormones glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) have been identified as key players in the complex fine tuning of CM appearance in the early prandial phase as well as in mediating CLD mobilization several hours after a meal (9, 15). Interestingly, the co-secreted gut hormones GLP-1 and GLP-2 have opposing effects on CM secretion, with GLP-1 inhibiting and GLP-2 promoting appearance of apoB48 lipoproteins. Enterocytes do not express receptors to either GLP-1 or GLP-2, therefore their modulation of CM secretion is through indirect mechanisms that remain to be fully elucidated (20).

## INCREASED CM PRODUCTION IN PREDIABETIC, INSULIN RESISTANT STATES

Prevalence of unfavorable postprandial hypertriglyceridemia (postprandial TG > 220 mg/dl) increases progressively from non-diabetic to prediabetic to T2D states in humans and was linked to increasing severity of hepatic IR (21). Both increased CM production and decreased clearance have been observed in insulin resistant states (1). We previously demonstrated increased production rate of apoB48-containing TRLs in insulin resistant humans (22, 23). Couture et al. demonstrated a 102% increase in TRL-apoB48 pool size and 87% increase in production rate in IR compared to insulin sensitive obese men in the fed state (23). A trend toward decreased apoB48 clearance rate was observed but did not reach statistical significance, while VLDL apoB-100 clearance was significantly reduced (23). When quantifying TG rather than apoB48 kinetics, men with metabolic

syndrome had elevated fed-state VLDL-TG and CM-TG due to increased production rates (24). Decreased CM clearance has also been observed in conditions of obesity and T2D, contributing to the elevated TRL concentrations in these states (25–27). In contrast to the increased secretion of CM that characterizes IR, which is usually also accompanied by chronic hyperinsulinemia, in the experimental hyperinsulinemic-euglycemic clamp setting, acute hyperinsulinemia suppresses CM secretion in healthy humans directly and in part by suppressing circulating FA (28). In animal models, intestinal IR can be elicited by high-fat (29) or high-fructose feeding (30, 31). A single oral bolus of palmitate in mice is sufficient to impair insulin suppression of CM production, possibly via ceramide-mediated inhibition of Akt signaling (32). This is consistent with ceramide inhibition of insulin signaling in muscle, liver and adipose. Therefore, despite the rapid turnover of enterocytes *in vivo*, persistent overnutrition including increased consumption of saturated FAs, may induce intestinal IR, with one possible mechanism being increased ceramide production. Indeed, plasma and tissue ceramide are elevated in humans in IR and T2D and upon excess saturated fat intake (33). From animal models it is apparent that intestinal IR increases CM synthesis with increased expression and activity of key proteins involved in lipogenesis and CM secretion, namely MTP, MGAT, DGAT, apoAIV, and sar 1 GTP ase (30, 34). The consequences of impaired intestinal insulin sensitivity are increased DNL, excess CM production and secretion (31, 35).

In accordance with animal models, humans with severe IR or diabetes have elevated intestinal MTP expression and protein abundance compared to more insulin sensitive individuals (36, 37). Individuals undergoing bariatric surgery who are markedly insulin resistant (HOMA-IR > 7) had decreased duodenal insulin signaling capacity as indicated by decreased phosphoAKT abundance and higher p38 MAPK compared to obese, more insulin sensitive patients (HOMA-IR < 3) (36). The insulin resistance was postulated to be caused by greater oxidative stress and inflammation, increased markers of which were observed in the diabetic duodenum. This perturbed metabolic state may be causal to the increased DNL and apoB48 biogenesis in IR (36). In contrast, when assessed in humans with modest IR, key intestinal genes involved in FA transport, and lipid/lipoprotein metabolism including SREBP-2, MTP, and DGAT2 were downregulated (23). In particular, the observed 25% decrease in MTP protein is intriguing in light of increased CM production rate in the same subjects. To address this discrepancy, the authors postulated that in modest IR states hyperinsulinemia may suppress MTP expression via the insulin responsive element of the MTP promoter region. In contrast, relative insulin insufficiency in T2D may allow for greater MTP expression (23). We speculate that in modest IR with normoglycemia total efficacy of insulin modulation of lipid metabolism may be fully intact whereas more severe IR insulin modulation of lipid metabolism may be significantly impaired leading to altered lipid metabolism. In both states, modest and severe IR, adipose IR increases circulating FA which may serve as substrates for intestinal CM synthesis and thus adaptive suppression of enterocyte DNL and fat absorption may occur (23, 38). Indeed, men with metabolic syndrome had a greater contribution to CM-TG from non-oral

FA than lean controls (24). Sources of non-oral FA may include circulating FA, pre-existing TG stores (e.g., enterocyte CLDs), or TG arising from DNL (24).

In the postprandial state, enteroendocrine L-cells lining the intestine secrete GLP-1 and GLP-2 in equimolar amounts in response to nutrients (39). GLP-1 has diverse physiological roles, including potentiation of glucose-stimulated insulin secretion, appetite suppression and inhibition of gastric emptying (40). In contrast, GLP-2 acts as an intestinotrophic hormone, stimulating intestinal proliferation and aiding in intestinal repair processes. Despite equimolar secretion, GLP-1 and GLP-2 have opposing effects on CM secretion. In animal models, intravenous GLP-1 reduced postprandial apoB48 and TG concentrations (41). In Phase 2/3 clinical assessments, GLP-1 analogs lower CM production in healthy humans whereas (42) pharmacological doses of GLP-2 robustly stimulate CM secretion in human and animal models (43–46). In normal, insulin sensitive states and in fructose-fed hamsters the effects of GLP-2 predominate with elevated postprandial lipemia (41).

High-fat feeding to induce IR in mice also induces leptin resistance as evidenced by a loss of the inhibitory effect of leptin on food intake (47). Leptin resistant animals have decreased glucose-stimulated GLP-1 secretion and fasted GLP-1 (47), suggesting leptin resistance may contribute to impaired GLP-1 secretion in obese humans. GLP-1 reduces postprandial apoB48 and TG (41, 42), therefore impaired GLP-1 secretion due to leptin resistance could be a contributing factor to elevated CM secretion. Leptin is classically described as an important satiety signal produced by the expanding adipocyte in the setting of net positive energy balance. Leptin is also secreted to a lesser extent from the gastric mucosa into the gastric lumen and circulation. Gastric leptin partially escapes hydrolysis and enters the intestinal lumen to bind the leptin receptor expressed on the luminal side of intestinal epithelial cells (48). Jejunal infused leptin has been shown to regulate intestinal MTP in the mouse independently of vagal innervation (49). In this regard, gastric leptin secretion in the early prandial phase may be important for regulating CM production and leptin resistance may be another contributing factor to increased CM production in IR states.

## DYSREGULATION OF INTESTINAL LIPOPROTEIN METABOLISM IN TYPE 2 DIABETES

IR is a prominent feature of T2D, accompanied by relative or absolute pancreatic insulin secretory insufficiency resulting in hyperglycemia, with plasma insulin concentrations ranging from elevated to low. Much of the above discussion of abnormal intestinal lipoprotein metabolism in IR therefore also pertains to those with T2D. In fact in patients with T2D, the acute inhibitory effect of insulin on apoB48 production is blunted (50). Similarly, the stimulatory effect of insulin on intestinal glucose uptake in obese subjects is diminished, although this was improved by bariatric surgery (51). In obese subjects with T2D, fasting and postprandial TGs were significantly reduced 2 weeks after bariatric surgery. Most importantly,

the incremental area under the curve of postprandial plasma TGs decreased by 60% compared to pre-surgery (52). In a detailed study involving kinetic assessment in the constant fed state in obese, non-diabetic humans, TRL-apoB48 concentration was significantly reduced, with a reduction in TRL-apoB48 when assessed 6 months post-sleeve gastrectomy compared to before surgery (53). While reduced dietary intake likely contributes to reduced TG post-surgery, this may also be partially mediated by improved intestinal function perhaps by restored intestinal insulin sensitivity. In addition, hyperchylomicronemia in diabetic dyslipidemia may be further exasperated by blunted insulin suppression of hepatic apoB100 production (50, 54), increasing competition for clearance and thereby increasing plasma retention time.

Hyperglycemia itself may further enhance CM secretion in the diabetic state. In healthy, non-diabetic adults, we have shown enhanced apoB48 production in response to intraduodenal and intravenous glucose, and in response to intraduodenal fructose (55, 56). Whether hyperglycemia in diabetes contributes directly to enhanced CM secretion is unknown.

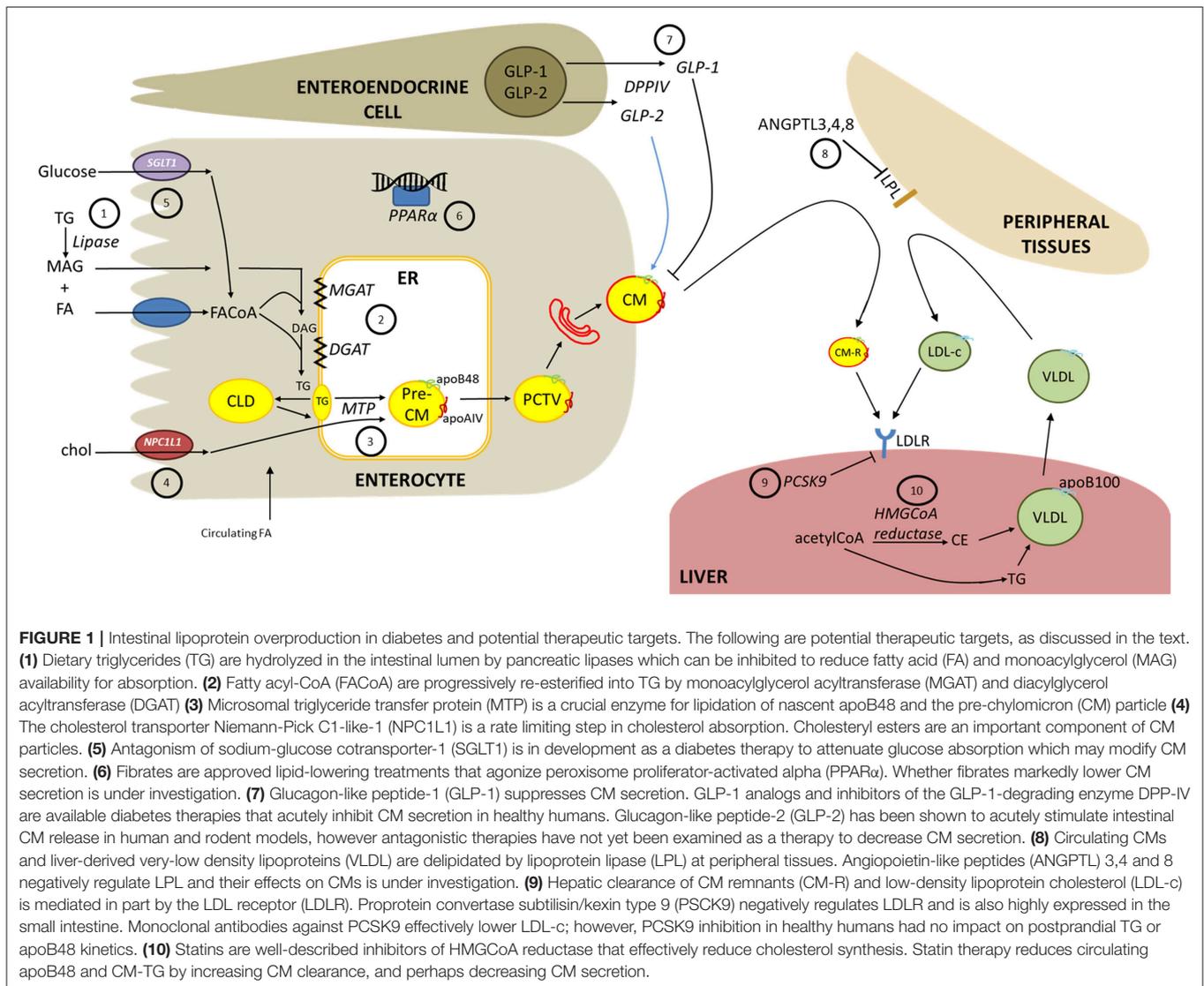
In addition to competition for clearance, altered CM apolipoprotein composition in diabetes may also contribute to delayed clearance and increased atherosclerotic risk in T2D. In animal models, CMs originating from diabetic animals are cleared more slowly than those from non-diabetic animals, possibly due to reduced apoE abundance on the CM particle (57). ApoAIV is produced primarily in the intestine in response to an oral lipid load and is increased in the circulation in IR (58). Increased plasma apoAIV has been observed association with hypertriglyceridemia in patients with T2D (59). In the circulation a portion of apoAIV associates with HDL or circulates lipid-free to influence glucose and lipid metabolism. Glycation of apoAIV in circulation is associated with coronary artery disease severity in patients with T2D (60). The extent to which alterations in apoAIV production by the intestine influence postprandial metabolism in T2D remains to be fully elucidated. ApoAIV knockout mice secrete larger CMs into the lymph (12) and thus altered apoAIV production may influence the rate of delipidation through alterations in CM size as larger CMs are lipolyzed at a faster rate than smaller particles in animal models (61, 62). The multitude of metabolic functions of apoAIV are an active area of research that may improve our understanding of the regulation of intestinal apoAIV production and its influence on lipoprotein clearance in metabolic disease (63).

## EFFECTS OF CURRENTLY APPROVED LIPID MODIFYING AND ANTIDIABETIC THERAPIES ON GUT LIPID HANDLING IN INSULIN RESISTANT STATES AND DIABETES

Statin treatment is effective in primary (64) and secondary (65) CV event prevention in patients with T2D. The effects of statin treatment on CV events reduction show a linear relationship between CV events reduction and LDL-c reduction suggesting that a possible effect of statin on CM secretion is likely to

be a minor factor of the anti-atherosclerotic benefits of the statins. However, it is interesting to note that statins also have minor effects in modulating intestinal lipoproteins (Figure 1, #10). Four weeks of cerivastatin therapy significantly decreased postprandial CM apoB48 in patients with T2D (66). Similarly, 6 weeks of atorvastatin treatment in obese men significantly reduced circulating apoB48 and remnant-like particle cholesterol following remnant-like emulsion infusion, perhaps due to increased hepatic clearance (67). Atorvastatin treatment in healthy, normolipidemic men decreased postprandial apoB48 by increasing clearance and decreasing secretion after a fat load (68). Statin-mediated inhibition of cholesterol synthesis induced compensatory increases in cholesterol absorption by increasing intestinal expression of Niemann-Pick C1-like 1 protein (NPC1L1) (69). Therefore, a common add-on therapy to statin is ezetimibe which inhibits NPC1L1 (Figure 1, #4). In patients with T2D, compared to simvastatin alone, adding ezetimibe produced significantly fewer CMs that were cholesterol-poor and decreased fasting and postprandial CM-TG (70). Similarly, when patients with T2D failed to reach LDL-c targets on simvastatin alone, addition of ezetimibe improved lipoprotein profile (71). Over and above the well-documented effects of statins in upregulating LDL-receptor-mediated clearance of LDL particles from the circulation, statin therapy may also exert some of its benefits through improved metabolism of postprandial lipoproteins including apoB48 CM remnants.

Fibrates are an alternative lipid-lowering option for the treatment of dyslipidemia; however, their questionable cardiovascular benefit limits their widespread use (72, 73). The transcription factor PPAR $\alpha$  is highly expressed in the intestine and is activated by several natural ligands, particularly polyunsaturated FAs (74) (Figure 1, #6). It regulates the expression of several apolipoproteins and genes involved in FA metabolism including the transcription factor sterol regulatory element binding protein-1c (SREBP-1c) (74). Recently, a more potent and selective PPAR $\alpha$  agonist called pemafibrate (K-877) has been developed that lowers plasma TG to a similar extent as fenofibrate but with minimal adverse events (75, 76). In a phase III trial, 52 weeks of pemafibrate treatment reduced fasting TG by 45% compared to placebo in patients with T2D (77). Notably, pemafibrate significantly decreased apoB48 by up to 56% (77). This could be due to decreased CM production and/or increased clearance. In mice, pemafibrate decreased small intestine expression of apoB to a greater extent than fenofibrate while eliciting no change in hepatic apoB expression (78). In LDL receptor knockout mice, pemafibrate decreased apoC3 expression and increased plasma LPL activity suggesting increased clearance capacity (79). Similarly, Araki et al. observed decreased plasma apoC3 in patients with T2D treated with pemafibrate (77). These studies suggest that pemafibrate could effectively modulate CM production to treat diabetic dyslipidemia. The ongoing Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study will evaluate major adverse cardiovascular events in T2D with suboptimal LDL-c lowering by statins (NCT03071692) (80).



Proprotein convertase subtilisin/kexin type 9 (PCSK9) is highly expressed in the liver, kidney, and small intestine and negatively regulates cell surface receptors, decreasing LDLR in liver and intestine leading to blunted hepatic TRL clearance (81) (Figure 1, #9). PCSK9 inhibition by monoclonal antibodies is an effective therapeutic strategy shown to lower LDL-c. PCSK9 knockout animals show decreased intestinal apoB output with no difference in lymphatic TG output suggesting an increase in CM size (82). This effect may be mediated by increased MTP abundance (83). Kinetic studies in healthy humans have shown increased clearance and decreased production of LDL-apoB; however, there was no impact on postprandial TG or apoB48 kinetics with evolocumab or alirocumab treatment (68, 84).

A discussion about diabetes therapies would be incomplete without considering the effects of some glucose lowering, antidiabetic therapies on intestinal lipoprotein metabolism.

Metformin, for example, accumulates in jejunal mucosa in humans and thus is likely to regulate metabolic processes of enterocytes (85). The observation that intravenous metformin does not improve glycemia to the same extent as oral metformin further supports a crucial role for the intestine as a site of metformin action (86). In patients with T2D poorly controlled by sulfonylureas, the addition of metformin significantly improved glycemic control and halved postprandial CMs and CM remnants (87). Metformin treatment in morbidly obese T2D patients decreased jejunal expression of SREBP-1c, acetyl-coA carboxylase involved in FA synthesis, and apoAIV involved in CM secretion, suggesting attenuation of DNL and lipoprotein synthesis by metformin (58). Metformin may indirectly attenuate CM secretion through increased production of GLP-1 or by delayed gastric emptying. Metformin increased fasting GLP-1 in patients with T2D (88, 89) potentially by modulating bile acid pools (88). Interestingly, timing of metformin delivery

may alter TG responses as pre-meal metformin decreased postprandial TG to a greater extent than post-meal delivery in patients with T2D and increased satiety with no difference in GLP-1 (90).

GLP-1 receptor agonists are known to lower postprandial TG. A reduction in postprandial TRL-apoB48 has been demonstrated in humans with T2D and in animal models and may occur independently of plasma insulin and gastric emptying (91, 92) (**Figure 1**, #7). In healthy humans, TRL particle kinetics were evaluated in the fed state with continuous duodenal liquid meal infusion and a pancreatic clamp to avoid confounding effects of gastric emptying and the effects of other hormones such as insulin and glucagon. This revealed that a single dose of exenatide acutely decreased apoB48 production rate with no effect on catabolism (42). We have previously reviewed the effects of incretin therapies on intestinal lipoprotein metabolism (93). When CM-TG kinetics were assessed in patients with T2D, lixisenatide reduced CM-TG appearance after a single meal likely via delayed gastric emptying (94, 95). However, over the course of a 12-h feeding protocol lixisenatide reduced CM-TG through increased clearance with no effect on production rate (95). Following 6 months of liraglutide treatment in T2D, apoB48 production was significantly decreased and clearance was increased (96). Incubating jejunal explants from mice with liraglutide reduced expression of key CM synthesis genes including apoB48, DGAT1, and MTP (96). Similarly, exenatide suppressed apoB48 expression in hamster enterocytes suggesting direct effects of GLP-1 receptor signaling on CM synthesis (92). GLP-1 agonists improve CVD outcomes in T2D (97, 98), perhaps in part by modulating intestinal CM production.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, which enhance urinary glucose secretion, are approved therapeutics in T2D. Recently, cardiovascular outcome trials showed improvements in CV outcomes in response to dapagliflozin (99), canagliflozin (100) and empagliflozin (101) in patients with T2D. The underlying mechanisms of CV protection are unclear. Three month canagliflozin treatment in T2D did not alter LDL-c or CM-c but increased HDL-c (102). Canagliflozin treatment at clinical doses modestly and transiently inhibits intestinal SGLT1, an important glucose transporter on the luminal side of enterocytes (103, 104) (**Figure 1**, #5). In humans, canagliflozin increased postprandial GLP-1 and peptide YY (PYY) (104), perhaps by increasing glucose delivery to the distal gut which has a higher density of incretin producing cells. In accordance with this, acarbose treatment which inhibits alpha glucosidase increases carbohydrate delivery to the distal gut and increases GLP-1 secretion (105). Similarly, specific SGLT1 inhibition in humans delayed intestinal glucose absorption and reduced GIP secretion while increasing GLP-1 and PYY secretion (106). Theoretically, SGLT1 inhibition could blunt early post-meal intestinal CM secretion by decreased glucose availability for DNL or by increased GLP-1-mediated inhibition of CM secretion, however gut DNL is likely a minor contributor to CM-TG. Dual inhibitor compounds targeting both SGLT2 and SGLT1 are under development, with pilot studies showing improved postprandial glucose control (107).

Combining this dual antagonist with the DPPIV inhibitor sitagliptin further increased active GLP-1 and PYY in patients with T2D (108). Therefore, SGLT1 inhibition may serve as a novel therapeutic strategy in T2D with potential indirect benefits on CM secretion.

## NOVEL THERAPIES TARGETING THE GUT FOR THE TREATMENT OF DIABETIC DYSLIPIDEMIA

Advances in our understanding of the intricacies of intestinal lipid handling and CM secretion as well as the atherogenic nature of CM remnant particles has led to the search for therapies to modify various aspects of CM production to ameliorate diabetic dyslipidemia. Beginning in the intestinal lumen, inhibition of gastric and pancreatic lipases by the drug orlistat (**Figure 1**, #1) developed for the treatment of obesity decreases intestinal TG absorption by 30% but adverse gastrointestinal (GI) effects were observed in 16–40% of patients (109). In T2D, orlistat significantly decreased TG and apoB compared to placebo (110). However, when given in combination with metformin improvements were observed in total cholesterol, LDL cholesterol and the LDL:HDL ratio but not in TG (111). Due to the relatively high incidence of adverse events and inconsistent efficacy, orlistat is not considered to be an effective therapy for treatment of diabetic dyslipidemia.

Inhibition of intestinal TG esterification is another avenue of active research to improve diabetic dyslipidemia (**Figure 1**, #2). Three isoforms of MGAT have been identified in humans and rodents. MGAT2 is highly expressed in the intestine of rodents and humans while MGAT3 is expressed only in the human intestine (112). Selective MGAT2 inhibition by orally administered small molecule inhibitor dose-dependently decreased postprandial CM-TG by up to 58% in mice (113). MGAT2 inhibition showed a similar phenotype to MGAT2 knockout and did not increase fecal fat suggesting no impact on fat absorption. Inhibition of TG re-esterification diverted FA toward beta oxidation in the small intestine (113). Human MGAT inhibitors have been identified by high-throughput screening methods (114), but it remains to be seen whether MGAT inhibition is efficacious and well-tolerated in humans and whether it has utility in treating diabetic dyslipidemia. Downstream of MGAT-mediated formation of diacylglycerol is DGAT, which catalyzes the final step in TG esterification. DGAT inhibition has been explored in human and animal models. Intestinal DGAT1 deficiency and pharmacological inhibition in mice decreased postprandial TG with delayed gastric emptying and inhibited CM secretion (115). Delayed gastric emptying may be attributable to increased GLP-1 secretion (116, 117). In humans, DGAT1 inhibition with pradigistat in patients with familial chylomicronemia syndrome decreased fasting TG primarily by decreasing CM-TG (118). However, adverse GI effects such as diarrhea were experienced by the majority of participants (118, 119). This is perhaps not surprising given that loss-of-function variants in DGAT1 are linked to

congenital diarrheal disorder (120). In patients with T2D, pradigistat dose-dependently decreased total cholesterol, TG, LDL-c, and body weight (121). Other DGAT1 inhibitory compounds have been investigated. Single administration of the selective DGAT1 inhibitor PF-04620110 dose-dependently decreased postprandial TG in healthy humans (122). Grape extract contains components that decrease DGAT1 activity *in vitro* and was shown to reduce serum TG without GI side effects in overweight/obese but otherwise healthy humans after a high-fat meal (123). Structural changes to DGAT1 inhibitors or further development of DGAT1 antisense oligonucleotides may yield novel therapeutics that reduce postprandial TG without GI intolerance (124–126).

The MTP inhibitor lomitapide has been approved for a number of years for the treatment of homozygous familial hypercholesterolemia (HoFH) and has been used off label for the treatment of severe hypertriglyceridemia (127, 128). Lomitapide use is severely curtailed by side effects of diarrhea and liver fat accumulation (129). Intestine-specific MTP inhibition (**Figure 1**, #3) lowers CM secretion without affecting hepatic lipoprotein production and thereby minimizing hepatotoxicity and hepatosteatosis. In hamsters, the small molecule intestine-specific MTP inhibitor JTT-130 suppressed CM-TG following oil gavage without suppressing hepatic TG secretion. Importantly, repeated dosing for 2 weeks did not induce hepatotoxicity (130). However, hamsters treated with JTT-130 show impaired FA absorption with increased fecal FA and cholesterol content suggesting diarrhea may still be a complication of intestine specific MTP inhibition (131). In rats and apoE<sup>-/-</sup> mice, the small molecule inhibitor SLx-4090 specifically inhibited CM secretion with no effect on hepatic TG secretion and effectively reduced postprandial lipids (132, 133). Similarly in Caco-2 cells, SLx-4090 decreased apoB secretion (132). Preliminary reports of a phase 2 clinical trial (NCT00871936) SLx-4090 given to patients with T2D on metformin demonstrated 35% decreases in both postprandial TG and FA, compared to placebo (134). MTP inhibitors are not currently approved for use in T2D and for the foreseeable future will likely serve as orphan drugs for the treatment of HoFH or severe hypertriglyceridemia.

Novel therapeutics for atherogenic dyslipidemia are emerging; however, their effects on intestinal lipoprotein secretion require further investigation. Apolipoprotein C-III (apoC3) is found on VLDL and CMs and inhibits LPL- and LDL receptor- mediated TRL and remnant clearance (135, 136). In humans, apoC3 is elevated in hyperlipidemia and T2D, thereby increasing plasma residence time of TRLs and their remnants. ApoC3 is an independent risk factor for CVD (137, 138). In patients with familial chylomicronemia syndrome due to homozygous or compound heterozygous *LPL* deficiency, the apoC3 antisense oligonucleotide (ASO) volanesorsen decreased CM-TG and apoB48 suggesting non-LPL mediated clearance (139). Interestingly, while apoC3 is known to increase hepatic VLDL secretion (140, 141), whole-body overexpression of human apoC3 in mice decreased dietary TG appearance in lymph, decreased FA absorption and

re-esterification, suggesting intestinal apoC3 inhibition might enhance CM appearance (142). However, apoC3 inhibition by ASO decreased fasting and postprandial plasma TG without altered intestinal fat absorption in mice (143). Whether apoC3 inhibition regulates CM secretion in humans remains to be established. In humans, a loss-of-function apoC3 variant associated with decreased TG and CVD protection had no effect on apoB concentration (144), perhaps suggesting no effect on CM secretion.

Several angiopoietin-like proteins (ANGPTLs), namely ANGPTL3, ANGPTL4, and ANGPTL8, have been identified as inhibitors of LPL activity resulting in increased plasma TG (145) (**Figure 1**, #8). In mice and humans, deletion or loss-of-function in any of these genes reduced plasma TG while overexpression increased plasma TG (145). ANGPTL3 ASO reduced VLDL cholesterol (146), however its effects on intestinal CM secretion have not been established. ANGPTL4 expression in adipose tissue is increased upon fasting to inhibit adipose LPL activity, redirecting TG to other tissues for oxidation (147). Upon high-fat feeding, enterocyte ANGPTL4 expression is increased possibly to inhibit pancreatic lipase and slow FA uptake into enterocytes to match FA uptake with TG secretion (148). Whether intestinal ANGPTL4 inhibition alters CM secretion remains to be investigated. Inactivating ANGPTL4 variants in humans are associated with reduced risk of coronary disease (149), however ANGPTL4 inhibition by monoclonal antibodies in mice and non-human primates was associated with lymphadenopathy (150). Whether this adverse response would be present in humans is unknown, although subjects with inactivating ANGPTL4 variants do not exhibit lymphatic abnormalities (150). In humans ANGPTL8 is exclusively enriched in the liver (151) and thus it is unlikely to modulate CM secretion. In mice its expression is enhanced by insulin signaling through the insulin responsive transcription factor liver X receptor  $\alpha$  to promote VLDL secretion (152). Of these ANGPTL peptides, ANGPTL4 is the only one known to be expressed in the intestine and thus may serve as a therapeutic target to modulate CM secretion, however adverse effects may preclude its further development. Whether ANGPTL3 or ANGPTL8 inhibition could modulate CM secretion remains to be determined.

## CONCLUSIONS

Diabetic dyslipidemia is characterized by increased fasting and postprandial TGs, packaged within apoB-containing lipoproteins, many of which are considered to be directly implicated in promoting atherosclerotic CVD. Worsening IR is correlated with increases in circulating CMs arising from increased production and decreased clearance. Increased intestinal CM production in insulin resistant states can be attributed to increased supply of lipogenic substrates and resistance to key modulatory signals that results in altered expression and activity of lipogenic and secretory pathways. Therapeutic strategies developed thus far to directly target

the gut have been limited by GI and other adverse events, precluding their widespread use. Approved lipid and glucose modifying therapies such as statins, fibrates, ezetimibe, SGLT2 inhibitors, metformin, and GLP-1 receptor agonists have also been shown to affect intestinal CM production. This is a very fertile area for drug development, but major challenges remain in improving the tolerability of agents that target gut lipid handling and CM secretion before these agents can be deployed to curb CVD risk in those with and without T2D.

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## AUTHOR CONTRIBUTIONS

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**Conflict of Interest:** GL holds the Drucker Family Chair in Diabetes Research and the Sun Life Financial Chair in Diabetes.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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