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Insights into incretin-based therapies for treatment of diabetic dyslipidemia

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ABSTRACT

Derangements in triglyceride and cholesterol metabolism (dyslipidemia) are major risk factors for the development of cardiovascular diseases in obese and type-2 diabetic (T2D) patients. An emerging class of glucagon-like peptide-1 (GLP-1) analogues and next generation peptide dual-agonists such as GLP-1/glucagon or GLP-1/GIP could provide effective therapeutic options for T2D patients. In addition to their role in glucose and energy homeostasis, GLP-1, GIP and glucagon serve as regulators of lipid metabolism. This review summarizes the current knowledge in GLP-1, glucagon and GIP effects on lipid and lipoprotein metabolism and frames the emerging therapeutic benefits of GLP-1 analogs and GLP-1-based multiagonists as add-on treatment options for diabetes associated dyslipidemia.

1. Introduction

The International Diabetes Federation (IDF) reports that 425 million people experienced diabetes in 2017 [1]. By the year 2045, this number is expected to rise to 629 million [1]. Four million people per year perish from the disease, with atherosclerotic cardiovascular complications being the major cause of death [1]. An increased risk for cardiovascular diseases (CVD) in diabetic patients is linked to several factors like age, gender and genetics, but is also independently related to a specific cluster of plasma lipid and lipoprotein abnormalities [2]. Obese individuals and diabetic patients typically display a "mixed" dyslipidemia, characterized by an atherogenic triad of hypertriglyceridemia, decreased levels of high-density lipoprotein-cholesterol (HDL—C) and a preponderance of small dense low-density lipoprotein (sdLDL) particles [3–6]. Hypertriglyceridemia, is characterized by the accumulation of triglyceride-rich lipoproteins (TRL) in the blood. TRL, including the apolipoprotein (apo) B-48 containing chylomicrons and the apoB100 containing very low-density lipoproteins (VLDL), and their atherogenic remnants are derived from two major sources, the endogenous and exogenous lipoprotein pathways (Fig. 1).

Single components of mixed dyslipidemia are directly associated with an increased risk for cardiovascular events. Elevated levels of low-density lipoprotein cholesterol (LDL-C) enhance the probability of intimal retention of LDL and contribute to development of arteriosclerotic plaque formation in a concentration dependent-manner [7–9]. Lowering LDL-C with statins remains the cornerstone in the management of dyslipidemia and leads to a significant reduction in the incidence of major CVD events [10]. Patients that do not achieve their LDL-C treatment goals despite high doses of statins may further be subjected to LDL-lowering add on therapies such as the ATP citrate lyase bempedoic acid [11,12], inhibitors of intestinal cholesterol absorption (ezetimibe) [13], or inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9) [14].

However, even in the setting of optimal LDL-C reduction, a substantial residual CVD risk remains in those patients with hypertriglyceridemia and low HDL-C levels [15,16]. Combining statins with other lipid-modifying therapies that favorably modulate lipid and lipoprotein profiles could incrementally reduce the residual CVD risk in T2D patients. There are three major classes of triglyceride (TG) lowering drugs: fibrates, niacin and omega-3 fatty acids. Both,

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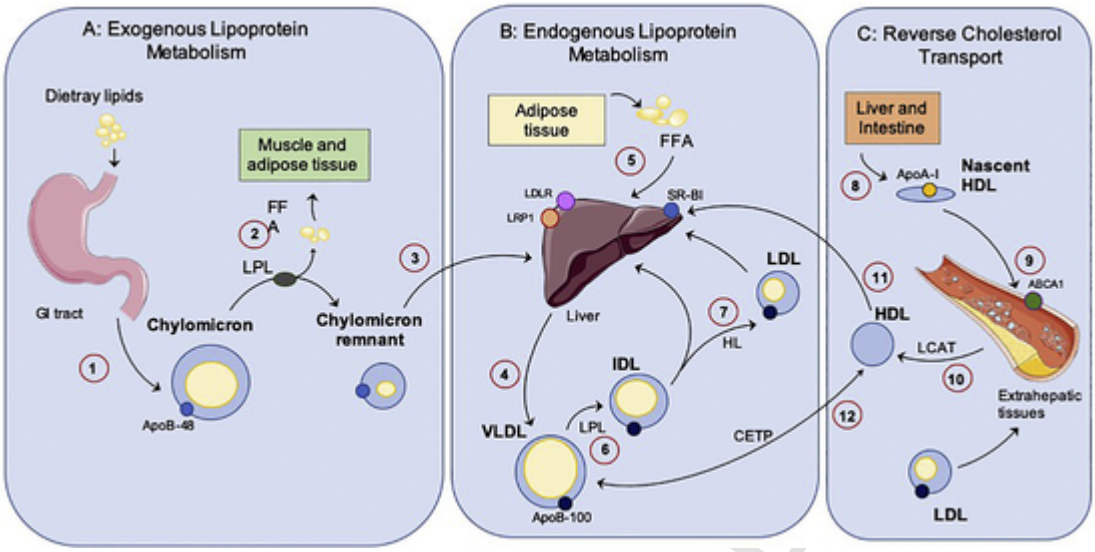

Fig. 1. Exogenous and endogenous lipoprotein metabolism and reverse cholesterol transport.A: Exogenous Lipoprotein Pathway: (1) Digested lipids enter the intestinal enterocytes where they are re-assembled into chylomicron particles by microsomal triglyceride transfer protein (MTP), the rate limiting enzyme that catalyzes the movement of TG to the apolipoprotein apoB48. Chylomicrons are subsequently secreted into lymphatic vessels of the small intestine (lacteals) and released to circulation. (2) In the capillary beds of the adipose tissue and muscles, chylomicrons are exposed to the lipolytic action of lipoprotein lipase (LPL), an enzyme that requires poC-II as a cofactor. LPL hydrolysis leads to a release of FFAs from the TG core, which enables sustained mitochondrial energy in muscle or for the storage of TG in adipose tissue. The de-lipidation process produces cholesterol-rich chylomicron remnants (3), which are endocytosed by hepatocytes in a process requiring ApoE, low-density lipoprotein receptor (LDLR) and LDLR–related protein.B: Endogenous Lipoprotein Pathway: (4) Hepatic VLDL secretion is controlled by the activity of MTP and by the availability of hepatic lipids from varying sources. Under fasting conditions, FFA are released from adipocytes (5) and delivered to the liver for re-esterification and secretion as VLDL particles. (6) In circulation, VLDL particles lose TG due to LPL-catalyzed hydrolysis and thus become smaller sized intermediate-density lipoproteins (IDL). (7) In a second step, IDL are further hydrolyzed by hepatic lipase (HL) to leave "remnant" LDL particles in which the TG core is largely depleted. These remnant LDL particles contain considerable amounts of cholesterol that serve as substrate for membrane or steroid hormone synthesis in distant cells.C: Reverse cholesterol transport (RCT): High density lipoprotein (HDL) removes excess LDL cholesterol from extrahepatic cells for hepatic clearance and is key in preventing excessive cholesterol accumulation in macrophage foam cells. (8) Nascent discoid HDL particles are synthesized by the intestine and the liver and use poA-I as the major lipoprotein constituent. (9) ApoA-I mediates the interaction of discoidal HDL particles with the ATP-binding cassette transporter ABCA1, which augments cholesterol efflux from extrahepatic cells. (10) Mobilized cholesterol is further converted into more hydrophobic cholesterol esters by the circulating enzyme lecitin:cholesterol acetyltransferase (LCAT) to allow for an efficient packaging into HDL particles and transport to the liver. (11) The cholesteryl esters from HDL can be directly taken up hepatocytes via the scavenger receptor BI (SR-BI). They can be further transferred by (12) cholesteryl ester transfer protein (CETP) to VLDL particles in exchange for the re-transfer of TG to HDL. The resulting triglyceride-rich VLDL HDL particles serve as a substrate for hepatic lipase, leaving small HDL particles, which can restart the uptake of cholesterol from extrahepatic cells. LPL and HL further hydrolyze TG from TG-rich VLDL particles to small, dense LDL particles. Such small and dense LDL particles are highly atherogenic. They demonstrate a reduced affinity for the LDLR and thus have a prolonged residence time in circulation. They further exhibit an increased arterial wall retention and increased susceptibility to oxidation.

fibrates and niacin, either as monotherapies or in combination with statins failed to reduce the rates of cardiovascular events in the overall study populations of the ACCORD-LIPID [17] and the AIM-HIGH trials [18]. Nonetheless, the selective analysis of patients with a combination of highest baseline hypertriglyceridemia and lowest HDL-C levels revealed a consistent reduction in the CVD event rate with both combination therapies [17,19]. Similar results were found in a recent prospective, placebo-controlled, randomized trial (REDUCE-IT) in patients undergoing co-therapy with statins and the omega-3 fatty acid ethyl-eicosapentaenoic acid (E-EPA) [20]. Specifically, the trial revealed a reduced risk of cardiovascular events in patients with elevated TG levels when E-EPA was added to their statin monotherapy. These studies suggest that patients with mixed dyslipidemia, as often evident in T2D, may specifically benefit from combination therapies aimed at lowering both LDL-C and TG levels. T2D patients, who are foremost focused on the control of their blood glucose levels, could thus benefit from glucose-lowering drugs that also show efficacy against diabetic dyslipidemia.

This review focuses on a new class of drugs with broad efficacy against both hyperglycemia and diabetic dyslipidemia in T2D patients. We specifically summarize the mechanistic characteristics of how pharmacological mimetics of glucagon-like peptide 1 (GLP-1), an incretin hormone with a plethora of beneficial effects on gut physiology as well as glucose and energy metabolism [21–23], can be useful add-on therapeutics in the treatment of diabetic dyslipidemia [24,25]. We will further discuss why the combination of GLP-1 with the glucose-dependent insulinotropic polypeptide (GIP) and/or glucagon might prove superior to the GLP-1 mono-agonists with respect to potential CVD benefit.

2. GLP-1 – an insulinotropic hormone with anorexigenic properties

Native GLP-1 is a product of proglucagon and is present as either GLP-1(1-37), GLP-1(7-36amide) or GLP-1(7-37). In the enteroendocrine L-cells of the intestine or in selected nuclei in the nucleus tractus solitarius (NTS), proglucagon is cleaved by the action of the prohormone convertase 1/3 (PC1/3; PCSK1/3) into GLP-1, GLP-2, oxyntomodulin, glicentin or the glicentin-related polypeptide (GRPP) [23,26,27]. In the alpha-cells of the pancreas, proglucagon is cleaved by the action of the prohormone convertase 2 (PC2, PSK2) into glucagon, GRPP or the major proglucagon fragment (MPGF) [23,28,29]. All these proglucagon cleavage products are secreted from the L-cells at equimolar levels [30,31].

GLP-1 secreting L-cells are located in the small and large intestine, with highest cell densities in the distal ilium and the colon [32,33]. L-cells are open-type enteroendocrine cells with microvilli extending to the intestinal lumen and thus are considered primary chemoreceptors capable of directly responding to luminal constituents [34]. Dietary and intra-duodenal infusion studies show that lipids, and to a lesser extent glucose and amino acids, can stimulate GLP-1 secretion in response to elevated circulating levels [35–37]. Upon its secretion, active GLP-1 which is either GLP-1(7-36 amide) or GLP-1(7-37) gets rapidly degraded at its second N-terminal amino acid (Ala8) by the dipeptidyl peptidase-4 (DPP-4), resulting in inac-

tive metabolites GLP-1 (9–36amide) or GLP-1(9–37) [38,39]. Enzymatic cleavage together with the rapid renal clearance limits the half-life of native GLP-1 to approximately 2 min [40].

The insulinotropic action of the endogenous incretin hormones GLP-1 and GIP jointly account for up to 70% of the postprandial insulin secretion and both incretins are thus essential contributors to glucose clearance after a meal [22,41,42]. Apart from decreasing blood glucose via its ability to stimulate insulin secretion. GLP-1 also decreases the release of glucagon from the alpha cells via direct and indirect effects, ultimately inhibiting hepatic glucose production, as comprehensively reviewed previously [23].

Notably, studies in type-2 diabetic patients suggest that the insulinotropic and the glucagonostatic effects of GLP-1 contribute equally to its ability to decrease blood glucose [43]. In addition to its action on the pancreas, GLP-1 suppresses gastric emptying, motility and acid secretion, thereby limiting nutrient entry into the small intestine [44–46]. Gastric emptying has a considerable impact on postprandial glycemia by altering the peak insulin response in both healthy subjects and T2D patients [47–51]. Accelerating gastric emptying by erythromycin treatment significantly attenuates the glucose lowering effect of co-infused GLP-1 [52]. Overall, these studies demonstrate that the direct glucose lowering effects of postprandially released GLP-1 are driven by independent and parallel mechanisms in the gastrointestinal tract and pancreas.

Apart from regulating blood glucose, GLP-1 is a multifaceted hormone with metabolic action far beyond its role to buffer against hyperglycemia. In line with this notion, GLP-1 lowers body weight through central inhibition of food intake [53–55]. These central effects of GLP-1 are attributed to GLP-1R expressing neurons in the hypothalamus [56] and on the vagal afferents that act via neurons in the NTS in the brain stem [57]. Peripheral administration of GLP-1RA stimulates neuronal activity in the hypothalamus [58,59] and in the brainstem [60]. There is also evidence that GLP-1 is directly synthesized by specific neurons of the NTS in the brain stem, from where it acts as a neuropeptide to modulate food intake [27]. However, details on the role of central vs. peripherally produced GLP-1, or on the relative contributions of GLP-1Rs expressed in different brain areas, remain to be determined. New evidence suggests that the GLP-1 producing neurons are specifically important for short-term limitation of feeding after unusually large food consumption and in mediating stress-induced hypophagia [61].

3. DPP-4 inhibitors and GLP-1 mimetics

Postprandial secretion of GLP-1 is reduced in the majority of obese individuals and in patients with T2D [62]. While native GLP-1 has a series of beneficial effects on whole-body metabolism, its short action profile limits its pharmacological potential to treat obesity and diabetes. To improve the pharmacological potential of endogenous GLP-1, a series of small molecules been developed that prevent its DPP-4 mediated N-terminal degradation. Such DPP-4 inhibitors extend the half-life of endogenous GLP-1. This leads to a two to three-fold increase in postprandial GLP-1 plasma concentrations, enhanced insulin secretion from β-cells and a reduction in blood glucose [63,64]. Numerous chemical DPP-4 inhibitors (such as sitagliptin, linagliptin, saxagliptin, alogliptin and vildagliptin) are approved for use in the U.S. and Europe while some others (anagliptin, gemigliptin, and teneligliptin) are only approved in Asian countries [65].

Over the years, a series of biochemically optimized GLP-1 receptor agonists (GLP-1RAs) were developed that provide a supraphysiological stimulation of the GLP-1R and improved stability from DPP-IV degradation. The various drugs can be classified as either short-acting (exenatide BID, lixisenatide) or as long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide, semaglutide). The chemical details of these molecules are described elsewhere [66,67]. In head-to-head clinical studies, all GLP-1 RAs were effective at reducing glycemia and body weight. However, differences exist in the magnitude of the efficacy and the frequency of adverse gastrointestinal side-effects [68]. Liraglutide (approved for treating diabetes and obesity), semaglutide and dulaglutide (both approved for diabetes) can be described as the best-in-class drugs to reduce HbA1c levels and body weight with minimized unwanted effects, although the clinical data suggest semaglutide to differentiate on greater efficacy readouts [69,70].

In 2008 the FDA mandated cardiovascular outcome trials (CVOT) to ensure new therapies in T2D provide cardiovascular safety. To date, CVOTs on seven different GLP-1RAs have been performed, including lixisenatide (ELIXA) [71], liraglutide (LEADER) [72], semaglutide (SUSTAIN-6) [73], exenatide QW (EXSCEL) [74], albiglutide (Harmony) [75], dulaglutide (REWIND) [76]; and oral semaglutide (PIONEER-6) [77]. Strikingly, liraglutide, subcutaneous semaglutide, albiglutide and dulaglutide have shown significant reductions in composite cardiovascular outcomes, indicative of their cardiovascular protection in high-risk patients with T2D. Of note, injectable semaglutide (1.0 mg) showed a 26% risk reduction in MACE [73] whereas dulaglutide (1.5 mg) showed a 12% risk reduction in MACE [76]. Based on these findings, these long-acting GLP-1R analogues are approved for the use to reduce risk of major cardiovascular events in adults with T2D and established cardiovascular disease. Furthermore, dulaglutide is approved for use in T2D patients without established cardiovascular disease but with multiple risk factors, which is the first approved use of a GLP-1 analogue in this patient sub-class.

The underlying cardiovascular protective mechanisms are incompletely understood and may include beneficial effects of GLP-1RA on blood pressure, the vascular endothelium, inflammation, myocardial ischemia and heart failure [78,79]. Preclinical studies in non-diabetic $ApoE^{-/-}$ and $LDLr^{-/-}$ mice further suggest an anti-atherosclerotic potential of the GLP-1-RAs and DPP-4 inhibitors [80–83]. In a recent study, liraglutide and semaglutide treatment significantly attenuated plaque lesion development in $ApoE^{-/-}$ and $LDLr^{-/-}$ mice. The reported effect was partially independent of the body weight lowering effect of the drugs [83]. The lack of GLP-1R expression on the vasculature furthermore suggests an indirect benefit or a receptor independent signaling mechanism, which likely includes an anti-inflammatory component [78,83]. Lipid lowering effects may further add to the anti-atherosclerotic effects of the GLP-1RAs, as discussed in this review.

While dyslipidemia is a key risk factor for CVD, it is also a hallmark of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), two conditions mainly characterized by an elevated deposition of free fatty acids (FFA), TG, and cholesterol in the liver [84]. Currently, no pharmacological treatment has proven efficacious and the first line of treatment for NAFLD and NASH remains body weight loss. Multiple pre-clinical and clinical trials have evaluated the efficacy of GLP-1RAs in NAFLD/NASH [85]. In the first published randomized controlled trial, the Liraglutide Efficacy and Action in NASH (LEAN) study, 48 weeks of treatment with liraglutide caused a significant resolution of NASH in 9/23 overweight and obese patients with histologically proven NASH, compared to 2/22 patients in the placebo group [86]. In this study, reductions in bodyweight and glycated hemoglobin (HbA1c) were similar in patients with and without hepatic improvements, suggesting mechanisms beyond the body weight and glucose lowering effects of GLP-1. Since GLP-1R expression on hepatocytes, stellate cells, Kupffer cells and other liver-resident cell types has not been conclusively established, it is possible that the beneficial effects of liraglutide on NASH were mediated by other indirect effects. GLP-1 mediated im-

provements in dyslipidemia could therefore contribute to the beneficial effects of GLP-1RA on hepatic steatosis.

4. Clinical trials evaluating the lipid lowering effect of GLP-1RA

4.1. Effects of GLP-1 and DPP-4 inhibitors on fasting lipid levels

To date phase 2 and 3 clinical trials of GLP-1RA have primarily focused on glycemic control and body weight loss and were not specifically designed to investigate lipid parameters. A recent network meta-analysis nonetheless ranked the effect size for different short and long-acting GLP-1RA (exenatide, exenatide extended release (ER), liraglutide and taspoglutide (discontinued in developmental phase 3) employed at different dosages upon lipid profiles in T2D patients [87]. Exenatide ER and liraglutide (1.8 mg) had no significant effects on HDL-C levels, but reduced total cholesterol, TG and LDL-C relative to treatment with placebo, insulin and thiazolidinediones [87]. A subsequent study confirmed the TG-lowering effect of liraglutide and both the short-acting (twice daily) and long-acting (once weekly) exenatide formulations, but unlike the preceding study, found significant increases in HDL-C after treatment with liraglutide and exenatide ER. Liraglutide, dulaglutide and semaglutide lowered LDL-C compared to the placebo groups. Total TG levels remained unaffected by treatment with lixisenatide, dulaglutide, albiglutide and semaglutide [79].

In general, GLP-1R agonism only moderately affects fasting levels of circulating lipids. The absence of the GLP-1R on hepatocytes [88] suggests that the observed GLP-1 effects on hepatic lipoprotein levels, which are most predominant during fasting, are indirectly mediated by effects on body weight and glycemic control. This is supported by the finding that DPP-4 inhibitors, which are considered weight neutral [89,90], were even less effective on fasting lipid parameters [91–93].

Nevertheless, even modest improvements in lipid profiles are considered of clinical relevance and can improve cardiovascular risk. In addition, most studies only examined quantitative changes in levels of LDL-C and HDL-C but did not analyze qualitative changes in lipoprotein particle compositions. Notably, despite similar LDL-C levels, differences may exist in the preponderance of pro-atherogenic sdLDL particles [94]. The latter are considered more atherogenic than normal sized LDL particles, as they provide a longer retention time in the plasma and are more prone to oxidation [95,96]. Those sdLDL specifically arise from large and TG-rich subpopulation of $VLDL_1$ particles, which are predominant in diabetes [5,96]. Whether GLP-1RA can cause a shift towards the less pro-atherogenic $VLDL_2$ subtype and lower sdLDL production, remains to be determined.

Likewise, changes in HDL-C levels have been detected in clinical trials, however with varying results. HDL-C has an important function in the removal of excess LDL-C from extrahepatic cells for hepatic clearance, by a process, named reverse cholesterol transport (RCT) (Fig. 1). This process is also key in preventing excess cholesterol accumulation in macrophage foam cells, which is an established risk factor for arteriosclerotic plaque formation [97]. There is increasing evidence that the anti-atherosclerotic effect of HDL does not solely depend on its concentration but rather on its functionality [98]. Indeed, dysfunctional HDL and loss of its cholesterol efflux capacity is playing a critical role in diabetes and its complications [99] and may be altered by GLP-1RA treatment.

4.2. Effects of GLP-1RA and DPP-4 inhibitors on postprandial lipid levels

Several clinical trials of DPP-4 inhibitors and GLP-1RA focused on potential benefits for postprandial lipid and lipoprotein metabolism. Briefly, the DPP-4 inhibitors alogliptin [100,101], vildagliptin [102,103] and sitagliptin [104–106] were all found to decrease postprandial plasma TG and chylomicron apoB48 levels (Table 1). Similar findings were observed after treatment with GLP-1RA, including exenatide [104,107–109], liraglutide [110–112] and semaglutide [113] in healthy subjects and T2D patients (Table 1). Together, these findings highlight the potential of GLP-1RA to improve postprandial hypertriglyceridemia. This is of high clinical relevance, as this condition has been independently associated with an increased CVD in T2D patients due to the increase in pro-atherogenic cholesterol rich remnant particles [114,115].

5. Potential mechanisms by which GLP-1 modulates the intestinal lipoprotein metabolism

5.1. Acute and body weight independent effects of GLP-1

Studies in laboratory animals, healthy human volunteers and small numbers of T2D patients all demonstrate a significant reduction of postprandial chylomicron levels following acute treatment with DPP-4 inhibitors or GLP-1R agonists. Intravenous infusion of native GLP-1 at a dose of 1.2 pmol kg(−1) min(−1) for 390 min is sufficient to prevent the normal rise in postprandial TGs in healthy subjects after a test meal [116]. Similarly, in patients with impaired glucose tolerance, a single subcutaneous injection of 10 μg exenatide prior to a fatty meal prevents the diabetes-related peak in postprandial TG, apoB48, chylomicron remnants and cholesterol [117]. Acute GLP-1 effects on intestinal lipoproteins are also observed in laboratory animals such as lean C57BL/6 mice, which show significantly decreased postprandial TRL-TG, TRL-cholesterol and chylomicrons levels following a single injection of exendin-4 [118]. Similar findings are observed in fructose-fed dyslipidemic hamsters, where a 30 min intravenous infusion of GLP-1 [119], or 3 weeks treatment with the DPP-4 inhibitor sitagliptin [118], blunts intestinal chylomicron overproduction. Furthermore, exendin-4 treatment in rats causes a 20% reduction of microsomal TG transfer protein (MTP) activity, which is indicative of impaired chylomicron synthesis [120]. An important role of GLP-1 in the regulation of postprandial intestinal lipoprotein levels is further supported by the finding of increased circulating chylomicron levels in $Glp1r^{-/-}$ mice [118]. Overall, these studies confirm the results from long-term clinical trials and provide clear evidence that GLP-1R agonism can improve postprandial lipid metabolism. Importantly, these beneficial effects on postprandial lipid metabolism appear to be independent from the body weight lowering effects of GLP-1. The exact mechanisms remain to be determined, but initial understandings of these mechanistic underpinnings are beginning to emerge, as outlined in the following section.

5.2. GLP-1 effects on chylomicron production and clearance

The increased chylomicron concentrations in obese and T2D patients were often attributed to an impaired chylomicron clearance. Such clearance of chylomicrons is mediated through an interaction with the insulin sensitive lipoprotein lipase (LPL) on capillary luminal endothelial cells in smooth and skeletal muscle, and adipose tissue. LPL activity is low in patients with T2D and increases upon acute and chronic insulin stimulation [121,122]. More recent data indicate that intestinal overproduction of chylomicrons is a main causative factor for the postprandial hypertriglyceridemia in the insulin resistant state [123–127]. Accordingly, the beneficial effects of DPP-4 inhibitors and GLP-1R agonists on postprandial hypertriglyceridemia could be the result of decreased secretion and/or increased clearance of chylomicrons. So far, only a few studies have analyzed the chylomicron kinetics using stable isotope labelling. Such studies allow for the direct evaluation of endogenously synthesized proteins. In healthy human volunteers subjected to an infusion with isotope-labelled leucine, a single dose of exenatide [108] or sitagliptin

Table 1
Changes in postprandial lipid parameters in response to GLP-1R agonists and DPP-4 inhibitors.

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
DPP-4 Inhibitors				
Sitagliptin	[106]	Healthy	Single dose (100 mg)	Mean ± SE • TRL-apoB-100 pool size [mg/kg]: no difference between groups • TRL-apoB-100 FCR [pools/d]: no difference between groups • TRL-apoB-100 PR [mg/kg per day]: no difference between groups • TRL-apoB-48 concentration [mg/l]: down vs. placebo **(*p* = .05)** • TRL-apoB-48 FCR [pools/day]: down vs. placebo (ns) • TRL-apoB-48 PR [mg/kg per day]: down vs. placebo **(*p* = .05)**
	[105]	T2D female	Once daily 100 mg for 6-weeks	AUC • TG [mmol/l/h]: −9.4% vs. placebo **(*p* = .006)** • ApoB-48 [ng/ml/h]: −7.8% vs. placebo **(*p* = .03)** • ApoB [g/l/h]: −5.1% vs. placebo **(*p* = .002)** • VLDL-C [mmol/l/h]: −9.3% vs. placebo **(*p* = .01)** • FFA [μM/h]: −7.6% vs. placebo **(*p* = .05)**

Table 1 (*Continued*)

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
Vildagliptin	[102]	T2D	Twice daily 50 mg for 4 weeks	iAUC (0–8 h); [h*mmol/l] • TG: −3.1 ± 1.2 vs. placebo **($p = .011$)** • CM-TG: −1.5 ± 0.4 vs. placebo **($p < .001$)** • CM-cholesterol: −0.13 ± 0.05 vs. placebo **($p < .020$)** • VLDL/IDL TG: −1.1 ± 0.9 vs. placebo ($p < .215$) • Cholesterol: −0.2 ± 0.3 vs. placebo ($p < .517$) • VLDL/IDL cholesterol: −0.22 ± 0.28 vs. placebo ($p < .409$)
Alogliptin	[101]	Healthy	Once daily 25 mg for 7 days	iAUC (0-8 h) • TG [h*mg/dl]: Control: 279 ± 31; Alogliptin: 182 ± 32 **($p = .01$)** • RLP-C [h*mmol/l]: Control: 29.3 ± 3.2; Alogliptin: 17.6 ± 3.3 mg **($p = .01$)** • ApoB-48 [h* μg/l]: Control: 15.4 ± 1.7; Alogliptin: 11.7 ± 1.1 **($p = .04$)** Total AUC (0-8 h) • Cholesterol [h*mg/dl]: Control: 1489 ± 248; Alogliptin: 1452 ± 252 ($p = .68$) • LDL-C [h*mg/dl]: Control: 819 ± 218; Alogliptin: 814 ± 228 ($p = .72$) • HDL-C [h*mg/dl]: Control: 532 ± 79 mg h/dl; Alogliptin: 514 ± 71 ($p = .10$)

Table 1 (*Continued*)

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
	[100]	T2D	Once daily 25 mg for 16 weeks	iAUC (0-8 h); Change from baseline. Mean (95% CI) • TG [h*mmol/l]: −3.472 vs. placebo (−5.008 to −1.936), (***p*** **< .001)** • CM-TG [h*mmol/l]: −1.334 vs. placebo (−1.815 to −0.853), (***p*** **< .001)** • CM-ApoB-48 [h*mgl/l]: −0.621 vs. placebo (−1.172 to −0.071), (***p*** **< .028)** VLDL1-TG [h*mmol/l]: −1.759 (−2.682 to −0.835), (***p*** **< .001)**
GLP-1 and GLP-1RA				
GLP-1	[116]	Healthy	iv. infusion (1.2 pmol/kg/min) for 390 mins	AUC Plasma TG [mmol/l]: Placebo: 82.8 ± 20.9 vs. GLP-1: 14.3 ± 4.9 (***p*** **= .011**) Plasma FFA [mmol/l]: 31 ± 5% suppression by GLP-1 (***p*** **< .01**)

Table 1 (*Continued*)

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
	[108]	Healthy	Single dose (10 μg)	Mean ± SE for the duration of a 10 h kinetic study. • TRL-apoB-100 concentration [mg/l]: Placebo: 56.53 ± 6.66; Exenatide: 62.67 ± 8.11 • TRL-apoB-100 FCR [pools/day]: Placebo: 3.83 ± 0.38; Exenatide: 3.03 ± 0.22 • TRL-apoB-100 PR [mg/kg per day]: Placebo: 9.88 ± 1.59; Exenatide: 7.84 ± 0.71 • TRL-apoB-48 concentration [mg/l]: Placebo: 1.83 ± 0.30; Exenatide: 1.24 ± 0.19 **($p < .05$)** • TRL-apoB-48 FCR [pools/day]: Placebo: 1.54 ± 0.22; Exenatide: 1.36 ± 0.24 • TRL-apoB-48 PR [mg/kg per day]: Placebo: 0.12 ± 0.02; Exenatide: 0.08 ± 0.02 **($p < .05$)**

Table 1 (*Continued*)

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
	[107]	T2D	Twice daily for 1 year Week 1–4: 5 μg, then 10 μg	iAUC (0-8 h); [h*mmol/l]. Mean change from baseline ± SE • TG [h*mmol/l]: −3.1 ± 1.2 vs. insulin glargine **(*p* = .014)** • FFA [10^{3}μg*h/l]: −0.90 ± 0.29 vs. insulin glargine **(*p* = .004)** • Cholesterol [h*mmol/l]: −0.30 ± 0.35 vs. insulin glargine (*p* = .398) • LDL-C [h*mmol/l]: 0.37 ± 0.20 vs. insulin glargine **(*p* = .076)** • HDL-C [h*mmol/l]: 0.30 ± 0.10 vs. insulin glargine **(*p* = .005)** • VLDL-C [h*mmol/l]: −1.0 ± 0.30 vs. insulin glargine **(*p* = .006)** • Apo-A1 [h*mg/dl]: 1.6 ± 7.8 vs. insulin glargine (*p* = .839) • Apo-A2 [h*mg/dl]: 1.8 ± 1.8 vs. insulin glargine (*p* = .316) • Apo-B48 [h*mg/dl]: −34.8 ± 9.2 vs. insulin glargine **(*p* < .001)** • Apo-B100 [h*mg/dl]: 1.2 ± 9.1 vs. in-suin glargine (*p* = .893) • Apo-C3 [h*mg/dl]: −0.6 ± 2.2 vs. insulin glargine (*p* = .771)
	[104]	T2D	Twice daily for 2 weeks Week 1: 5 μg Week 2: 10 μg or 100 mg (q.a.m.) sitagliptin	AUC (0-240 min) Plasma TG [mg·min/dL]: Mean ratio exenatide to sitagliptin: 0.90 ± 0.04 (95% CI: 0.84–0.98; **p = .0118**)

Table 1 (*Continued*)

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
	[109]	T2D	Once daily for 12 days Day 1–5: 5 μg Day 6–11: 10 μg	• TG [mg/dl]: Placebo: 186 ± 104 vs. Exenatide: 172 ± 77 (p = .4) • Cholesterol [mg/dl]: Placebo: 163 ± 36 vs. Exenatide: 150 ± 33 (**p = .002**) • LDL-C [mg/dl]: Placebo: 80 ± 10 vs. Exenatide: 81 ± 28 (p = .8) • HDL-C [mg/dl]: Placebo: 38 ± 8 vs. Exenatide: 36 ± 7 (**p = .048**)
Liraglutide	[110]	T2D	Once daily for 3 weeks Week 1: 0.6 mg Week 2: 1.2 mg Week 3: 1.8 mg	iAUC (0-8 h); [h*mmol/l]. Mean (95% CI) • TG: −3.9 vs. placebo (−5.8 to −2.0; (**p = .008**) • ApoB48: −0.03 vs. placebo (−0.05 to −0.02; (**p = .003**) • FAA: 0.31 vs. placebo (−0.38 to 0.99; p = .34)

Table 1 (*Continued*)

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
	[112]	T2D	Once daily 1.8 mg for 16 weeks	AUC (0-8 h); [h*mmol/l]. Change from baseline (mean ± SD) • TG: Placebo: 1.5 ± 6.3 (12.2%), p = .612; Liraglutide: −5.0 ± 6.2 (−19%), (**p = .011**) • Chylomicron TG: Placebo: 1.4 ± 2.5 (40.5%), p = .128; Liraglutide: −2.1 ± 2.7 (30.0%), (**p = .005**) • VLDL1 TG: Placebo: 0.1 ± 2.5 (12.2%), p = .866; Liraglutide: −2.4 ± 3.4 (−21.0%), (**p = .02**) • RLP-C: Placebo: 1.8 ± 39.2 (14%), p = .866; Liraglutide: −33.8 ± 43.6 (−24.6%), (**p = .008**) • TRL-C: Placebo: −4.5 ± 69.1 (4.3%), p = .866; Liraglutide: −52.3 ± 70.4 (−17.9%), (**p = .011**) • ApoCIII: Placebo: −2.2 ± 21.0 (0.4%), p = .735; Liraglutide: −18.3 ± 29.5 (−14.8%), (**p = .020**) • ApoB48: Placebo: 7.1 ± 31.0 (13.9%), p = .735; Liraglutide: −23.2 ± 56.8 (−11.2%), (p = .100) • FFA: Placebo: −201 ± 438 (−4.9%), p = .398; Liraglutide: −179 ± 477 (−4.2%), (p = .140)

Table 1 (*Continued*)

Compound	Reference	Subjects	Dosing	Postprandial lipid parameters
Semaglutide	[113]	Healthy Obese	Once weekly 1 mg for 12-weeks	AUC (0-8 h); [mmol/l] • TG: −40.7% vs. placebo **($p < .01$)** • VLDL: −42.8% vs. placebo **($p < .01$)** • ApoB48: −49.6% vs. placebo **($p < .01$)** • FAA: No difference

AUC: Area Under Curve; iAUC: Incremental AUC; TG: Triglycerides; CM: Chylomicrons; RLP: Remnant like particle; PR: Production rate; FCR: Fractional catabolic rate.

[106], as well as a 6-week treatment of T2D patients with sitagliptin [128] reduced chylomicron production but not the fraction of intravascular apoB48 catabolized per day (fractional catabolic rate (FCR), Table 1). These results suggest that GLP-1 decreases chylomicron output rather than their clearance. Subsequent studies interpreted the GLP-1 mediated decrease in plasma TRL-ApoB levels as a result of a reduced chylomicron output. Nevertheless, since long-term GLP-1R agonism causes body weight loss, and thereby improved insulin sensitivity, chylomicron clearance could also be affected through the restoration of LPL activity. The latter has so far not been examined in detail. Using stable isotope techniques, two recent studies report an increase in chylomicron catabolism after 6 months of treatment with liraglutide (1.2 mg) [129] and 4 weeks of treatment with lixisenatide [130].

5.3. Direct GLP-1 effect on lipid metabolism in enterocytes

The pronounced decrease in postprandial chylomicron output following acute and chronic GLP-1RA treatment suggests a direct impairment in chylomicron synthesis. In vitro studies in primary enterocytes isolated from chow-fed hamsters demonstrated a reduction in apoB48 secretion into the cell culture media after treatment with exendin-4 [118]. This direct and GLP-1 receptor mediated effect is supported by the finding that blockade of endogenous GLP-1R signaling by the GLP-1R antagonist exendin(9-39) reverses the apoB48 lowering effect of exendin-4 in mice [118]. When exendin(9-39) is, however, administered alone, it increases the levels of apoB48 after a fat load by blocking the action of endogenous GLP-1 [118]. In jejunal explants, exposure with liraglutide reduces the expression of enzymes essential for chylomicron production such as ApoB48, MTP, and DGAT1 (diacylglycerol O-acyltransferase 1) [129].

Based on such functional data it is surprising that the abundance of the GLP-1 receptor in enterocytes of the upper intestine, which is the main area of chylomicron synthesis, is rather scarce. In monkeys and humans, GLP-1R protein level was primarily demonstrated in the central nervous system and in peripheral tissues such as the pancreas, the cardiac atrium of the heart, kidney, lung, and, albeit at a low amount in adipose tissue [23,131]. In the gastrointestinal tract, protein expression of the GLP-1R was only detected in the HCL-secreting parietal cells and the smooth muscle cells of the stomach, the Brunner's gland of the duodenum, cells of the nervous plexus [132] and intestinal intraepithelial lymphocytes [133], but not on chylomicron forming enterocytes.

Effects of GLP-1 on chylomicron synthesis in enterocytes could be directly mediated by a novel unidentified receptor system. GLP-1 could however also regulate postprandial chylomicron levels via indirect mechanisms. Such effects could be the result of an GLP-1-driven inhibition of gastric emptying and intestinal motility, GLP-1's action as an incretin, or by modulation of the autonomous innervation of the gut following the direct activation of GLP-1R signaling in the central nervous system (CNS).

5.4. GLP-1 lowers chylomicron output by inhibiting gastric emptying

Gastric emptying and small intestinal motility are tightly controlled processes that deliver ingested lipids to the duodenum and jejunum, from where they are absorbed and assembled into chylomicron particles. A GLP-1-induced deceleration of gastric emptying [44–46] or intestinal motility [134–136] may directly translate into reduced chylomicron output and prevent the increase in postprandial TG plasma levels.

Indeed, intravenous GLP-1 infusion prior to a mixed meal reduces gastric emptying in male healthy volunteers and leads to diminished postprandial TG levels [116]. However, this mechanism may only be relevant for short acting GLP-1RAs, where the delay in gastric emptying is seemingly not subjected to tachyphylaxis [137,138]. After 12 weeks of treatment with the long acting GLP-1RA semaglutide, postprandial lipid excursions were decreased, despite the lack of an effect on gastric emptying [113] (Table 1). It remains to be determined if pharmacological inhibition of small intestinal motility by GLP-1 RAs would directly affect chylomicron output.

Independent from diminishing the rate of gastric emptying and/or motility, GLP-1 can directly affect postprandial TRL secretion. In mice receiving exendin-4 1 h after an oral lipid load, which provides sufficient time for entry of the fat into the small bowel, intestinal TRL production is decreased [118]. In rats recombinant GLP-1 inhibited apoB48 secretion in response to intra-duodenal lipid infusion [139]. Studies in humans confirmed the direct effect of GLP-1 on chylomicron secretion. Specifically, when healthy human volunteers receive lipids via a nasoduodenal tube directly into the duodenum, a subcutaneous exenatide injection still lowers chylomicron output by 38% [108]. Likewise, T2D patients that have been treated for 3 weeks with liraglutide [110] or for 12 weeks with semaglutide [113] experience a reduction in postprandial apoB48 levels that are independent from GLP-1 effects on gastric emptying.

Alternatively, it seems possible that GLP-1 directly inhibits TG absorption from the intestine, possibly through inhibition of gastric lipase secretion [140]. This explanation would align with the finding of a decreased absorption of intraduodenally delivered triolein in GLP-1 treated rats, which is paralleled by a reduction in intestinal lipoprotein production [139]. Similarly, when hamsters were given an oral gavage of radiolabeled TG the recovery of the radioisotope in

the plasma was lowered by a paralleled infusion of GLP-1 [119]. Limiting lipid absorption should increase the amount of fecal TG levels, which is indeed observed in mice that are chronically treated with the GLP-1RA taspoglutide compared to metformin treated controls [141]. It should however be noted that steatorrhea, i.e. the excessive excretion of lipids via the feces, has not been observed in patients during the initial period of GLP-1RA treatment, a phase often marked with profound yet transient gastrointestinal side effects.

5.5. GLP-1 decreases intestinal lymph flow

Newly formed chylomicrons are secreted through the basolateral membrane into the lymphatic vessels of the small intestine (lacteals) to enter the blood stream via the thoracic duct at the level of the left subclavian vein [142]. This route bypasses the portal venous system, thereby allowing an immediate supply of absorbed dietary lipids to all tissues. In an alloxan-induced diabetes model, the lymph flow through the thoracic duct is significantly higher than in healthy controls [143]. A possible underlying mechanism is the increase in interstitial glucose levels and higher tissue colloid pressure that enhances the interstitial fluid absorption and lymph production [144]. Interestingly, infusion of GLP-1 via the jugular vein was found to decrease intestinal lymph flow by 50% in a lymph duct-cannulated rat model. This reduction in lymph flow was paralleled by a significant decrease in plasma TG, apo B and apo A-IV levels [139]. The underlying mechanisms by which GLP-1 decreases the intestinal lymph flow remains elusive. Accumulating evidence suggests that the flow of lymph through the lymphatic vessel is more than simply a passive conduit and is largely achieved through an active pumping mechanism mediated by contractions of the lymphatic smooth muscle cells [145,146]. If and how GLP-1 reduces the contractile tone of lymphatic smooth muscle cells and lymph flow in general remains to be determined.

5.6. Indirect GLP-1 action via enhanced insulin secretion

Acute insulin exposure of cultivated human jejunal explants [147], normoglycemic hamster [126] and humans [148] resulted in the suppression of intestinal chylomicron production. Such direct insulin action, driven by the presence of insulin receptor on the intestinal epithelium [149,150], may explain some of the ability of incretin GLP-1RA to decrease postprandial lipoprotein secretion. Several studies nonetheless argue against this hypothesis. Evidence comes from healthy human volunteers, in which TRL particle kinetics were evaluated during continuous duodenal liquid meal infusions and a parallel pancreatic clamp to avoid confounding effects of hormones such as insulin and glucagon. In these subjects, infusions of exendin-4 led to a profound, lasting and insulin-independent suppression of apoB48 but not apoB100 particle production [108]. In a similar study, single injections of sitagliptin blunted the output of chylomicrons independent from changes in pancreatic hormones, circulating levels of glucose or free fatty acids [106]. Last, 1-week of treatment of healthy volunteers with alogliptin (25 mg/day for 7 days) suppressed the postprandial elevation in serum TG and remnant cholesterol without changes in pancreatic hormones and circulating levels of glucose or free fatty acids [101].

Collectively, these studies suggest that acute effects of GLP-1RA on chylomicron levels are insulin-independent. Systemic improvements in insulin sensitivity due to GLP-1RA induced weight loss may nonetheless enable direct effects of insulin on chylomicron secretion. The inhibitory effects of insulin on chylomicron secretion are suppressed in a state of insulin resistance, as observed in hamsters or humans [126,148,151,152]. Insulin resistance was moreover associated with an altered expression and activity of lipogenic and secretory pathways in enterocytes contributing to increased levels of circulating chylomicrons [126]. Restoring insulin sensitivity, both systemically and at the level of the enterocytes, may thus also directly suppress chylomicron secretion. However, treatment of T2D patients with the insulin sensitizer rosiglitazone improved overall insulin sensitivity, but increased rather than decreased circulating apoB48 levels [153]. Direct effects of GLP-1RA on the enterocytes are thus a more likely explanation for the observed modulation in chylomicron output in subjects undergoing weight loss.

5.7. GLP-1 reduces chylomicron output via brain-gut feedback circuitry

The central action of GLP-1 on food intake is well described and important for body weight homeostasis [23]. Intracerebroventricular (icv) injections of GLP-1 were shown to regulate metabolic processes in peripheral organs. For instance, icv GLP-1 was demonstrated to enhance sympathetic nervous system activity in brown [154,155] and white adipose tissue [156], leading to increased thermogenesis and a reduction of lipogenic gene expression, respectively. Whether central GLP-1 action can also regulate chylomicron production has nonetheless not been addressed in detail. A recent study by Farr and co-workers showed that the icv. Injection of exendin-4 significantly blunted TRL and apoB48 levels while similar but milder effects were observed after icv. Injection of the DPP-4 inhibitor MK-0626 [120]. Chylomicron-lowering effects of centrally applied exendin-4 were absent when the mice received cotreatment with the GLP-1RA exendin 9-39. However, when exendin-4 was injected peripherally, the icv. application of exendin 9-39 no longer impeded the effects on chylomicron synthesis [120]. This suggests that the acute postprandial lipoprotein lowering effects of GLP-1 are due to both central and peripheral GLP-1R activation. However, the clinical relevance of central GLP-1 actions on intestinal lipid metabolism remain undefined. Similarly, additional studies are required to address whether central GLP-1 action can modulate hepatic lipid metabolism and lipoprotein profiles in humans.

5.8. Effects of the GLP-1 and GLP-2 interplay

GLP-2, like GLP-1 is a product of preproglucagon. Upon nutrient ingestion, it is co-secreted with GLP-1 from intestinal L-cells and by specific neurons of the caudal brainstem. The main biological actions of GLP-2 are related to the regulation of energy absorption from the intestine by modulating nutrient uptake, improving mucosal integrity, reducing gut permeability and modulating microvilli length [157–161]. GLP-2 mitigates crypt cell proliferation and inhibits apoptosis of the intestinal epithelium [162–164]. These biological effects on gut morphology and function have led to the development of degradation-resistant, long-acting GLP-2 receptor agonists for the treatment of short bowel syndrome [164].

GLP-2 appears to have opposing roles to GLP-1 in intestinal lipid handling. In animal models, GLP-2 enhanced intestinal lipid absorption and subsequent chylomicron output by the enterocytes [165,166], while GLP-1 was shown to reduce chylomicron output. Contrary to GLP-1, the acute application of GLP-2 in humans increased postprandial plasma apoB48, TG and FFA concentrations [167,168]. The GLP-2 receptor is localized on enteroendocrine cells of the jejunum, enteric neurons and intestinal subepithelial myofibroblasts, but not on the enterocytes [164]. Accordingly, the GLP-2 effect on these cells appears to be indirectly mediated by endocrine, neuronal or paracrine mechanisms, which remains to be determined. A recent study in lymph duct cannulated rats suggests that GLP-2 stimulated intestinal TG output primarily by enhancing lymph flow [146], which once again is opposite to the effect of GLP-1 to decrease it.

GLP-1 and GLP-2 may have opposing physiological actions on postprandial lipid absorption and chylomicron secretion, but their net effect on lipid metabolism is undefined and likely depends on their rate of secretion and local availability as well as their degradation and excretion. Both peptides are co-secreted from the L-cells in a 1:1 M ratio. The plasma half-life of each peptide is short, 7 min for GLP-2 as compared to two for GLP-1 [169,170]. Whether this modestly sustained time action of GLP-2 also translates to a dominance of endogenous biological action of GLP-2 remains to be tested. Co-infusion of equimolar concentrations of exogenous GLP-1 and GLP-2 in insulin resistant hamsters resulted in a net increase in lipid absorption and an increase in TRL-TG and apoB48 after 30 min, while the prolonged infusion for up to 120 min led to a decrease in postprandial lipidemia [119]. In a recent study in diet-induced obese mice, 4 weeks of treatment with a dual GLP-1/GLP-2 receptor co-agonist (GUB09-123) markedly reduced plasma cholesterol but had no effect on TG levels [171]. It remains to be determined if this effect was secondary to the body weight lowering effect of the peptide. Together, these findings indicate that GLP-1 and GLP-2 have opposing actions on postprandial lipidemia, and that GLP-2 perhaps dominates the hypolipidemic action of GLP-1. However, the application of protracted GLP-1RA seems to shift that balance towards a lipid lowering effect.

6. GLP-1-based dual and triple agonists, and their effects on diabetic dyslipidemia

The therapeutic spectrum of GLP-1R agonism has recently been enriched with the development of unimolecular sequence-intermixed peptide hybrids that combine the glucose and weight lowering effects of GLP-1 with the incretin action of GIP and/or the thermogenic action of glucagon [66,172–177]. Such dual GLP-1/GIP and GLP-1/glucagon receptors agonists, and the tri-agonist combining GLP-1, GIP and glucagon achieve synergistic reductions of adiposity and hyperglycemia in pre-clinical models [66,172–176,178,179]. Various co-agonists are currently in clinical study where they appear to offer a more effective treatment of diabetes and obesity, with fewer adverse effects than selective GLP-1RA [180–182].

6.1. GLP-1/glucagon

Glucagon is best known as a glucogenic hormone that increases blood glucose under conditions of hypoglycemia by rapidly stimulating hepatic glucose production through acceleration of glycogenolysis and gluconeogenesis [183,184]. Beyond its glycemic effects in the liver, pharmacological applications of glucagon were also demonstrated to modulate food intake [185], energy expenditure [186], insulin secretion [187] and lipid metabolism [188]. Some studies have also proposed a protective role of glucagon in NAFLD [189,190].

The lipolytic action of glucagon has been described in various species including rats [191–193], mice [194], birds [195] and humans [196–201]. The liver shows the highest glucagon receptor (GCGR) expression [202] and is considered the primary target organ for glucagon mediated effects on lipid metabolism. In murine hepatocytes, glucagon stimulates ß-oxidation and inhibits lipogenesis [188,194], which may also contribute to reduced hepatic lipid accumulation and VLDL secretion, as observed in rats after repeated glucagon dosing [203,204]. Glucagon was shown to enhance LDL uptake and degradation by stimulating LDL-receptor activity in cultured rat hepatocytes [205] and in vivo [192]. Opposite findings were achieved with the GCGR antagonists MK-0893 and LY2409021, both of which resulted in a significant increase in plasma LDL-C concentrations in rats [206] and humans [190], respectively. In addition to these findings, LY2409021 induced a significant increase in hepatic lipid content, as assessed by magnetic resonance imaging [190]. Together, these studies suggest that intact hepatic GCGR signaling is required to prevent dyslipidemia as well as liver steatosis.

Direct lipolytic effects of glucagon were also demonstrated in adipocytes of different species. In rat adipocytes glucagon was shown to enhance the activity of hormone-sensitive lipase (HSL), the key lipolytic enzyme stimulating TG hydrolysis [207]. Other studies confirmed the lipolytic effect of glucagon in isolated adipocytes of rats [191,193], birds [195] and humans [197,198,208], albeit with considerable species differences regarding the effective glucagon concentration [188].

In addition to the lipolytic effects in liver and adipose tissue, high glucagon concentrations can also indirectly contribute to lipolysis by stimulating the secretion of growth hormone [209,210] and catecholamines [211,212], which have potent lipolytic actions in various tissues and cell types [213,214]. Glucagon can cross the blood brain barrier [215]. Additional contribution may come from a central regulation of lipid metabolism as GCGR is expressed in the dorsal vagal complex of the brainstem and in the hypothalamus [216]. In dogs, the central administration of glucagon caused hypolipidemia and hypocholesterolemia [217]. Moreover, acute icv. Administration of glucagon decreases hepatic TAG levels and increases the biliary excretion of cholesterol in hyperlipidemic rats and hamsters [218].

The lipid lowering effects of glucagon suggest that the net benefits of a GLP-1/glucagon co-agonist should go beyond a superior body weight and glucose lowering effect of GLP-1 to also specifically target diabetic dyslipidemia.

Different variants of GLP-1/glucagon co-agonists have been developed and were tested in pre-clinical and clinical trials primarily for their body weight lowering and anti-glycemic effects. Some of the studies reported additional effects on dyslipidemia and NAFLD/ NASH (Table 2). In DIO mice, treatment with a co-agonist, which was designed based on a glucagon-derived sequence, reduced body weight, fat mass and glycemia better than mono-agonist treatment. The co-agonist also reduced hepatic TG levels and liver steatosis, as well as, plasma TG, LDL-C and total cholesterol [172]. Moreover, treatment with the GLP1/glucagon co-agonist decreased plasma cholesterol with a similar trend in apo-B48 levels [219]. Treatment with a different GLP-1/glucagon co-agonist (DualAG), which was composed of an oxyntomodulin-based sequence, also caused reductions in body weight and hepatic steatosis in DIO mice [173]. A single injection of DualAG in fasted DIO mice decreased plasma concentration of TGs, cholesterol, and LDL [178]. Moreover, DualAG significantly decreased hepatic de novo lipogenesis, enhanced LDL receptor expression, decreased VLDL secretion and elevated fatty acid oxidation [178]. Equimolar doses of the positive control liraglutide suppressed de novo lipogenesis but had no effect on any other lipid parameters, suggesting a glucagon-specific effect on lipid serology [178].

The central nervous system may play a role in the GLP-1/glucagon mediated decrease in dyslipidemia. This became evident by a study in hamsters in which the central application of GLP-1/glucagon co-agonist decreased intestinal lipid absorption and hepatic TAG secretion, and increased the biliary excretion of cholesterol leading to lower plasma and liver lipid levels [220]. The lipid lowering effect was partially blocked by the central co-administration of either a GLP-1RA antagonist or a GCGR antagonist, and was abolished by experimental denervation of the GI tract and liver using vagotomy [220].

The promising effects in the pre-clinical models prompted the testing for efficacy and safety of two GLP-1/glucagon co-agonists (SAR425899 and MEDI0382) in Phase 2 trials. Both co-agonists showed weight and glucose lowering efficacy [182,221]. SAR425899 treatment had a mild cholesterol lowering effect under

Table 2
Changes in lipid parameters in response to GLP1/glucagon, GLP-1/GIP, GLP1/GIP/Glucagon and respective comparators.

Compound	Compound variant, Reference	Comparator	Experimental design	Sample collection	Body weight	Lipid parameters
GLP-1 / Glucagon	Aib2 C24 lactam 40 k [172] [70 nmol/kg]	GLP-1 (Aib2 C24 40 k) [70 nmol/kg]	DIO mice Once daily for 27 days	After 6 h of fasting	Change vs. vehicle • GLP-1: −20.1% ($p < .001$) • GLP-1/Glucagon −28.1% ($p < .001$)	Total cholesterol [mg/dl] (mean ± SE) • Vehicle: 254.0 ± 25.33 • GLP-1 (Aib2 C24 40 k): 200.8 ± 29.58 ($p < .05$ vs. vehicle) • GLP-1/ Glucagon 106.9 ± 6.3 ($p < .001$ vs. vehicle; $p < .05$ vs. GLP1) Liver fat (Oil Red O staining) • GLP-1/ Glucagon < GLP-1 < Vehicle
	Aib2 C24 lactam 40 k [172] [70 nmol/kg]	GLP-1 (Aib2 C24 40 k) [70 nmol/kg]	DIO mice Once daily for 9 days	After 6 h of fasting	Not shown	FPLC • LDL-C: GLP-1/ Glucagon < GLP-1 < Vehicle • HDL—C: GLP-1/ Glucagon < GLP-1 < Vehicle

Table 2 (*Continued*)

Compound	Compound variant, Reference	Comparator	Experimental design	Sample collection	Body weight	Lipid parameters
	DualAG Gluc [173] [1.9 μmol/kg]	GLP-1 (GLPAG) [1.9 μmol/kg]	DIO mice Once every other day for 2 weeks	Not specified	Change vs. vehicle • GLP-1: −12% ($p < .05$) • GLP-1/Glucagon −25% ($p < .05$)	Total cholesterol [mg/dl] (mean ± SE) • Vehicle: 153 ± 6 • GLP-1: 107 ± 5 ($p < .05$ vs. vehicle) • GLP-1/ Glucagon vs. vehicle: 76 ± 7 ($p < .05$ vs. vehicle; $p < .05$ vs. GLP-1) TG [mg/dl] (mean ± SE) • Vehicle: 68 ± 8 • GLP-1: 47 ± 6 ($p < .05$ vs. vehicle) • GLP-1/ Glucagon: 44 ± 5 ($p < .05$ vs. vehicle) FFA [mM] (mean ± SE) • Vehicle: 0.2 ± 0.0 (n.s) • GLP-1: 0.3 ± 0.0 (n.s) • GLP-1/ Glucagon: 0.4 ± 0.1 (n.s) Liver fat (histology) • GLP-1/ Glucagon < GLP-1 < Vehicle
	PEG-GLP-1/ glucagon [219] [30 nmol/kg]	none	DIO mice Once every fourth day for 33 days	After 4 h of fasting	Change vs. vehicle −26.49 ± 4.93% ($p < .001$)	Total cholesterol [mg/dl] • GLP-1/ Glucagon: down vs. vehicle ($p < .05$)

Table 2 (*Continued*)

Compound	Compound variant, Reference	Comparator	Experimental design	Sample collection	Body weight	Lipid parameters
	Aib2 C24 lactam 40 k [266] [0.5 mg/kg]	Glucagon [2.5 mg/kg]; GLP-1 (Exendin-4) [8 μg/kg] Pair feeding to co-agonist	DIO mice Twice daily for 28 days	After 6 h of fasting	Change vs. vehicle • GLP-1: −6.3% ± 5.1% ($p < .01$) • Glucagon: −12.8% ± 5.1% ($p < .01$) • GLP-1/Gluc: −19.0% ± 4.3% ($p < .01$)	Total cholesterol [mg/dl] (mean ± SE) • Vehicle: 147.4 ± 5.3 • GLP-1: 133 ± 4.5 (n.s.) • Glucagon: 114.4 ± 3.0 ($p < .01$) • GLP-1/ Glucagon: 81.6 ± 5.5 ($p < .01$) • Pair fed: 124.8 ± 9.5 TG [mg/dl] (mean ± SE) • Vehicle: 195.1 ± 14.4 • GLP-1: 176.5 ± 14.6 (n.s.) • Glucagon: 166.7 ± 21.6 • GLP-1/ Glucagon: 128.8 ± 12.2 ($p < .05$) • Pair fed: 179.9 ± 17.8 LDL-C [mg/dl] (mean ± SE) • Vehicle: 65.3 ± 4.9 • GLP-1: 43.2 ± 4.9 ($p < .01$) • Glucagon: 45.3 ± 6.9 ($p < .01$) • GLP-1/ Glucagon: 27.9 ± 6.3 ($p < .01$) • Pair-fed: 69.5 ± 8.2 Liver TG [mg/g tissue] (mean ± SE) • Vehicle: 11.9 ± 0.3 • GLP-1: 7.6 ± 1.1 ($p < .01$) • Glucagon: 9.2 ± 0.4 (n.s.) • GLP-1/ Glucagon: 3.5 ± 0.4 ($p < .01$) • Pair fed: 10.2 ± 0.5

	DualAG [178] [25 nmol/kg]	GLP-1 (Liraglutide) [25 nmol/kg]	DIO mice Single sc. injection	After 2 h of fasting	Not determined	Total cholesterol [mg/dl] (mean ± SD) • GLP-1: no change • GLP-1/ Glucagon: down vs. vehicle ($p < .001$) TG [mg/dl] (mean ± SD) • GLP-1: no change • GLP-1/ Glucagon: down vs. vehicle ($p < .001$) LDL-C [mg/dl] (mean ± SD) • GLP-1: no change • GLP-1/ Glucagon: down vs. vehicle ($p < .05$) HDL-C [mg/dl] (mean ± SD) • GLP-1: no change • GLP-1/ Glucagon: no change Liver TG [mg/g tissue] (mean ± SD) • GLP-1: no change • GLP-1/ Glucagon: no change Liver Cholesterol [mg/g tissue] (mean ± SD) • GLP-1: up vs. vehicle ($p < .05$) • GLP-1/ Glucagon: up vs. vehicle ($p < .05$)

	Aib2 C24 Chimera [267] [150 μg/kg]	Chow fed mice	DIO mice Twice daily for 40 weeks with the start of HFD feeding	Not specified	Total body weight: Vehicle > > GlP1/ Glucagon ($p < .05$ vs. vehicle) > chow fed control ($p < .05$ vs. vehicle)	Total cholesterol [mg/dl] (mean ± SE) • Chow feeding: down vs. vehicle ($p < .05$) • GLP-1/ Glucagon: down vs. vehicle ($p < .05$) TG [mg/dl] (mean ± SE) • Chow feeding: down vs. vehicle ($p < .05$) • GLP-1/ Glucagon: down vs. vehicle ($p < .05$) LDL-C [mg/dl] (mean ± SE) • Chow feeding: down vs. vehicle ($p < .05$) • GLP-1/ Glucagon: down vs. vehicle ($p < .05$) FFA [mM] (mean ± SE) • Chow feeding: down vs. vehicle ($p < .05$) • GLP-1/ Glucagon: down vs. vehicle ($p < .05$) Liver TG [mg/g tissue] (mean ± SE) • Chow feeding: down vs. vehicle ($p < .05$) • GLP-1/ Glucagon: down vs. vehicle ($p < .05$) Liver Cholesterol [mg/g tissue] (mean ± SE) • Chow feeding: down vs. vehicle ($p < .05$) • GLP-1/ Glucagon: down vs. vehicle ($p < .05$)

	Aib2 C24 lactam 40 k [268] [75 μg/kg] and [150 μg/kg]	none	Cholesterol fed hamsters Twice daily for 8 weeks	Not specified	Not determined	Total cholesterol [mg/dl] vs. vehicle (mean ± SE) • GLP-1/ Glucagon (75): −38.5 ± 7.0% ($p < .05$) • GLP-1/ Glucagon (150): −66.7 ± 3.1% ($p < .05$) TG [mg/dl] vs. vehicle (mean ± SE) • GLP-1/ Glucagon (75): −39.5 ± 3.8% ($p < .05$) • GLP-1/ Glucagon (150): −60.6 ± 3.4% ($p < .05$) VLDL [mg/dl] vs. vehicle (mean ± SE) • No changes LDL [mg/dl] vs. vehicle (mean ± SE) • GLP-1/ Glucagon (75): −49.8 ± 5.2% ($p < .05$) • GLP-1/ Glucagon (150): −68.3 ± 3.8% ($p < .05$) FFA [mM] vs. vehicle (mean ± SE) • GLP-1/ Glucagon (75): down ($p < .05$) • GLP-1/ Glucagon (150): down ($p < .05$) Liver TG [mg/g tissue] vs. vehicle (mean ± SE) • GLP-1/ Glucagon (75): −37.9 ± 5.7% ($p < .05$) • GLP-1/ Glucagon (150): −55.7 ± 5.7% ($p < .05$)

	Aib2 C24 lactam 40 k [268] [300 μg/kg]	Pair feeding to co-agonist	Cholesterol fed hAPoB100 / hCETB overexpressing mice. Once daily for 4 weeks	Not specified	Not determined	Total cholesterol [mg/dl] (mean ± SE) • Vehicle: 965.0 ± 18.2 • GLP-1/ Glucagon: 464.0 ± 11.7 ($p < .05$) • Pair-fed (150): 850.2 ± 41.6 TG [mg/dl] (mean ± SE) • Vehicle: 1610.0 ± 35.7 • GLP-1/ Glucagon: 871.8 ± 54.4 ($p < .05$) • Pair-fed: 1495.3 ± 31.2 LDL [mg/dl] v (mean ± SE) • Vehicle: 519.7 ± 16.5 • GLP-1/ Glucagon: 195.4 ± 8.6 ($p < .05$) • Pair-fed: 480.6 ± 11.3 FFA [mM] (mean ± SE) • Vehicle: 2.4 ± 0.1 • GLP-1/ Glucagon: 1.6 ± 0.2 ($p < .05$) • Pair-fed: 2.2 ± 0.2 Liver TG [mg/g tissue] (mean ± SE) • Vehicle: 28.8 ± 2.1 • GLP-1/ Glucagon: 14.7 ± 1.1 ($p < .05$) • Pair-fed: 25.2 ± 3.8 Liver cholesterol [mg/g tissue] (mean ± SE) • Vehicle: 7.1 ± 0.5 • GLP-1/ Glucagon: 3.8 ± 0.3 ($p < .05$) • Pair-fed: 6.5 ± 0.7

	SAR425899 [182] Ascending doses: [0.06–0.12-0.18 mg]	None	Heathy human (BMI: 25–30 kg/m ^{2}) Once daily for 21 days	Morning trough samples at day 21	GLP-1/Glucagon: −5.32 kg relative to baseline	Total cholesterol [mmol/l] (mean ± SD) • Placebo (Day 0): 4.99 ± 0.85 GLP1/Glucagon (Day 0): 6.0 ± 1.32 • Placebo (Day 21): 5.39 ± 0.80 GLP1/Glucagon (Day 21): 5.39 ± 0.39 TG [mmol/l] (mean ± SD) • Placebo (Day 0): 1.19 ± 0.51 GLP1/Glucagon (Day 0): 1.18 ± 0.54 • Placebo (Day 21): 1.60 ± 0.54 GLP1/Glucagon (Day 21): 0.88 ± 0.15 FFA [mmol/l] (mean ± SD) • Placebo (Day 0): 0.60 ± 0.19 GLP1/Glucagon (Day 0): 0.81 ± 0.38 • Placebo (Day 21): 0.60 ± 0.25 GLP1/Glucagon (Day 21): 0.80 ± 0.22

	SAR425899 [182] Ascending doses: [0.06–0.12-0.18 mg]	None	Heathy human (BMI: 20–30 kg/m ^{2}) and T2D patients (BMI 28–42 kg/m ^{2}) Once daily for 28 days	Morning trough samples at day 28	Change from baseline (mean ± SD) • Placebo: −2.37 ± 1.71 kg (ns) • GLP-1/Glucagon: −5.46 ± 1.98 kg ($p < .05$)	Total cholesterol [mmol/l] (mean ± SD) • Placebo (Day 0): 4.88 ± 1.03 GLP1/Glucagon (Day 0): 4.85 ± 0.85 • Placebo (Day 21): 4.37 ± 0.97 GLP1/Glucagon (Day 21): 4.25 ± 1.15 TG [mmol/l] (mean ± SD) • Placebo (Day 0): 3.00 ± 1.25 GLP1/Glucagon (Day 0): 2.12 ± 0.96 • Placebo (Day 21): 2.51 ± 0.81 GLP1/Glucagon (Day 21): 1.76 ± 0.74 FFA [mmol/l] (mean ± SD) • Placebo (Day 0): 0.90 ± 0.27 GLP1/Glucagon (Day 0): 0.97 ± 0.85 • Placebo (Day 21): 4.37 ± 0.97 GLP1/Glucagon (Day 21): 4.25 ± 1.15
	MEDI0382 (Cotadutide) [222] Ascending doses: [50–300 μg]	none	T2D Once daily for 49 days	Fasted state, day 49	Change from baseline (90% CI) • Placebo: −0.08% [−1.45, 1.28] • MEDI0382 −3.41% [−4.37, −2.44] ($p = .002$)	Change from baseline (90% CI) TG [mmol/l] • Placebo: 0.11 (−0.20, 0.42) • MEDI0382: −0.40 (−0.62, −0.18) ($p = .031$) FFA [mmol/l] • Placebo: 0.03 (−0.05, 0.10) • MEDI0382: −0.04 (−0.09, 0.02) ($p = .293$) LDL cholesterol [mmol/l]: • Placebo: 0.05 (−0.18, 0.29) • MEDI0382: −0.27 (−0.43, −0.11) ($p = .066$) Total cholesterol: HDL • Placebo: 0.00 (−0.27, 0.26) • MEDI0382: −0.03 (−0.21, 0.16) ($p = .905$)

GLP1/GIP	PEG GLP-1/GIP [175] [70 nmol/kg]	Acyl GLP-1/GIP [70 nmol/kg]; Liraglutide [70 nmol/kg]	DIO mice Once daily for 2 weeks	After 6 h of fasting	• PEG GLP-1/GIP −26.9% vs. vehicle ($p < .05$) • Acyl GLP-1/GIP −31.4% vs. vehicle ($p < .05$) • Liraglutide −15.6% vs. vehicle ($p < .05$)	Total cholesterol [mg/dl] • PEG GLP-1/GIP: down vs. vehicle ($p < .001$) • Acyl GLP-1/GIP: down vs. vehicle ($p < .001$) • Liraglutide: down vs. vehicle ($p < .001$) TG [mg/dl] (mean ± SE) • PEG GLP-1/GIP: down vs. vehicle ($p < .05$) • Acyl GLP-1/GIP: down vs. vehicle ($p < .05$) • Liraglutide: down vs. vehicle (ns) FFA [mmol/l] • PEG GLP-1/GIP: no change • Acyl GLP-1/GIP: no change • Liraglutide: up vs. vehicle ($p < .05$) Liver fat (Oil Red O staining) • PEG GLP-1/GIP = Acyl GLP-1/GIP < Liraglutide < Vehicle

	NNC0090–2746 [180] [1.8 mg]	Liraglutide [1.8 mg]	T2D patients Once-weekly for 12 weeks	Fasted state; week 12	• NNC0090; ETD [95%] −1.67% [−3.43; 0.09] vs. placebo (p = .0621) • Liraglutide ETD [95%] −1.23% [−3.00; 0.54] vs. placebo (p = .1710)	Total cholesterol [mmol/l] • NNC0090: Down vs. placebo (p = .0214) • Liraglutide: Down vs. placebo (p = .5325) TG [mmol/l] • NNC0090: Down vs. placebo (p = .2805) • Liraglutide: Down vs. placebo (p = .0068) VLDL [mmol/l] • NNC0090: Down vs. placebo (p = .5700) • Liraglutide: Down vs. placebo (p = .0932) LDL [mmol/l] • NNC0090: Down vs. placebo (p = .13739) • Liraglutide: no change HDL [mmol/l] • NNC0090: Down vs. placebo (p = .1418) • Liraglutide: no change FFA [mmol/l] • NNC0090: Down vs. placebo (p = .2770) • Liraglutide: Up vs. placebo (p = .1772)

	LY3298176 [181] [15 mg]	Dulaglutide [1.5 mg]	T2D patients Once-weekly for 26 weeks	Fasted state	Changes from baseline (mean ± SD) • Placebo −0.4 ± 0.81 kg • LY3298176 −11.3 ± 0.88 kg ($p < .01$) • Dulaglutide −2.7 ± 0.78 kg ($p < .05$)	Changes from baseline (mean ± SD) Total cholesterol [mmol/l] • Placebo: 0.3 ± 0.13 • LY3298176: 0.1 ± 0.12 • Dulaglutide: −0.2 ± 0.12 ($p < .05$) TG [mmol/l] • Placebo: 0.3 ± 0.16 • LY3298176: −0.8 ± 0.16 ($p < .01$) • Dulaglutide: −0.3 ± 0.15 ($p < .05$) VLDL [mmol/l] • Placebo: 0.0 ± 0.05 • LY3298176: −0.2 ± 0.05 ($p < .01$) • Dulaglutide: −0.1 ± 0.04 ($p < .05$) LDL [mmol/l] • Placebo: 0.2 ± 0.12 • LY3298176: 0.1 ± 0.03 • Dulaglutide: 0.0 ± 0.03 HDL [mmol/l] • Placebo: 0.0 ± 0.03 • LY3298176: 0.1 ± 0.03 • Dulaglutide: 0.0 ± 0.03
GLP-1/GIP/ Glucagon	Triagonist [176] [3 nmol/kg]	Acyl GLP1/GIP [3 nmol/kg]	DIO mice Once daily for 20 days	After 4 h of fasting	• Triagonist −26.6% vs. vehicle ($p < .001$) • Acyl GLP1/GIP −15.7% vs. vehicle	Liver fat (Oil Red O staining) Triagonist < Acyl GLP-1/ GIP < < Vehicle
	Triagonist [179] [10 nmol/kg]	none	DIO mice (males and females) Once daily for 27 days	After 4 h of fasting	• Triagonist (males) • −25.33 ± 1.67% vs. vehicle ($p < .001$) • Triagonist (females) • −18.55 ± 1.28% vs. vehicle ($p < .001$)	TG [mmol/l] • Triagonist (m): down vs. vehicle ($p < .05$) • Triagonist (f): down vs. vehicle ($p < .05$) FPLC (m/f) • LDL-C: Triagonist < Vehicle • HDL—C: Triagonist < Vehicle Liver fat (Oil Red O staining) (m/f) • Triagonist < < Vehicle

DIO (diet induced obese); ETD (estimated treatment difference); FFA (free fatty acids), TG (triglycerides).

fasting conditions [182]. MEDI0382 (Cotadutide) reduced LDL cholesterol levels as well as total cholesterol:HDL ratio, and caused significant reductions in plasma TG levels, compared to placebo controls [222]. The concomitant reductions in circulating TRL and liver fat in preclinical trials highlights a potential of GLP-1/glucagon co-agonists in the treatment of both dyslipidemia and NAFLD. Whether dyslipidemia is a cause or a consequence of NAFLD is not clear. Given that NAFLD is a disorder of hepatic lipid homeostasis, lipid lowering drugs appear as reasonable treatments for NAFLD. The combination of the beneficial effects of the GLP-1 moiety on postprandial dyslipidemia paired with the lipolytic action of glucagon in the liver and adipose tissue may therefore provide an exciting novel pharmacological approach. The safety and efficacy of MEDI0382 in obese subjects with NAFLD/non-alcoholic steatohepatitis (NASH) are currently being tested in phase 2 clinical trials.

6.2. GLP1/GIP

Acute exposure to dietary lipids serves as the strongest stimulus for GIP secretion from the K-cells located in the proximal duodenum [223,224]. In rodents, prolonged high-fat diet feeding increases intestinal GIP expression and the presence of GIP in the circulation [225,226]. Similar to GLP-1, GIP increases insulin secretion in a glucose-dependent manner [227–229]. The biological function of GIP is terminated by DPP-4 mediated cleavage and renal clearance leading to a half-life of approximately 7 min in healthy human subjects and 5 min in T2D patients [38].

Existing studies of GIP secretion in T2D patients are conflicting, with some studies showing enhanced [230–234], or unchanged [62,235,236] secretion in T2D patients, yet the majority of studies did not correct for possible confounding effects of body weight. Seemingly more solid clinical evidence exists regarding the insulinotropic effect of GIP, which is diminished in T2D patients relative to normal glycemic individuals [237,238]. It is important to note that the insulinotropic effect of GLP-1 is also similarly diminished in these T2D patients. Normalization of glycemia by insulin therapy restored the ß-cell responsiveness to GIP in T2D patients [239], an important realization that might also explain why GLP-1/GIP dual-agonism may offer superior glycemic benefits over GLP-1 (or GIP) monotherapy.

The presence of the GIP receptor (GIPR) on adipose tissue and its downregulation in subcutaneous tissue of obese patients [240] suggests that GIP serves as an important regulator of lipid homeostasis. Although GIP did not change fasting lipids [241], it has been reported to regulate TG turnover and promote postprandial lipid clearance in dogs [242] and rats [241]. GIP enhanced LPL activity in cultured murine [243,244] and human adipocytes [244,245], and in rat epididymal adipose explants [246]. GIP increased FFA uptake in human adipocytes [245] and inhibited glucagon stimulated lipolysis [247]. Surprisingly, despite these findings, GIP alone or in combination with insulin did not significantly affect the clearance of an “intralipid” TAG-emulsion in humans [248,249]. The reason for this discrepancy remains to be determined.

An important role for GIP in lipid storage of adipose tissue is supported by findings from studies in global GIPR KO mice which were protected from diet-induced obesity and insulin resistance [250]. Similar findings were found in a mouse model with K-cell ablation [251]. Interestingly, HFD-fed adipose tissue-specific GIPR knockout ($GIPR^{adipo-/-}$) mice had a comparable adipose tissue volume, but with improvements in diet-induced insulin resistance and hepatic steatosis compared to the WT controls [252]. Accordingly, GIP ablation seems to induce metabolic improvements that go beyond its effect on adipose tissue, but the underlying mechanisms and target tissues remain to be identified. Targeting GIP nonetheless is as an attractive pharmacological target for obesity and comorbid sequelae. Indeed, therapeutic approaches based on immunization against GIP [253,254] or GIP antagonism showed promising anti-obesogenic effects in mice [255] and in humans [256,257]. Conversely, there is also convincing experimental evidence that the amplification of GIPR signaling in GIP overexpressing mice can reduce body weight [258]. Similarly, structurally-refined GIP receptor agonists promoted body weight loss via inhibiting food intake [259]. The treatment of mice with a DPP-4 resistant D-Ala^2-GIP agonist for 2 weeks led to reductions in body weight and LPL activity [260]. Accordingly, an ongoing debate about the clinical benefits of GIP antagonism vs. agonism persists to date.

Single molecule GLP-1/GIP dual agonists have been developed, one of which (NNC0090-2746; MAR709) [175,180] already completed phase 2 clinical trials. NNC0090-2746 was designed to provide nearly balanced activity at GLP1R and GIPR [175]. A second one, tirzepatide (LY3298176) [181] just entered phase 3 clinical trials. Tirzepatide displays a roughly 5-fold greater affinity to the GIPR relative to the GLP1-R. Both dual agonists have minimal activity at glucagon receptors [261]. In pre-clinical and clinical trials, both dual agonists demonstrated improvements in glycemic control and body weight [180,181]. Tirzepatide showed greater efficacy on body weight loss and glucose control compared to dulaglutide over 26 weeks of treatment [181]. Only few lipid parameters have been investigated in these studies (Table 2). For NNC0090-2746, an 8% decrease in total cholesterol from baseline was observed, whereas liraglutide alone had no effect. Similarly, tirzepatide reduced mean total cholesterol with a higher efficacy compared to dulaglutide, but no differences were reported for HDL-C and LDL-C [181].

Acute and chronic studies on the effects of both dual-agonists on postprandial lipid metabolism have yet to be performed. Similarly, results for effects on sdLDL particles and HDL activity are lacking. Consequently, what effect these co-agonists might constitute in treatment of arthrosclerosis remains to be determined. Whether dual agonism at the GIPR and GLP1R leads to a superior postprandial lipid lowering by simultaneously acting on chylomicron production and clearance presently remains an unanswered question.

6.3. GLP-1/GIP/glucagon

Similar peptide analogs of GLP-1, GIP and glucagon facilitated the design of an intermixed single-sequence peptide for the parallel targeting of the two incretin and glucagon receptors [176,262]. Several single molecule peptides of varying inherent potency and relative activity balance across the three receptors have been developed [176,263]. Highest efficacy on body weight and glycemic control in murine models was achieved by a tritagonist with balanced action at the GLP-1, GIPR and GCGR. In a comparative study, the balanced, fully potent triagonist produced greater body weight loss in obese mice than the respective equimolar doses of respective co-agonists and mono-agonists [176]. Moreover, the triagonist decreased plasma cholesterol, which was attributed to a dose dependent and substantial reduction in LDL with a slight reduction in HDL in male and female mice [179]. Similar to findings in male mice [176], the triagonist potently improved diet-induced NAFLD in female mice and with similar efficacy as compared to the males [179] (Table 2).

The triagonist MAR423 is being assessed in early clinical trials by Novo Nordisk, with results not yet published. A second long-acting triagonist (HM15211), was studied in several different preclinical models, and reported to provide therapeutic efficacy against obesity, NAFDL, T2D, and Parkinson's disease in various preclinical models [264,265] and was recently approved for treatment of biliary and sclerosing cholangitis. Strikingly, HM15211 significantly lowered total cholesterol and hepatic steatosis in two different NASH models [265] and is currently being tested in phase 1 clinical trials for common obesity and NASH by Hanmi Pharmaceutical.

7. Conclusion

Postprandial lipid lowering effects of GLP-1RA and DPP-4 inhibitors are increasingly recognized as drivers for the anti-atherogenic and cardioprotective effects observed with these drugs. Acute benefits of GLP-1 on postprandial lipid metabolism can be mediated by the direct peripheral activation of GLP-1R and subsequent changes in pancreatic hormone secretion, lymph flow and gastric emptying. GLP-1RA may further modulate postprandial lipid metabolism indirectly via CNS GLP-1R with improvements in body weight, glucose control coupled to the autonomous control of hepatic lipid metabolism. These benefits of GLP1RA can be enhanced by including additional coordinated functionality through GIP and/or glucagon

activity. The initial hybrid peptide drug candidates were recently shown to induce synergistic reductions in body weight and hyperglycemia, as well as profound benefits in lipoprotein metabolism and for the treatment of NAFLD. Current best-in-class lipid lowering drugs are specifically designed to predominantly target high LDL-C levels and thus address only a fraction of the abnormal lipid profile of T2D patients. These patients remain to have a considerable residual risk for CVD. An add-on treatment with lipid lowering drugs such as niacin, fibrates and omega-3 fatty acids were shown to help reducing that risk in patients with hypertriglyceridemia. Similar benefits on dyslipidemia and the CVD risk were recently reported for incretin-based drugs such as GLP-1RA and the related multi-agonists. These new incretin-based drugs show remarkable capacities to sustainably lower body weight and hyperglycemia, and their lipid-lowering profile may place them in a unique position as ideal supplemental add-on therapy to statins in T2D patients suffering from diabetic dyslipidemia. At the least, GLP-1RA and the related multi-agonists may offer a new complimentary avenue in the personalized management of high body adiposity, postprandial hyperglycemia and diabetic dyslipidemia.

Declaration of competing interest

KS and TDM declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review. BF is currently an employee of Novo Nordisk. RDD is a cofounder of Marcadia, a company that pioneered the discovery of glucagon mixed agonists. It was acquired by Roche and later Novo Nordisk. He is a co-inventor on several patents owned by Indiana University. MHT serves as a scientific advisory board member of ERX Pharmaceuticals, Inc., Cambridge, MA.

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