

Glucagon-Like Peptide-1 Receptor Agonists and Dual Glucose-Dependent Insulinotropic Polypeptide/Glucagon-Like Peptide-1 Receptor Agonists in the Treatment of Obesity/Metabolic Syndrome, Prediabetes/Diabetes and Non-Alcoholic Fatty Liver Disease—Current Evidence

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Abstract

The obesity pandemic is accompanied by increased risk of developing metabolic syndrome (MetS) and related conditions: non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), type 2 diabetes mellitus (T2DM) and cardiovascular (CV) disease (CVD). Lifestyle, as well as an imbalance of energy intake/expenditure, genetic predisposition, and epigenetics could lead to a dys-metabolic milieu, which is the cornerstone for the development of cardiometabolic complications. Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs promote positive effects on most components of the “*cardiometabolic continuum*” and consequently help reduce the need for polypharmacy. In this review, we highlight the main pathophysiological mechanisms and risk factors (RFs), that could be controlled by GLP-1 and dual GIP/GLP-1 RAs independently or through synergism or differences in their mode of action. We also address the evidence on the use of GLP-1 and dual GIP/GLP-1 RAs in the treatment of obesity, MetS and its related conditions (prediabetes, T2DM and NAFLD/NASH). In conclusion, GLP-1 RAs have already been established for the treatment of T2DM, obesity and cardioprotection in T2DM patients, while dual GIP/GLP-1 RAs appear to have the potential to possibly surpass them for the same indications. However, their use in the prevention of T2DM and the treatment of complex cardiometabolic metabolic diseases, such as NAFLD/NASH or other metabolic disorders, would benefit from more evidence and a thorough clinical patient-centered approach. There is a need to identify those patients in whom the metabolic component predominates, and whether the benefits outweigh any potential harm.

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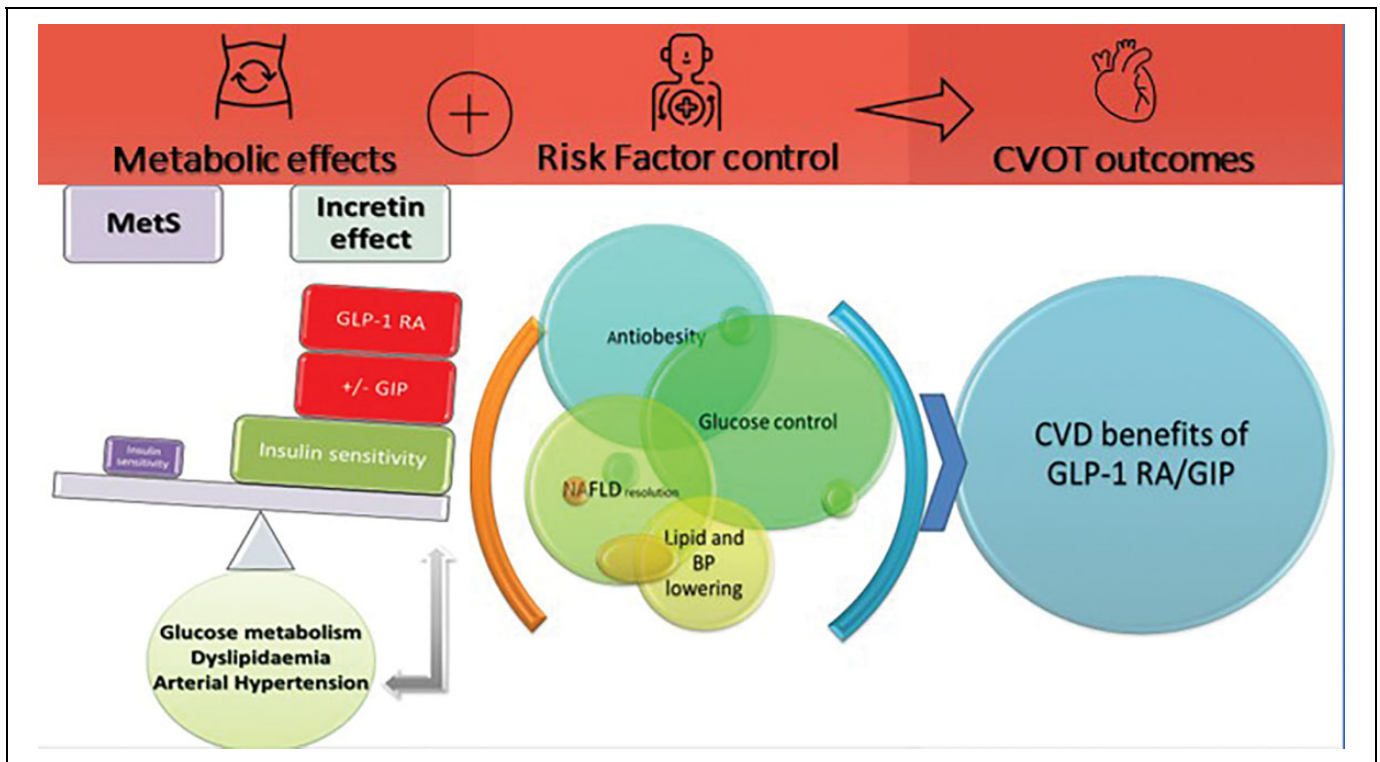
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Introduction

The pandemic proportions of obesity, defined as “abnormal or excessive fat accumulation that presents a health risk”, have received major attention.¹ Obese patients are at increased risk of developing metabolic syndrome (MetS) and its related conditions: non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), type 2 diabetes mellitus (T2DM) and cardiovascular (CV) disease (CVD).²

MetS includes a cluster of several CV risk factors (RFs) that may lead to CVD and NAFLD-related complications.³ The overlap between CV and NAFLD-related RFs (e.g., obesity, dyslipidaemia, hypertension, and T2DM), is driving the increase in the worldwide prevalence of NAFLD.⁴ The prevalence of NAFLD is >90% in patients undergoing bariatric surgery (severely obese), >76% of T2DM patients, and about 70% among CVD patients, compared with ~25% for the global general adult population.⁵⁻⁷

Genetic predisposition, epigenetics, lifestyle, as well as an imbalance of energy intake/expenditure could lead to a dysmetabolic milieu, which is the cornerstone for the development of both, NAFLD/NASH and CVD.⁸⁻¹¹ In fact, the considerable impact of dysmetabolism on NAFLD incidence and severity has been widely recognized and led to the proposal of a nomenclature change from NAFLD to Metabolic Associated Fatty Liver Disease (MAFLD).^{12,13} Given the similar pathophysiology, there is

emerging evidence that medications that can reduce CV morbidity and mortality (as well as reducing RFs for CVD) could also be used for the treatment of NAFLD/NASH.¹⁴ Furthermore, treatment of NAFLD/NASH must extend beyond the liver disease to include CVD risk reduction to reduce CVD mortality.¹⁴

Following the US Food and Drug Administration’s (FDA) requirement, since 2008 every new treatment option for T2DM¹⁵ is subject to major CV outcome trials (CVOTs).¹⁵ Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) represent significant progress in the treatment of T2DM patients because they affect a broad array of CVD RFs through body weight (BW) reduction,¹⁶ lipid level improvement, and positive effects on blood pressure (BP).¹⁷ Due to their CVD risk reduction properties,¹⁸⁻²³ GLP-1 RAs should be considered in patients with T2DM and possibly NAFLD.¹⁴

Glucose-dependent insulinotropic polypeptide (GIP), the dominant incretin hormone in healthy individuals, also enhances meal-stimulated insulin secretion in a glucose-dependent manner; however, in patients with T2DM insulin secretion after GIP stimulation is diminished.²⁴ Although GIP acts synergistically with GLP-1 RAs in promoting BW reduction by signaling satiety through receptors in the hypothalamus, there are also differences between the action of GIP and GLP-1 RAs.^{25,26} GIP showed no effect on glucagon response to hyperglycemia, while it strongly potentiated insulin secretion.²⁶ In contrast, during hypoglycemic

and fasting conditions, GIP increased glucagon levels without a significant effect on insulin secretion.²⁶ In addition, dual GIP and GLP-1 RAs showed robust effects on glycemic control and meaningful BW loss, indicating their potential use in the treatment of T2DM.²⁷ This has also raised the question of the possibility of their use in the treatment of other dysmetabolic conditions such as NAFLD/NASH.

This review will address the evidence on the use of GLP-1 and dual GIP/GLP-1 RAs for the treatment of obesity/MetS, prediabetes, NAFLD, T2DM and CV complications. We also highlight the main pathophysiological mechanisms and RFs that could be controlled by GLP-1 and dual GIP/GLP-1 RAs.

Literature Search

A PubMed electronic database search was conducted, without any limitation by publication date. A focus was placed on clinical studies, especially those published in the last 2 decades. A combination of Medical Subject Heading (MeSH) terms and non-MeSH terms was used, including glucagon-like peptide-1 receptor agonists, glucose-dependent insulinotropic polypeptide agonists, obesity, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, metabolic syndrome, prediabetes, type 2 diabetes mellitus, pathophysiology, and cardiovascular disease. Reference lists of selected publications were also searched. Since this was a narrative review, some articles, not retrieved during this search strategy, were added at the discretion of the authors if they were considered useful. All selected articles were in English and were peer-reviewed.

Pathophysiology of GLP-1 Receptor (GLP-1R) Agonism in Cardiometabolic RFs

GLP-1 binds to G-protein receptors on target tissues: pancreatic α - and β -cells, central and peripheral nervous system, skeletal muscle, heart, endothelium, kidneys, lungs, digestive system, adipose tissue (AT), lymphocytes, and eyes.²⁸ Food is the strongest stimulus for GLP-1 secretion. GLP-1 exerts insulinotropic effects through GLP-1R which are dominantly expressed in β pancreatic cells.²⁹ However, the expression of GLP-1Rs in other organs is responsible for the extrapancreatic actions of GLP-1 and its metabolic effects.^{29,30} When released into the blood, GLP-1 exerts several physiological effects (Figure 1): in the pancreas it increases the mass of β -cells and decreases apoptosis, stimulates glucose-dependent insulin secretion, reduces glucose-dependent glucagon secretion and slows gastric emptying, postprandial hyperlipidemia, intestinal motility, and gastric acid secretion.³⁰⁻³⁵

The effect of GLP-1 RAs on BW is independent of and distinct from its effect on plasma glucose levels.³⁶ The mechanisms for reducing BW are inhibition of gastric emptying and induction of satiety.³⁷ GLP-1 reduces appetite, and food intake, and increases satiety via GLP-1Rs in the hypothalamus.^{24,37,38} The action of GLP-1 RA affects meal onset and energy intake, not energy expenditure.³⁹ The sites of GLP-1R expression within the central nervous system and consequently

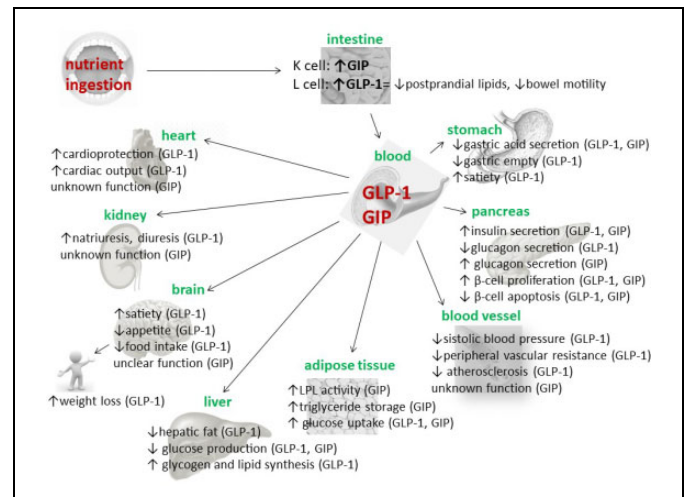


Figure 1. The pleiotropic effects of GLP-1 and GIP. GIP indicates glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1.

representative targets for GLP-1 action are neurons in the area postrema, hypothalamus, hindbrain, hippocampus, thalamus, lateral parabrachial nucleus, nucleus accumbens, vagal afferent neurons and nucleus tractus solitarius.⁴⁰

It is not completely clear whether BP and lipid profile improvement is a direct consequence of GLP-1 RA treatment, or a result of changes in body composition, BW loss, and/or better glucose regulation.¹⁶ The pathophysiological mechanisms responsible for the antihypertensive effect of GLP-1 RAs have not been fully clarified. Nevertheless, treatment with GLP-1 RAs affects cardiac performance and peripheral vascular resistance, which may partly explain their effect on BP.¹⁷ In addition, GLP-1R in the kidney can induce natriuresis and diuresis in the renal proximal tubule, through inhibition of NHE3 (Na⁺/H⁺ exchanger isoform 3).⁴¹ GLP-1R-induced natriuresis and diuresis are also accompanied by increases in glomerular filtration rate and renal plasma flow.⁴¹

Apart from the BW loss and positive effect on glucose regulation, GLP-1 can also influence triglyceride (TG) and total cholesterol (TC) levels.⁴² GLP-1R signaling modulates key enzymes of lipid metabolism in the liver and reverses cholesterol transport, reduces hepatic TG content (HTGC) and very low very-low-density lipoprotein (VLDL)-TG production rate from the liver, and impairs hepatocyte de novo lipogenesis and β -oxidation.⁴² Short- and long-term treatment with GLP-1 RAs reduced fasting and postprandial lipid levels in T2DM patients as well as in healthy populations.⁴² There is also evidence that some GLP-1 RAs can lower the concentration of distinct atherogenic lipoproteins in plasma⁴³; it is of clinical significance that GLP-1 RAs with proven cardiovascular benefit, such as liraglutide, are able to reduce the levels of small, dense LDL,^{44,45} since these particles are associated with the formation and progression of atherosclerosis.⁴⁶

In the liver, AT, and skeletal muscle cells, GLP-1 increases glucose utilization by stimulating glycogen and lipid synthesis

independent of insulin.⁴⁷ To date, it is still controversial whether the liver expresses GLP-1Rs, so, the effects of GLP-1 on the liver may be mediated indirectly. Indeed GLP-1 and GLP-1 RAs showed beneficial effects on the liver.⁴⁸ Some beneficial liver effects include postprandial GLP-1-mediated insulin secretion and inhibition of hepatic gluconeogenesis indirectly via the gut-pancreas-liver axis.⁴⁸ In addition, exendin-4 (a peptide with 39 amino acid residues isolated from the saliva of the Gila monster) or GLP-1 can activate key signaling molecules downstream of insulin receptor substrate-2 (a key substrate for insulin signaling in β -cells),⁴⁸ which consequently leads to insulin-like effects.

Numerous CV trials have reported improvements in CV outcomes in patients treated with GLP-1 RAs.^{49,50} GLP-1 has pleiotropic CV effects, including anti-inflammatory effects, cardioprotection in ischemia, and decreased platelet aggregation.³⁸ In addition, activation of GLP-1R resulted in various anti-atherosclerotic effects, e.g., reversing endothelial dysfunction (stimulates nitric oxide [NO] production and endothelial NO synthase [eNOS] activation, eliciting vasorelaxation in arterial endothelium), improving vascular smooth muscle cell dysfunction, reducing macrophage inflammation and foam cell formation, inhibiting NLRP3 (Nucleotide-Binding Domain, Leucine-Rich-Containing Family, Pyrin Domain-Containing-3) inflammasome and improving cardiomyocyte/cardiac fibroblast dysfunction.^{51,52} They also influence hypertension through renal and non-renal mechanisms.^{30,53} Based on the above mentioned cardiometabolic effects of GLP-1 RAs, these drugs are likely to be increasingly used to treat cardiometabolic disorders, other than DM.

Pathophysiology of GIP Receptor (GIPR) Agonism on Cardiometabolic RFs

GIP exerts important biological effects in many tissues, some of which remain to be explored (Figure 1). In addition to the pancreas, the human GIPR is widely distributed in AT, intestine, bone, and trachea, and is also detected in smaller amounts in the brain, heart, spleen, thymus, blood cells, lungs, and kidneys.⁵⁴ In the pancreas, it mediates its insulinotropic effects like GLP-1, but unlike GLP-1, GIP acts as a bifunctional stabilizer of blood glucose and stimulates glucagon secretion at lower glucose concentrations.^{55,56} Some effects of GIP differ from GLP-1: under conditions of insulin resistance (IR); it promotes lipid deposition in mice subcutaneous fat cells, it does not affect gastric emptying, and its effect on blood glucose is impaired in chronic hyperglycemia.^{24,57-59}

The reports on the role of GIP and GIPR in regulating BW make it an interesting target for addressing obesity. Obesity leads to GIP resistance in AT and a decrease in GIPR, whereas BW loss leads to an increase in GIPR and improves GIP activity.⁶⁰⁻⁶² In mice models, GIPR deficiency protects against diet-induced neuronal leptin resistance, a key problem in obesity.⁶³ A centrally administered antibody that neutralizes GIPR was effective against obesity in obese mice, therefore antagonism of GIP could be a therapeutic approach to prevent obesity.⁶³

However, the metabolic benefits of GIP antagonism have not yet been tested in humans.⁶⁴ Paradoxically, studies have shown that GIPR agonism and antagonism have similar effects on BW and glucose tolerance.⁶⁵ The effect of GIP on the hypothalamus and food intake is not clear, but in recent years hybrid molecules have been developed that promote greater BW loss than GLP-1 RAs alone by activating GIPR.^{66,67} However, GIP is another incretin that may enhance the metabolic effects of GLP-1 through complementary or synergistic actions. Surprisingly, when GIP was combined with GLP-1 and glucagon, glycemic control in obese mice improved, as did BW loss and reversal of NASH.^{67,68}

The effect of GIP on arterial hypertension is still under investigation. Patients with peripheral arterial disease have an increased GIP concentration, which correlates with peripheral arterial disease independently of diabetes mellitus (DM), CVD, age, sex, body mass index (BMI), hypertension, and smoking.⁶⁹ These observations identified GIP as a counterregulatory vasoprotective peptide.⁶⁹

GIP plays an important role in human lipid metabolism.^{70,71} Fat is the most potent nutrient that stimulates the release of GIP in humans.^{72,73} Results have shown that GIP plays a physiological role in promoting lipid deposition in AT in response to overeating by increasing lipoprotein lipase activity.^{74,75} On the other hand, GIP has been shown to reverse the accumulation of TG in AT, liver, and muscle.⁷⁶ Interestingly, GIP is a mediator of the increased TG storage in AT that leads to BW gain and obesity.^{24,51}

The presence of GIPR in the liver is controversial. It is also known that GIP mediates the development of fatty liver in response to the consumption of high glycemic index foods.⁷⁷ Studies in animal models suggest that GIP promotes the deposition of lipids in the liver, and GIP release/signaling mediates the development of fatty liver in response to high intake of carbohydrates, particularly sucrose.⁷⁸

The role of GIP in CVD is still unclear.^{79,80} In vitro, GIP can exhibit both pro-atherogenic (e.g., endothelin-1 production in vascular endothelial cells) and anti-atherogenic properties (enhancement of nitric oxide [NO] production, inhibition of cell proliferation in vascular smooth muscle cells, and suppression of inflammatory processes in adipocytes, macrophages, and monocytes).⁸¹⁻⁸³ In animal studies, GIP also increases hormone-sensitive lipase and cardiac TG.⁷⁹ Human studies showed that GIP increases heart rate,⁸⁴⁻⁸⁷ NO levels,^{88,89} interleukin (IL)-6, IL-1 β , monocyte chemoattractant protein 1,⁹⁰ vascular adhesion molecule-1 in blood and epithelium,⁹¹ and stimulates osteopontin expression in the vasculature via endothelin-1.⁹² It could lead to the progression of atherosclerosis in obese humans but prevent plaque formation in mice.^{93,94}

In addition, in vivo, pharmacological concentrations of GIP are likely to be protective against atherosclerosis in both, DM and non-DM patients.⁸¹ However, the question arises whether GIPR agonism or antagonism has CV benefits in humans. There is a need for further clarification.

Effects of GLP-1 RAs and GIPR agonists on dysmetabolic milieu/diseases are shown in Figure 2.

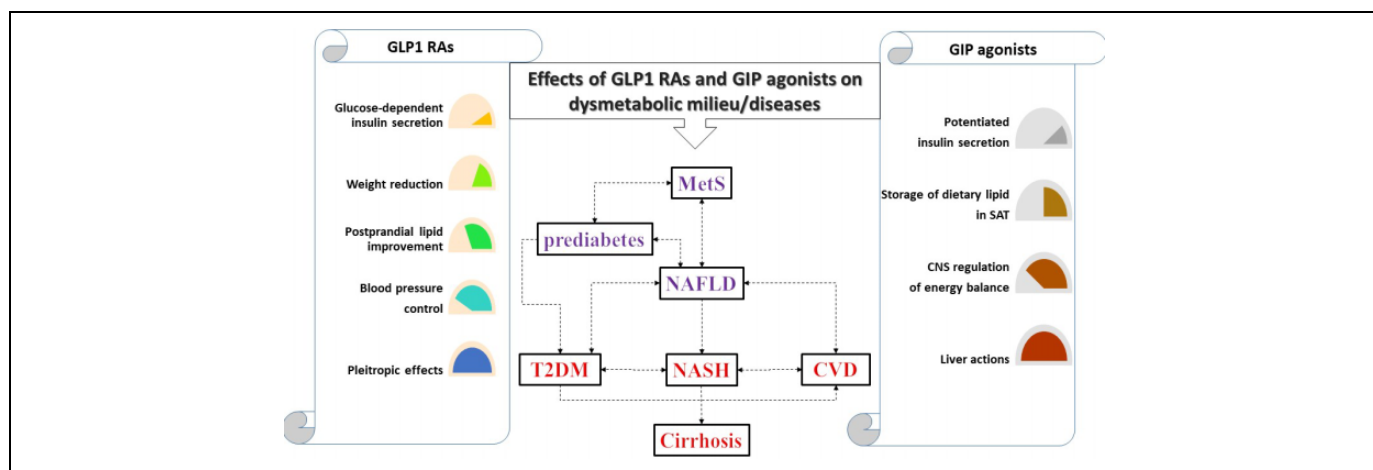


Figure 2. Effects of GLP-1 RAs and GIPR agonists on dysmetabolic milieu/diseases. CNS indicates central nervous system; CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RAs, glucagon-like peptide I receptor agonists; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SAT, subcutaneous adipose tissue; T2DM, type 2 diabetes mellitus.

GLP-1 RAs and Dual GIP/GLP-1 RAs in the Treatment of Non-Diabetic Obesity and Pre-Diabetes—Current Evidence

Obesity is phenotypically diverse, with some proportion of obese individuals who are metabolically healthy, without BP- or lipid-lowering medication, and with no abnormalities in insulin action.⁹⁵ However, in most individuals, obesity is closely associated with IR, the key pathophysiological driver of disturbed glucose-metabolism and a CV RF.⁹⁶ BW loss has benefits regardless of whether the pathophysiological origin of T2DM is β -cell dysfunction or IR.⁹⁷ While insulin-resistant individuals benefit most from BW loss, in patients with a primary defect in β -cell function, BW reduction might reduce β -cell gluco-lipototoxicity and minimize pharmacotherapy requirements.⁹⁷

Moderate weight loss of 5% to 10% is encouraged for glycemic and cardiometabolic RF control.⁹⁸ However, sustained loss of at least 15% BW has a major effect on the progression of T2DM, inducing remission in a large proportion of patients and markedly improving metabolic status.⁹⁹

Achieving the desired BW loss is extremely challenging and pharmacotherapy can be used in this setting. Treatment of obesity based on GLP-1 RAs proved to decrease morbidity and mortality in the adult population.¹⁰⁰ Two agents of the GLP-1 RA class are approved by one or more regulatory authorities worldwide for chronic BW management (liraglutide 3.0 mg subcutaneously (SC) and semaglutide 2.4 mg SC), in individuals without DM.⁹⁷ The remaining GLP-1 RA are recognized to promote BW loss while primarily prescribed for their glucose-lowering actions. Only exenatide, liraglutide, and semaglutide have been studied for their role in prediabetes progression in patients with obesity.^{101,102} Obesity may also complicate type 1 DM (T1DM) and “obese-induced insulin resistance” in T1DM children could be the main “driver” for NAFLD development.¹⁰³

Exenatide and liraglutide have been studied in these patients who also have suboptimal glycemic control or obesity;

consistent BW loss was demonstrated.¹⁰⁴ Dual agonists combining GLP1 with GIP are in the pipeline for obesity management and their potential role in T2DM.¹⁰⁵ Due to impressive BW loss in nondiabetic obese, who received tirzepatide, this agent will presumably affect T2DM risk and reversion of prediabetes.¹⁰⁶ The dual GIP/GLP-1 RAs, directly and indirectly, improve white AT function and ectopic lipid accumulation and subsequently whole-body insulin sensitivity.¹⁰⁷

Exenatide

Exenatide, the first approved GLP-1 RA, was developed for the treatment of T2DM. In this category of patients, in addition to its glucose-lowering effects, exenatide has shown significant improvement in many cardiometabolic parameters, including endothelial function and subclinical atherosclerosis.¹⁰⁸ Exenatide was also studied in nondiabetic patients with obesity and patients with prediabetes (with impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]) for its effects on BW and glucose tolerance. Exenatide-treated (10 μ g SC with a 4-week 5 μ g dose-initiation period) participants lost 5.1 ± 0.5 kg from baseline versus 1.6 ± 0.5 kg with placebo ($P < .001$), and the placebo-adjusted difference in percent BW reduction was $-3.3\% \pm 0.5\%$ ($P < .001$). Consequently, after 24 weeks, 77% of patients with prediabetes returned to normoglycemia, compared with 56% of patients treated with placebo.¹⁰¹ Another study targeted BW loss in nondiabetic women with short exenatide intervention and demonstrated that a subset of women had a robust response to exenatide treatment (30% of subjects who lost $\geq 5\%$ BW), while the other 30% even gained BW.¹⁰⁹

Liraglutide

Liraglutide was the first GLP-1 RA approved by the FDA and the European Medicines Agency (EMA) specifically for BW loss (ranging from 5%-10% reduction of initial BW). In a

network meta-analysis, liraglutide 3.0 mg SC was associated with significant excess BW loss versus placebo at 1 year -5.3 kg (95% confidence interval [CI]: -6.06 to -4.52 kg).¹¹⁰

The SCALE (Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities) trial aimed to evaluate the efficacy and safety of 3.0 mg of liraglutide administered once-daily SC in overweight or obese adults who did not have DM at baseline.¹¹¹ Patients ($n = 3731$; 56-week duration) treated with liraglutide lost 8.4 ± 7.3 kg, while those in the placebo group lost 2.8 ± 6.5 kg of BW (95% CI: -6.0 to -5.1 kg; $P < .001$).¹¹¹ In addition, fewer patients in the placebo group achieved at least 5% of BW loss from the baseline, compared with patients treated with liraglutide (27.1% vs 63.2%, $P < .001$). Besides the BW loss of $8.0\% \pm 6.7\%$, patients in the liraglutide group had improvements in beta-cell function and insulin sensitivity. Furthermore, T2DM developed in more patients in the placebo group than in the liraglutide group during the course of treatment.¹¹¹ One of 4 trials in the SCALE program targeted individuals ($n = 2254$) with prediabetes with the primary outcome: duration to the onset of DM. Over 160 weeks of treatment with liraglutide showed greater BW loss compared with placebo (-6.1% vs -1.9% , $P < .0001$), and the time to onset of DM among all randomized individuals was 2.7 times longer with liraglutide than with placebo (95% CI: 1.9-3.9, $P < .0001$), resulting in a hazard ratio (HR) of 0.21 (95% CI: 0.13-0.34).¹¹² Only 3% in the liraglutide-treated group developed DM by the end of the trial, compared with 11% in the placebo group. The main finding was highly prevalent prediabetes to normoglycemia conversion in the liraglutide group; 66% versus 36% in the placebo group ($P < .0001$).¹¹²

In accordance with this finding, an earlier, but a small, double-blind study of liraglutide 1.8 mg SC versus placebo that included older individuals ($n = 68$) with overweight/obesity and prediabetes, demonstrated that 75% of individuals treated with liraglutide achieved normal fasting glucose compared with 19% on placebo.¹¹³ Peripheral IR, as opposed to hepatic IR, was directly measured (with the modified version of the insulin suppression test) at baseline and after 14 weeks of liraglutide or placebo demonstrated that BW loss achieved with liraglutide was associated with a significant 29% improvement in IR.¹¹³

Semaglutide

Semaglutide, the most recently approved once-weekly (OW) GLP-1 RA, has been associated with pronounced BW loss in combination with dietary and physical activity counseling.^{102,114-116} The STEP (Semaglutide Treatment Effect in People with Obesity) trial program supported a market authorization approval for semaglutide for obesity treatment.^{102,115,116}

The STEP-1, a double-blind trial ($n = 1961$ adults), included either patients with obesity or overweight patients with at least one CV RF, who did not have DM.¹⁰² After randomization (in a 2:1 ratio) enrolled patients were treated with semaglutide (2.4 mg, OW SC) or placebo, plus lifestyle intervention, for 68 weeks. Treatment with semaglutide was

associated with sustained, clinically relevant -14.9% mean change in BW from baseline.¹⁰² In addition, treatment with semaglutide showed greater BW loss, from baseline to week 68, compared with patients in the placebo group (-15.3 vs -2.6 kg; 95% CI: -13.7 to -11.7). Weight loss of 15% or more of initial BW was achieved in 50.5% of patients treated with semaglutide and 4.9% of patients treated with placebo ($P < .001$).¹⁰² In the exploratory endpoints, the authors noted that 84.1% of participants in the semaglutide group who had prediabetes at baseline, as compared with 47.8% of participants in the placebo group with prediabetes reverted to normoglycemia.¹⁰²

In the STEP-3 trial ($n = 611$ patients with obesity/overweight plus one additional CV RF, without DM; randomized double blind), treatment with semaglutide (2.4 mg, OW SC) compared with placebo showed significantly greater estimated mean BW change from baseline to week 68 (-16.0% vs -5.7% , 95% CI: -12.0 to -8.6 ; $P < .001$).¹¹⁶ Weight loss of 15% or more of initial BW was achieved by 55.8% of patients treated with semaglutide and 13.2% of patients treated with placebo ($P < .001$).¹¹⁶

In the STEP-4 trial, after a 20-week run-in period (semaglutide, 2.4 mg OW SC), Rubino et al¹¹⁵ demonstrated that maintaining semaglutide treatment compared with switching to placebo showed continued BW reduction during the next 48 weeks (mean BW change -7.9% in the semaglutide group vs $+6.9\%$ with the switch to placebo, $P < .001$).

Daily SC semaglutide (doses from 0.05 to 0.4 mg) versus liraglutide (3.0 mg) and placebo for the treatment of non-diabetic obesity over 52 weeks led to the following estimated mean percentage BW reductions; -6.0% (0.05 mg), -8.6% (0.1 mg), -11.6% (0.2 mg), -11.2% (0.3 mg), and -13.8% (0.4 mg) for the semaglutide group versus -2.3% BW loss for the placebo group. Mean reductions in BW for 0.2 mg or more of semaglutide were all significantly greater than with liraglutide (-13.8% to -11.2% vs -7.8%). Estimated BW loss of $\geq 10\%$ occurred in 37% to 65% of participants receiving ≥ 0.1 mg of semaglutide.¹¹⁴

The STEP 1, 3, and 4 trials^{102,115,116} collectively included a large cohort of adults with prediabetes ($n = 1536$) and provide robust data on the effects of semaglutide on normoglycemia conversion during the 68 weeks of treatment. Among participants with baseline prediabetes, significant improvements in glucose metabolism and a high likelihood of normoglycemia were proven (STEP 1, 84.1%; STEP 3, 89.5%; STEP 4, 89.8%).¹¹⁷

Tirzepatide

A novel dual GIP/GLP-1 RA, tirzepatide (39-amino acid synthetic peptide), was developed for the treatment of T2DM, obesity/overweight with weight-related comorbidities, NAFLD/NASH, CV complications in T2DM, and heart failure. Its efficiency and safety led, in May 2022, to the first approval in the USA for improving glucose-regulation in T2DM patients.^{118(p202)} Furthermore, in October 2022, the FDA granted tirzepatide a Fast Track designation for the treatment of obesity and overweight.¹¹⁹

The SURMOUNT (A Study of Tirzepatide in Participants With Obesity or Overweight) trials were designed to test the ability of tirzepatide to produce BW loss in people who are overweight/obese but do not have DM. Recently, the SURMOUNT-1 trial (n = 2539 obese/overweight patients without DM, randomized double-blind phase 3 trial; duration 72 weeks) was published and showed that treatment with tirzepatide (5, 10, and 15 mg, OW SC) induced substantial and sustained BW loss (the mean percentage change in BW -15.0% , -19.5% , -20.9% , respectively). This was statistically significant when compared with placebo (mean percentage change in BW -3.1%) ($P < .001$).¹⁰⁶ The percentage of patients who had BW loss of $\geq 20\%$ was 50% (95% CI: 46-54) in the 10 mg and 57% (95% CI: 53-61) of patients in the 15 mg groups, compared with 3% in patients treated with placebo ($P < .001$ for all).¹⁰⁶ Furthermore, most of the prediabetes patients (95.3%) at baseline, treated with tirzepatide, had reverted to normoglycemia, when compared with 61.9% of patients treated with placebo.¹⁰⁶ Tirzepatide improved markers of beta-cell function and insulin sensitivity, and analysis of homeostasis model assessment-estimated (HOMA)-IR suggests that only 20% to 30% of the improvement in insulin sensitization by tirzepatide is due to BW loss, suggesting dual receptor agonism confers distinct mechanisms regarding glycemic control.¹²⁰

The antiobesity potential of GLP-1 and dual GIP/GLP-1 RAs in obese nondiabetic patients and individuals with prediabetes is summarized in Table 1.

Considerations Regarding Potential Clinical Use of GLP-1 and Dual GIP/GLP-1 RAs for the Treatment of Prediabetes in the Obese: Simplicity, Safety, and Tolerability

Since GLP-1 and GIP signaling is impaired in obesity and T2DM, restoring these mechanisms with incretin-based therapies is a reasonable option. Furthermore, the GLP-1 RA proven improvements in β -cell function in both preclinical studies and short-term clinical studies are promising for individuals with prediabetes. However, since T2DM prevention can be achieved by intensive lifestyle modification alone¹²² and since lifestyle modifications provide better long-term effects than medications,¹²³ tolerability and safety profile of potential pharmacotherapy should be thoroughly considered before clinical use. Several pharmacologic interventions besides GLP-1 RA have been shown to lower the incidence of T2DM in specific populations: metformin,¹²² acarbose,¹²⁴ rosiglitazone,¹²⁵ insulin glargine¹²⁶ and testosterone.¹²⁷ Up to now, no pharmacologic agent has been approved by the FDA specifically for T2DM prevention. However the use of metformin is encouraged in specific high risk populations by the American Diabetes Association.⁹⁸

A Cochrane database systematic review investigating the prevention or delay of T2DM with GLP-1 RA use included 7 trials with 2702 participants at increased risk for developing T2DM.¹²⁸ The analysis found limited-quality evidence that at-risk patients taking GLP-1 RAs are less likely to progress to

DM (number needed to treat (NNT) = 23). More individuals who received GLP-1 RA had serious adverse events than those who received placebo, 15.1% versus 12.7% (RR 1.18, 95% CI 0.94-1.47); absolute risk increase = 2.4%; number needed to harm (NNH) = 42. No comparisons among the different GLP-1 RA could be made because of the small number of participants for some GLP-1 RA class members.¹²⁸ The potential of a DM prevention intervention lies predominantly in the BW loss achieved by individuals at risk of T2DM.¹²⁹ It is also likely that some sub-phenotypes of individuals with prediabetes may benefit more of GLP-1 RAs rather than other therapeutic agents, and this highlights the importance of a more tailored approach for screening, prevention and management.¹³⁰ Therefore, further long-term comparative studies of interventions with novel potent anti-obesity medications of the GLP-1 RA class are needed to identify any differences in intervention effects.¹²³

GLP-1 RA for Weight Control in DM Patients

All GLP-1 RA class agents have proven efficacy in both, glucose control and concurrent clinically relevant BW reduction in patients with T2DM.¹³¹ However, patients with T2DM have more difficulty in losing BW compared with individuals without DM,¹³² and the mean BW loss difference between GLP-1 RAs and placebo in patients with and without DM was 4% to 6.2% versus 6.1% to 17.4%, respectively.¹³²

Trujillo et al¹³³ rated the drug members according to BW lowering potency in the following order: semaglutide > liraglutide > dulaglutide > exenatide extended-release = exenatide (twice daily) = lixisenatide. In addition, a meta-analysis rated SC semaglutide as the most potent in reducing BW, followed by oral semaglutide, exenatide twice daily and liraglutide, in patients with T2DM.¹³⁴

Liraglutide

In the SCALE Diabetes, among patients with T2DM who are overweight/obese, liraglutide treatment led to a more significant BW reduction, 6.0% (3.0 mg SC daily) and 4.7% (1.8 mg SC daily) when compared with placebo (estimated treatment difference [ETD]: -4.00% and -2.71% ; $P < .001$ for both).¹³⁵ BW reduction 10% or more occurred in 25.2% and 15.9% versus 6.7% of patients treated with liraglutide 3.0 mg and 1.8 mg SC versus placebo ($P < .001$ and $P = .006$, respectively).¹³⁵ Furthermore, in the SCALE Insulin randomized controlled trial (n = 396 T2DM patients with obesity treated with insulin) liraglutide (3 mg SC daily) as an adjunct to intensive behavioral therapy induced greater BW reduction when compared with placebo (mean BW change: -5.8% vs -1.5% , ETD: -4.3% [95% CI -5.5 to -3.2]; $P < .0001$).¹²¹

Semaglutide

In the STEP-2 trial (n = 1210 patients with T2DM, phase 3, double-dummy and double-blind superiority study,

Table 1. The Antiobesity Potential of GLP-1 and Dual GIP/GLP-1 RAs in Obese Nondiabetic Patients and Individuals With Prediabetes.

	GLP-1 RA/ dual GIP/GLP-1 RA	Primary outcome	Duration (weeks)	Population	Mean BW loss from baseline (kg)	The placebo-adjusted subtracted difference in percent BW (%)	Prediabetes to normoglycemia conversion vs placebo (%)
Rosenstock et al ¹⁰¹	Exenatide	Antiobesity efficacy	25	Nondiabetic patients with obesity	-5.1	-3.3	77 vs 56
Pi-Sunyer et al ¹¹¹	Liraglutide 3.0 mg SC (The SCALE trial)	Antiobesity efficacy	56	Overweight or obese nondiabetic patients	-8.4	-5.3	
le Roux et al ¹¹²	Liraglutide 3.0 mg SC (SCALE Obesity and Prediabetes)	Prediabetes to normoglycemia reversion	160	Individuals with prediabetes	N/A	-4.3	66 vs 36
Wilding et al ¹⁰²	Semaglutide 2.4 mg SC (The STEP trial 1, 3, 4)	Antiobesity efficacy	68	Overweight or obese nondiabetic patients	-15.3	STEP 1: -12.4 STEP 3: -10.3 STEP 4: -12.4/14.8 from week 20-68	See below
Rubino et al ¹¹⁵ Wadden et al ¹¹⁶							
Perreault et al ¹¹⁷	Semaglutide 2.4 mg SC (The STEP trial 1, 3, 4)	Prediabetes to normoglycemia reversion	68	Overweight or obese patients with prediabetes	See above	See above	STEP 1, 84.1 vs 47.8; STEP 3, 89.5 vs 55.0; STEP 4, 89.8 vs 70.4 79.7 vs 37.0
Garvey et al ¹²¹	Semaglutide 2.4 SC The STEP-5 trial	Prediabetes to normoglycemia reversion	104	Individuals with prediabetes	-16.1	-12.6	
Jastreboff et al ¹⁰⁶	Tirzepatide 5, 10, and 15 mg SC (The SURMOUNT-1 trial)	Antiobesity efficacy	72	Overweight or obese nondiabetic patients	N/A	-11.9, -16.4, -17.8	95.3 vs 61.9

Abbreviations: BW, body weight; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; SC, subcutaneous; SCALE trial, Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities trial; STEP trial, Semaglutide Treatment Effect in People with Obesity; SURMOUNT-1, A Study of Tirzepatide in Participants With Obesity or Overweight.

BMI ≥ 27 kg/m²) treatment with semaglutide (2.4 mg OW SC), compared with placebo, resulted in 6.2% ETD in mean BW loss ($P < .0001$).¹³⁶ In addition, after 68 weeks of the treatment, 68.8% of patients in the semaglutide (2.4 mg) group achieved BW reduction of $\geq 5\%$, compared with 28.5% of patients in the placebo group (odds ratio [OR]: 4.88, $P < .0001$).¹³⁶ It is important to mention that patients treated with insulin were excluded from the STEP-2 trial.¹³⁶

In the SUSTAIN-7 trial, semaglutide (1.0 mg OW SC) showed a significantly higher potency for BW reduction compared with dulaglutide (1.5 mg OW SC) in patients with T2DM (6.5 vs 3.0 kg, ETD -3.55 kg; $P < .0001$).¹³⁷

Tirzepatide

Tirzepatide is being investigated in the SURPASS (A Study of Tirzepatide in Participants With Type 2 Diabetes Not Controlled With Diet and Exercise Alone) phase 3 clinical trial program.¹³⁸ A 5 mg dose led to 7.6 kg (8.2%) BW loss, a 10 mg dose led to 9.3 kg (9.3%) and a 15 mg dose led to 11.2 kg (11.9%) BW loss over 40 weeks, in the SURPASS-2 study ($n = 1879$), and the reductions in BW were dose-dependent.¹³⁹ Reductions in BW were greater with tirzepatide at all doses (5, 10, or 15 mg, OW SC) than with semaglutide at a dose of 1 mg, with ETD -1.9 , -3.6 , and -5.5 kg, respectively ($P < .001$ for all).¹³⁹ In addition, approximately 8% of patients treated with semaglutide (1 mg OW SC) achieved a BW loss of $\geq 15\%$, compared with 15%, 24%, and 36% of patients treated with tirzepatide at doses of 5, 10, and 15 mg, respectively.¹³⁹

The SURMOUNT-2 trial, designed to test the ability of tirzepatide to produce BW reduction in participants with obesity who also have T2DM, is ongoing and is expected to be published in the first half of 2023.

Other Components of MetS: BP and Lipid Levels

The importance of CV RF is best illustrated by the fact that a 10 mmHg decrease in systolic BP reduces CVD risk by 11%,¹⁴⁰ while a 1 mmol/L lowering in low-density lipoprotein cholesterol (LDL-C) reduces the annual rate of CVD by approximately 20% in very diverse groups of patients.¹⁴¹

Although determining the isolated (independent of glycemic and BW reduction or changes in body composition) effects of GLP-1 RA on lipid levels and BP, requires well-designed studies, expert opinions confirm positive, but moderate effects on lipid levels and BP.¹⁷ According to a 2018 narrative review of head-to-head trials of 6 GLP-1 RA,¹⁴² the greatest statistical difference in BP was 2.7 mmHg (liraglutide resulted in a significantly greater decrease from baseline in systolic BP compared with dulaglutide).¹⁴³ Semaglutide 1.0 mg SC once weekly (OW) also significantly decreased systolic BP compared with exenatide 2 mg SC OW with a difference of 2.4 mmHg.¹⁴⁴ For diastolic BP, no significant between-treatment differences were reported in any of the included trials.¹⁴² The most recent GLP-1 RA, oral semaglutide (that

was not included in the previously mentioned review) demonstrated reductions of systolic BP (-2 [-5 to 0] mmHg; $P = .07$) compared with placebo.¹⁴⁵

Several large as well did some smaller dedicated GLP-1 RA clinical trials collected lipid data as secondary outcomes proving favorable effects on lipoprotein metabolism, with modest LDL-C, total cholesterol (TC), and fasting TG lowering. Some have also demonstrated substantial blunting of the postprandial rise in serum TGs.¹⁴⁶ Postprandial hypertriglyceridemia is a potential risk predictor of atherosclerotic CVD even in the presence of normal fasting TG levels.^{147,148} Its relevance is further enhanced because of the assumption that postprandial rise in serum TGs is a contributor to residual vascular risk despite aggressive LDL-C lowering.^{147,148} Notably, in a real-world prospective study involving obese T2DM patients, the reduction in triglyceride levels by liraglutide was the main contributor of the reduction in subclinical atherosclerosis, highlighting the importance of the triglycerides-lowering effect by GLP-1 RAs for vascular risk reduction.¹⁴⁹

One of the first double-blinded, randomized, placebo-controlled, crossover studies examining the lipid-lowering effect of GLP-1 RA was conducted in 35 subjects with IGT or recent-onset T2DM. It demonstrated the effect of a single SC injection of exenatide on postprandial lipids, remnant lipoproteins, and apolipoproteins. Exenatide reduced postprandial lipid and lipoprotein levels without the reduction in BW or fasting glucose and TG levels that usually occur with prolonged therapy.¹⁵⁰ In a recent first randomized trial, that addressed the possible effects of antidiabetic interventional drugs such as GLP1 RAs on endothelial and arterial stiffness indexes as surrogate markers of vascular damage, subjects treated with dulaglutide showed significantly lower values of mean serum TC and LDL-C.¹⁵¹

Oral semaglutide at the highest dose improves the fasting lipid level profile compared with placebo; it demonstrated a modest, but superior reduction in TC, LDL-C, and most pronounced reduction (OR 0.90 [0.83 to 0.99] in triacylglycerols (oral semaglutide 14 mg).¹⁴⁵ Compared with another GLP-1 RA (liraglutide), oral semaglutide was not significantly different.^{145,152} A randomized clinical trial is currently investigating the direct and indirect anti-atherosclerotic mechanisms of oral semaglutide, including its effect on the full spectrum of plasma lipids and lipoproteins.¹⁵³

Tirzepatide and any further dual GLP-1/GIP RAs that could be developed seem to be promising options for lipoprotein profile improvement in patients with T2DM. Tirzepatide dose-dependently decreased TG over time compared with placebo and dulaglutide, tirzepatide 5, 10, and 15 mg decreased TG levels by 28.8%, 37.7%, and 41.4%, respectively, compared with placebo.¹⁵⁴ It is speculated that the relative treatment effect would not be different regardless of the participant's baseline CV risk level, since similar changes in CV surrogate markers (BP and lipoproteins) by tirzepatide were observed in studies, that included participants with either high or moderate CV risk.¹⁵⁵ The SURMOUNT-1 trial demonstrated that in nondiabetic obese treatment with tirzepatide

(5, 10, and 15 mg, OW SC) induced substantial placebo subtracted change in systolic and diastolic BP (-6.2 and -4.0 mmHg, accordingly) and -20.3% change in TG level.¹⁰⁶ The reductions in BP and lipid levels of GLP-1 RA and dual incretin agonists cannot be directly translated into CV outcomes and seem to be complementary to other protective pleiotropic actions of this drug class.

GLP-1 RAs in the Treatment of NAFLD/NASH

The association of NAFLD and NASH with obesity and T2DM encouraged the investigation of the effect of GLP-1RAs in animal and human models of NAFLD/NASH.^{156,157} The fact that GLP-1RAs lead to improvement in hepatic steatosis through weight loss has been reported.^{158,159} However, experimental evidence based on both, animal models and human hepatocytes, have shown that GLP-1RAs may also play a direct role in ameliorating hepatic steatosis (by reducing de novo lipogenesis), mediated by the activation of genes associated with insulin sensitivity and fatty acid β -oxidation and improving several elements of the insulin signaling pathways.^{88,158,160,161} In patients with NAFLD/NASH, glucose-induced GLP-1 secretion is deficient, while GIP secretion is preserved.¹⁶²

The beneficial effects of GLP-1 RAs on the individual histological scores of NASH are multifactorial, due to the combined indirect effects on IR/hyperglycemia and BW reduction, as well as the result of a direct beneficial effect on the liver (regardless of weight loss and hyperglycemia).¹⁶³ These direct effects are fundamental for the establishment of GLP-1 RAs as a treatment option for NAFLD/NASH in patients in whom the fatty liver disease is not mainly driven by obesity.¹⁶⁴

Nevertheless, the presence or absence of GLP-1R in hepatocytes is controversial.^{34,160,165,166} GLP-1 increases glucose utilization in the liver, skeletal muscle, and AT by inducing glycogen and lipid synthesis independently of insulin level.⁴⁷ On the other hand, GLP-1RAs can stimulate lipolysis, AT browning, and pre-adipocyte differentiation.³⁴ Liraglutide and exenatide showed antioxidant effects via the c-Jun N-terminal kinase pathway or upregulation of protective antioxidant enzymes.¹⁶¹ GLP-1RAs attenuate endoplasmic reticulum stress responses by suppressing apoptosis.¹⁶⁷ In addition, GLP-1 RA exenatide attenuated fatty liver by activating sirtuin 1, an upstream regulator of adenosine monophosphate-activated protein kinase in hepatocytes, supporting the rationale for GLP-1-based NAFLD/NASH therapy.¹⁶⁸ Preclinical studies that recruited patients with NASH suggested that GLP-1 RAs might reduce hepatic inflammation through mechanisms that are at least partly independent of weight loss.¹⁵⁶ Mechanistically, as hepatocytes, stellate cells, and Kupffer cells do not express the canonical GLP-1R, the actions of GLP-1 on the liver are primarily indirect.

Exenatide may be an effective treatment for reducing hepatic fat content in patients with T2DM and obesity, but these effects are mainly dependent on BW reduction.¹⁶⁹ In a study

($n = 44$ patients with T2DM and obesity, HTGC was assessed with MRI and proton MRI spectroscopy, at baseline and 26 weeks after). In patients treated with exenatide, HTGC reduction was significantly related to body weight reduction ($r = 0.47$, $P = .03$), but was not associated with an improvement in IR, glycated hemoglobin level or adiponectin.¹⁶⁹

Armstrong et al in a randomized, double-blinded, multicenter, placebo-controlled phase 2 study evaluated SC injections of liraglutide (1.8 mg daily) versus placebo in patients who are overweight and showed clinical evidence of NASH.¹⁷⁰ Treatment with liraglutide led to histological resolution of NASH and was well tolerated and safe. After treatment, 39% of patients who were treated with liraglutide and underwent end-of-treatment liver biopsy had resolution of definite NASH versus 9% of patients treated with placebo (relative risk [RR] 4.3, 95% CI: 1.0-17.7; $P = .019$).¹⁷⁰ However, the LEAN (Liraglutide Efficacy and Action in NASH) trial suggested that liraglutide should be started early during the course of NAFLD, since in NASH patients with advanced fibrosis, it might not be useful.¹⁷⁰ In women ($n = 72$) with polycystic ovary syndrome (a well-known IR state), treatment with liraglutide promoted BW loss (-5.2 kg [5.6%]), reduced liver fat content (LFC) (by 44%) and showed reduction of the NAFLD prevalence by two-thirds ($P < .01$ for all).¹⁷¹

Katsiki et al in 2017 emphasized the need for investigation of the effects of semaglutide in patients with NAFLD.¹⁷² In a randomized, double-blind, placebo-controlled trial, liver stiffness was evaluated by MRI elastography and LFC by MRI proton density fat fraction [MRI-PDFF]; treatment with semaglutide significantly reduced LFC compared with placebo ($P < .0001$) but did not change liver stiffness in patients with NAFLD.¹⁷³ In patients with T2DM and obesity, semaglutide significantly reduced ALT activity and high-sensitivity C-reactive protein (hsCRP) levels.¹⁷⁴ Summarized data collected from CV and weight outcome trials showed that at the end-of-treatment ALT activity reductions were 6% to 21% ($P < .05$ for doses ≥ 0.2 mg/day).¹⁷⁴ The results of the meta-analysis showed that semaglutide, when compared with other GLP-1RAs liraglutide and dulaglutide was superior in decreasing the AST activity.¹⁷⁵ Newsome et al¹⁷⁶ evaluated the effects of semaglutide treatment in the resolution of NASH without worsening of fibrosis ($n = 320$ patients with biopsy-proven NASH and liver fibrosis of stage F1, F2, or F3). NASH resolution was achieved in 40%, 26% and 59% in the semaglutide 0.1-, 0.2-, and 0.4 mg groups versus 17% in the placebo group ($P < .001$ for semaglutide 0.4 mg SC vs placebo).¹⁷⁶

Treatment with dulaglutide improved AST, ALT, and gamma-glutamyl transferase (GGT) activity when compared with placebo, in a pattern consistent with LFC reductions.¹⁷⁷ Kuchay et al¹⁷⁸ in their study ($n = 64$ patients with T2DM and MRI-derived proton density fat fraction-assessed LFC of $\geq 6.0\%$ at baseline) evaluated the effects of dulaglutide treatment (OW for 24 weeks) on LFC. Treatment with dulaglutide significantly reduced GGT levels (mean between-group difference -13.1 U/l, $P = .025$) compared with controls, but there were no significant reductions in ALT, AST activity and

change in liver stiffness measurement (LSM in kPa) ($P = .10$, $P = .075$, and $P = .123$, respectively).¹⁷⁸ In addition, in patients with NAFLD dulaglutide significantly reduced LFC (control-corrected absolute change in LFC -3.5% , $P = .025$; relative change of -26.4% , $P = .004$), corresponding to a 2.6-fold greater reduction compared with controls.¹⁷⁸

Recent meta-analyses^{163,179-181} reported that GLP-1 RAs (mostly semaglutide and liraglutide) are highly promising pharmacological agents in the treatment of NAFLD or NASH. In the meta-analysis by Mantovani et al ($n = 2597$ individuals, 10 studies, included T2DM patients treated with GLP-1 RAs) treatment with semaglutide or liraglutide, as well as treatment with pioglitazone promoted resolution of NASH without worsening of fibrosis. GLP-1 RA treatment improved some of the NASH histological features, such as steatosis, lobular inflammation or ballooning.¹⁸¹ In another meta-analysis ($n = 936$ patients, 11 studies), Mantovani et al¹⁶³ reported that treatment with GLP-1 RAs, when compared with reference treatment or placebo, for a median of 26 weeks significantly decreased ALT (pooled weighted mean difference [WMD] -7.21 IU/L, $P = .02$) and GGT activity (pooled WMD -0.97 IU/L, $P < .001$), while AST activity did not differ between groups ($P = .27$).¹⁶³ More importantly, there was a significant reduction in the absolute percentage of LFC (using MRI-based techniques) (pooled WMD -3.92% , 95% CI: -6.27% to -1.56%) and greater histological resolution of NASH without worsening of liver fibrosis (pooled random-effects odds ratio [OR] 4.06, 95% CI: 2.52-6.55; for liraglutide and semaglutide only).¹⁶³ GLP1-RAs improve hepatic function, histology, and inflammation, by body weight reduction, improving glycemia, and decreasing hepatic fat. In this context, Ghosal et al¹⁷⁹ in their meta-analysis ($n = 615$ patients, 297 on GLP1-RA and 318 in the control group, 8 randomized controlled trials) evaluated effects of GLP-1 RAs in patients with both, T2DM and NAFLD. Treatment with GLP-1 RAs showed a significant improvement in AST activity (standardized mean difference [SDM]: -0.44 , 95% CI: -0.64 to -0.24 , $P < .01$), ALT (SDM -0.56 , 95% CI: -0.88 to -0.25 , $P < .01$), and GGT activity (SDM -0.60 , 95% CI: -0.86 to -0.34 , $P < .01$). As expected, GLP-1 RAs treatment showed a decrease in BW (SDM -0.66 , 95% CI: -0.88 to -0.44 , $P < .01$), glycosylated hemoglobin (SDM -0.40 , 95% CI: -0.61 to -0.19 , $P < .01$), as well as the reduction in LFC (SDM -0.43 , 95% CI: -0.74 to -0.12 , $P < .01$), compared with standard of care or placebo. This meta-analysis also showed a very significant improvement in liver histology in the group of patients treated with GLP-1 RAs (rate ratio, 6.60, 95% CI: 2.67-16.29, $P < .01$).¹⁷⁹

GLP-1 RAs demonstrated higher efficacy in LFC lowering when compared with insulin-based therapies or metformin.^{180,182} In a meta-analysis ($n = 1454$ patients, 8 studies), treatment with GLP-1 RAs significantly reduced LFC (SMD -1.05 ; $P < .001$) when compared with controls, and when compared with insulin-based therapies and metformin (SMD -0.66 , $P < .001$ and -0.63 , $P = .02$, respectively).¹⁸⁰ In addition, GLP-1RA significantly reduced ALT (SMD -1.69 , $P < .001$), AST (SMD -1.46 , $P < .001$), and GGT (SMD -2.10 ;

$P < .001$) activity.¹⁸⁰ When compared with insulin-based therapies, treatment with GLP-1 RAs resulted in significantly lower ALT activity (SMD -0.96 ; $P = .02$), and when compared with metformin treatment with GLP-1 RAs resulted in significant decreases in GGT and ALT activity (SMD -1.04 ; $P < .001$ and SMD -0.66 ; $P = .03$, respectively).¹⁸⁰ However, thiazolidinediones were superior when compared with GLP-1 RAs in the improvement in ALT, AST, and GGT activity.¹⁸⁰ When added to metformin, liraglutide reduced intrahepatic lipid content, promoted weight loss and reduced subclinical atherosclerosis (carotid intima-media thickness) in patients with NAFLD and T2DM.^{183,184} Furthermore, when added to pioglitazone, liraglutide and semaglutide were considered the most effective intervention for achieving NASH resolution.^{185,186}

Dual GIP/GLP-1 RAs in the Treatment of NAFLD/NASH

In patients with NASH, ingestion of saturated fatty acids is associated with prolonged GIP response, β glucometabolic parameters and carotid intima-media thickness-cell dysfunction, and with adipokine imbalance, and liver injury, which favors GIP antagonism in non-diabetic patients with NASH.¹⁸⁷ In addition, a doubling in fasting GIP levels may be associated with improved LDL clearance but with an unhealthy fat distribution independent of insulin levels.¹⁸⁸ These effects of GIP have not encouraged the further use and establishment of GIP monotherapy in metabolic-associated diseases, including NAFLD/NASH.

GIP and GLP-1 appear to activate distinct subsets of hypothalamic neurons coupled to a reduction in food intake,¹⁸⁹ and furthermore, the glucose-lowering effects of simultaneous GLP-1R agonism could rapidly restore GIP sensitivity, thus enabling superior glucose-lowering action when combined.¹⁹⁰ In patients with T2DM, higher tirzepatide doses significantly increased adiponectin levels and decreased NASH-related biomarkers.¹⁹¹ Hartman et al¹⁹² in their phase 2 trial ($n = 316$ T2DM patients, 26-weeks duration, treated with dulaglutide (1.5 mg SC), tirzepatide OW [1, 5, 10, or 15 mg SC] or placebo) evaluated the effect of tirzepatide on AST and ALT activity as well as adiponectin levels. Treatment with tirzepatide significantly decreased ALT (all tirzepatide doses, $P < .01$) and AST (all tirzepatide doses except 10 mg, $P < .05$) activity at 26 weeks. In addition, at 26 weeks of treatment, adiponectin increased significantly from baseline with tirzepatide 10 and 15 mg ($P < .001$).¹⁹²

In a recent substudy of the SURPASS-3 trial (SURPASS-3 MRI study; $n = 296$, randomized, open-label, parallel-group, phase 3, T2DM patients, BMI ≥ 25 kg/m², evaluated change in LFC measured by MRI-PDF, 52-week duration), pooled tirzepatide (10 and 15 mg doses, OW SC) promoted a significant reduction in LFC, visceral AT when compared with insulin degludec (-8.09% vs -3.38%), with the ETD versus degludec -4.71% (95% CI: -6.72 to -2.70 ; $P < .0001$).¹⁹³

The potential of GLP-1 and dual GIP/GLP-1 RAs in the treatment of NAFLD/NASH is summarized in Table 2.

Table 2. The GLP-1 and Dual GIP/GLP-1 RAs in the Treatment of NAFLD/NASH.

Reference	GLP-1 RA/ Dual GIP/GLP-1 RA		Included subjects	Duration (weeks)	Method	Study outcomes	Other findings
	GLP-1 RA/ Dual GIP/GLP-1 RA	Included subjects					
Dutour et al ¹⁶⁹	Exenatide	n = 44, T2DM + obesity	26	3T MRI+proton MRS	Significant reduction in LFC (-23.8% ± 9.5%)	Effects were mainly BW loss-dependent	
Kuchay et al ¹⁷⁸	Dulaglutide	n = 52, T2DM + MRI-PDFF-assessed LFC of ≥ 6.0% at baseline	24	MRI-PDFF-assessed LFC LSM measured by vibration-controlled transient elastography, and change in liver enzymes	LFC of -3.5% (95% CI: -6.6 to -0.4; P = .025) and relative change of -26.4% (P = .004), corresponding to a 2.6-fold greater reduction of GGT	Non-significant reductions in liver stiffness, serum AST and ALT levels	
Armstrong et al ¹⁷⁰	Liraglutide 1.8 mg SC	n = 52, overweight + clinical evidence of NASH	48	Liver histology	Histological resolution of NASH (RR 4.3 [95% CI: 1.0-17.7]; P = .019)		
Newsome et al ¹⁷⁴	Semaglutide 0.5 or 1.0 mg/week) / semaglutide 0.05-0.4 mg SC/day	n = 3268, CVOT subjects with obesity and/or T2DM	104	Change in liver enzymes	Normalization of elevated baseline ALT occurred in 25%-46%	Changes in ALT were not statistically significant after adjustment for BW change	
Newsome et al ¹⁷⁶	Semaglutide 0.5 or 1.0 mg SC/week) / semaglutide 0.05-0.4 mg SC/day	n = 320, with or without T2DM, biopsy-confirmed NASH and liver fibrosis of stage F1, F2, or F3	72	Liver histology	Significantly higher percentage of patients with NASH resolution + fibrosis stage improved in 43% of the patients in the 0.4 mg group	No difference between groups in the percentage of patients with an improvement in fibrosis stage	
Flint et al ¹⁷³	Semaglutide 0.4 mg SC/day	n = 67, subjects with liver stiffness 2.50-4.63 kPa MRE and liver steatosis ≥ 10% by MRI-PDFF)	48	MRI-PDFF, MRE	Significantly reduced liver steatosis	Decreases in liver enzymes, BW and HbA _{1c} also observed	
Hartman et al ¹⁹²	Dual GIP/GLP-1 RA tirzepatide 1, 5, 10 mg, and 15 mg SC	n = 316, T2DM	26	Changes from baseline in ALT, AST, keratin-18, procollagen III and adiponectin	Significant reductions from baseline in ALT (all groups), AST (all groups except tirzepatide 10 mg) levels	Significantly decreased NASH-related biomarkers and increased adiponectin levels	
Gastaldelli et al ¹⁹³	Dual GIP/GLP-1 RA tirzepatide 5, 10, and 15 mg SC vs degludec	n = 502, T2DM	52	MRI-PDFF	Significantly greater reduction in LFC for the pooled tirzepatide 10 mg and 15 mg groups (-8.09% ± 0.57%)	Reduction in LFC was significantly correlated with baseline LFC, reductions in VAT + BW	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BW, body weight; CI, confidence interval; CVOT, cardiovascular outcome trial; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; GGT, γ -glutamyl transpeptidase; HbA_{1c}, glycated hemoglobin; LFC, liver fat content; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MRI-PDFF, MRI-derived proton density fat fraction-assessed; MRS, magnetic resonance spectroscopy; NASH, non-alcoholic steatohepatitis; RR, relative risk; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue.

Current Evidence on GLP-1 RAs Use in Patients With DM and CVOTs

The risk of CVD is increased 2-fold in people with DM regardless of other conventional RFs.¹⁹⁴ In the last decade, the CV safety of drugs to lower blood glucose in T2DM has been questioned, such that any drug should preclude increased CV risk.¹⁵ Since then, several CVOTs have been conducted. Either a neutral effect or a reduction in CV events has been reported for the different GLP-1 RAs^{18-21,36,195,196} and, overall, a beneficial reduction in the risk for the distinct cardio-renal endpoints has been obtained by the analysis of available data.¹⁹⁷

Indeed, nine published CVOTs studies examined the effects of GLP-1 RAs compared with placebo on major adverse CV events (MACE) incidence in T2DM patients: (1) Lixisenatide 20 µg/day SC (the Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA] trial; n = 6068; duration 2.1 years; 100% prevalence of CVD),¹⁹⁵ (2) Liraglutide 1.8 mg SC/day (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER]; n = 9340; duration 3.8 years, 81% prevalence of CVD),¹⁸ (3) Exenatide ER 2 mg SC /week (Exenatide Study of Cardiovascular Event Lowering Trial [EXSCEL]; n = 14752; duration 3.2 years, 73% prevalence of CVD),¹⁹⁶ (4) Albiglutide 30 to 50 mg SC/week (HARMONY; n = 9463; duration 1.6 years, 100% prevalence of CVD),³⁶ (5) Dulaglutide 1.5 mg SC/week (Researching Cardiovascular Events With a Weekly Incretin in Diabetes [REWIND] n = 9901; duration 5.4 years, 31% prevalence of CVD),²⁰ (6) Semaglutide 0.5 to 1 mg SC/week (Semaglutide unabated Sustainability in Treatment of Type 2 Diabetes [SUSTAIN]-6 n = 3297; duration 2.1 years; 83% prevalence of CVD),¹⁹ and (7) Oral semaglutide 14 mg/day (Peptide Innovation for Early Diabetes Treatment [PIONEER-6] n = 3181; duration 1.3 years; 85% prevalence of CVD).²¹ Furthermore, [AMPLITUDE-O] (Effect of Efpeglenatide on Cardiovascular Outcomes) n = 4076; duration 1.8 years) included more patients (32%) with renal disease (eGFR 25-60 mL/min) than the other trials and was the first clearly positive CVOT with an exendin-4-based GLP-1 receptor agonist.¹⁹⁸

The FREEDOM (Clinical Impact of ITCA 650 [an injection-free preparation delivering exenatide via a mini osmotic pump placed in the subdermal tissue of the abdominal wall], a Novel Drug-Device GLP-1 Receptor Agonist, in Uncontrolled Type 2 Diabetes and Very High Baseline HbA1c; n = 4,156, duration 16 months) studies evaluated exenatide delivered via an implanted minipump (ITCA 650) in patients with T2DM. ITCA 650 was non-inferior to placebo in CV outcomes, however longer-duration CVOT is needed to more precisely define the CV effects.¹⁹⁹ Trials that reported a reduced HR for the primary composite CV endpoint of first occurrence of nonfatal myocardial infarction or stroke or death from CV causes were LEADER (HR 0.87, 95% CI: 0.78-0.97), SUSTAIN-6 (HR 0.74, 95% CI: 0.58-0.95), HARMONY (HR 0.78, 95% CI: 0.68-0.90), and REWIND (HR 0.88, 95% CI: 0.79-0.99). Lixisenatide (ELIXA), exenatide (EXSCEL), and oral semaglutide (PIONEER) were non-inferior to placebo on

the primary composite outcome of MACE (respectively, 1.02, 95% CI: 0.89-1.17; 0-91, 95% CI: 0.83-1.00; 0.79, 95% CI: 0.57-1.11).

CVOT for tirzepatide (SURPASS-CVOT) is ongoing. However, Sattar et al¹⁵⁵ recently published a pre-specified CV meta-analysis of all 7 randomized controlled trials (n = 144 T2DM patients) from the SURPASS trial program. The HRs comparing tirzepatide versus controls were 0.90 (95% CI: 0.50-1.61) for CV death, 0.80 (95% CI: 0.57-1.11) for MACE-4 and 0.80 (95% CI: 0.51-1.25) for all-cause death.¹⁵⁵

A recent meta-analysis of 7 CVOTs⁴⁹ showed that GLP-1 RAs reduced MACE by 12% (HR 0.88; *P* < .001), CV mortality by 12% (HR 0.88; *P* = .003), fatal or nonfatal stroke by 16% (HR 0.84; *P* < .001), and fatal or nonfatal myocardial infarction by 9% (HR 0.91; *P* = .043). Another meta-analysis of the same 7 CVOTs found that the number of treatments required to prevent MACE was 73 (95% CI: 45-212).²⁰⁰

Expert Opinion

In conclusion, the well-established GLP-1 RAs and novel dual GIP/GLP-1 RAs are drug classes with various effects that cover a wide range of “*dysmetabolic milieu*” disorders associated with obesity. Given the clear association of obesity with MetS and its components, prediabetes, T2DM, cardiometabolic complications, and NAFLD/NASH, GLP-1 RAs and dual GLP-1/GIP RAs promote crucial positive effects on the most components of the “*cardiometabolic continuum*” and consequently help reduce the need for polypharmacy.

Clinical evidence from well-designed trials and real-life data indicates that currently, the GLP-1 RAs are the most promising drugs for the treatment of obesity. Moreover, the novel GLP-1/GIP RA tirzepatide shows even greater potential for weight reduction. This finding is in line with the GIPR agonism potential for ameliorating the GLP-1 RA dose-related gastrointestinal side effects and the proposed synergy of the incretins to promote satiety. Their combined weight-related potential is translated into the improvement of components of the MetS (e.g., dyslipidaemia, hypertension, reduction of visceral AT, etc.), which are also CV RFs. The postulated BW-independent effects of GIP RA on lipid metabolism suggest that the dual agonists play an important role in improving the lipoprotein profile.

It is well-known that GLP-1 RAs are the most potent non-insulin drugs for the treatment of T2DM, with currently limited use in terms of the treatment of prediabetes and the prevention of T2DM. With few exceptions,²⁰¹ there is a large lack of head-to-head trials with the use of 2 GLP-1 RAs as direct comparators, since in any trial the comparator to the studied agent is the so-called “standard of care”, and this limits the utility of information for clinicians. Although direct comparisons are not possible since differences in study designs exist, considering normoglycemia conversion rates were approximately 66% with liraglutide, 84% with semaglutide, and >95% with tirzepatide. Furthermore, tirzepatide demonstrated restoration of insulin sensitivity irrespective of the BW loss magnitude. It is irrefutable and clear that an adequate dietary regimen is still the

cornerstone of T2DM prevention and prediabetes treatment, with possible additional and favorable use of both, GLP-1 and dual GLP-1/GIP RAs after assessing the benefits and risks for each patient individually. The results of the registration studies of GLP-1/GIP RA tirzepatide indicate robust improvements in glycemic control in patients with T2DM, without increased risk of hypoglycemia, with the safety profile which was consistent with GLP-1 RAs. Comparatively, these results are likely to pave the way for tirzepatide in clinical practice guidelines and its incorporation in the treatment algorithm, as one of the initial treatment options.

Understanding and positioning of GLP-1 and GLP-1/GIP RAs in the treatment of NAFLD/NASH is complex. It is important to emphasize that the pathogenesis of NAFLD/NASH can be explained in part by a genetic component, and in part by a metabolic component. The mechanisms underlying these components are fundamentally different. Metabolic components are characterized by the hepatic oversupply of substrates (e.g., sugars, lipids, and amino acids), while the genetic component is characterized by impaired hepatic mitochondrial function, making the liver less able to metabolize these substrates. This leads to the conclusion that the use of GLP-1 and dual GLP-1/GIP RAs requires more evidence and a thorough clinical patient-centered approach, intending to identify those patients in whom the metabolic component predominates. Given the complex etiology of NAFLD, future studies require better design to avoid the various biases that cloud this field and to pave the way for the right use of GLP-1 and GLP-1/GIP RA in the treatment of NAFLD/NASH and other “*dysmetabolism*” complications.

The place of GLP-1 RAs in CV diabetology is clearly and unequivocally expressed by the guidelines for the treatment of T2DM, as a crucial and most important drug class in patients with atherosclerotic CVD, which was clearly shown through published GLP-1 RAs CVOTs.²⁰² Moreover, CVOT for tirzepatide (SURPASS-CVOT) is ongoing and its results are expected soon.

Author Contributions

Emir M. Muzurović contributed to the conception and design, wrote the manuscript, contributed to the research data discussion, and reviewed the data and manuscript. Špela Volčanšek contributed to the conception and design, wrote the manuscript, contributed to the research data discussion, and reviewed the data and manuscript. Karin Zibar Tomšič contributed to the conception and design, wrote the manuscript, contributed to the research data discussion, and reviewed the data. Andrej Janež contributed to the conception and design, drafting, and critical review of the manuscript. Dimitri P. Mikhailidis contributed to the conception and design, drafting, and critical review of the manuscript. Manfredi Rizzo contributed to the conception and design, drafting, and critical review of the manuscript. Christos S. Mantzoros contributed to the conception and design, drafting, and critical review of the manuscript. All authors reviewed and approved the final version of the manuscript.

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References

1. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362
2. Ansari S, Haboubi H, Haboubi N. Adult obesity complications: challenges and clinical impact. *Ther Adv Endocrinol Metab*. 2020;11:2042018820934955. doi:10.1177/2042018820934955
3. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. *Metabolism*. 2019;92:82-97. doi:10.1016/j.metabol.2018.11.014
4. Muzurović E, Peng CCH, Belanger MJ, Sanoudou D, Mikhailidis DP, Mantzoros CS. Nonalcoholic fatty liver disease and cardiovascular disease: a review of shared cardiometabolic risk factors. *Hypertension*. 2022;79(7):1319-1326. doi:10.1161/HYPERTENSIONAHA.122.17982
5. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793-801. doi:10.1016/j.jhep.2019.06.021

6. Portillo-Sanchez P, Bril F, Maximos M, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. *J Clin Endocrinol Metab.* 2015;100(6):2231-2238. doi:10.1210/jc.2015-1966
7. Ajmal MR, Yaccha M, Malik MA, et al. Prevalence of nonalcoholic fatty liver disease (NAFLD) in patients of cardiovascular diseases and its association with hs-CRP and TNF- α . *Indian Heart J.* 2014;66(6):574-579. doi:10.1016/j.ihj.2014.08.006
8. Polyzos SA, Mantzoros CS. Making progress in nonalcoholic fatty liver disease (NAFLD) as we are transitioning from the era of NAFLD to dys-metabolism associated fatty liver disease (DAFLD). *Metabolism.* 2020;111:154318. doi:10.1016/j.metabol.2020.154318
9. Meroni M, Longo M, Rustichelli A, Dongiovanni P. Nutrition and genetics in NAFLD: the perfect binomium. *Int J Mol Sci.* 2020; 21(8):E2986. doi:10.3390/ijms21082986
10. Muzurović E, Mikhailidis DP, Mantzoros C. Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. *Metabolism.* 2021;119:154770. doi:10.1016/j.metabol.2021.154770
11. Angelidi AM, Papadaki A, Nolen-Doerr E, Boutari C, Mantzoros CS. The effect of dietary patterns on non-alcoholic fatty liver disease diagnosed by biopsy or magnetic resonance in adults: a systematic review of randomised controlled trials. *Metabolism.* 2022;129:155136. doi:10.1016/j.metabol.2022.155136
12. Méndez-Sánchez N, Bugianesi E, Gish RG, et al. Global multi-stakeholder endorsement of the MAFLD definition. *Lancet Gastroenterol Hepatol.* 2022;7(5):388-390. doi:10.1016/S2468-1253(22)00062-0
13. Valenzuela-Vallejo L, Mantzoros CS. Time to transition from a negative nomenclature describing what NAFLD is not, to a novel, pathophysiology-based, umbrella classification of fatty liver disease (FLD). *Metabolism.* 2022;134:155246. doi:10.1016/j.metabol.2022.155246
14. Przybyszewski EM, Targher G, Roden M, Corey KE. Nonalcoholic fatty liver disease and cardiovascular disease. *Clin Liver Dis (Hoboken).* 2021;17(1):19-22. doi:10.1002/cld.1017
15. U.S. Food and Drug Administration. Clinical perspectives on FDA. *Guidance for Industry: Diabetes Mellitus: Evaluating CV risk in new Anti-Diabetic Therapies to Treat T2DM.* Diabetes Mellitus. 8. Published online 2008. Accessed November 18, 2022. <https://www.fda.gov/media/71297/download>
16. Muzurović E, Dragnić S, Medenica S, Smolović B, Bulajić P, Mikhailidis DP. Weight-centric pharmacological management of type 2 diabetes mellitus—an essential component of cardiovascular disease prevention. *J Diabetes Complications.* 2020;34(8): 107619. doi:10.1016/j.jdiacomp.2020.107619
17. Muzurović E, Mikhailidis DP. Impact of glucagon-like peptide 1 receptor agonists and sodium-glucose transport protein 2 inhibitors on blood pressure and lipid profile. *Expert Opin Pharmacother.* 2020;21(17):2125-2135. doi:10.1080/14656566.2020.1795132
18. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016; 375(4):311-322. doi:10.1056/NEJMoa1603827
19. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
20. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019; 394(10193):121-130. doi:10.1016/S0140-6736(19)31149-3
21. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2019;381(9):841-851. doi:10.1056/NEJMoa1901118
22. Muzurović EM, Vujošević S, Mikhailidis DP. Can we decrease epicardial and pericardial fat in patients with diabetes? *J Cardiovasc Pharmacol Ther.* 2021;26(5):415-436. doi:10.1177/10742484211006997
23. Muzurović EM, Mikhailidis DP. Diabetes mellitus and noncardiac atherosclerotic vascular disease—pathogenesis and pharmacological treatment options. *J Cardiovasc Pharmacol Ther.* 2021; 26(1):25-39. doi:10.1177/1074248420941675
24. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest.* 1993;91(1):301-307. doi:10.1172/JCI116186
25. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an intensive lifestyle intervention on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA.* 2017; 318(7):637-646. doi:10.1001/jama.2017.10169
26. Christensen M, Vedtofte L, Holst JJ, Vilsbøll T, Knop FK. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. *Diabetes.* 2011;60(12):3103-3109. doi:10.2337/db11-0979
27. Rosenstock J, Wysham C, Frias JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. *Lancet.* 2021;398(10295):143-155. doi:10.1016/S0140-6736(21)01324-6
28. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet.* 2006;368(9548):1696-1705. doi:10.1016/S0140-6736(06)69705-5
29. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab.* 2013; 17(6):819-837. doi:10.1016/j.cmet.2013.04.008
30. Rameshrad M, Razavi BM, Lalau JD, De Broe ME, Hosseinzadeh H. An overview of glucagon-like peptide-1 receptor agonists for the treatment of metabolic syndrome: a drug repositioning. *Iran J Basic Med Sci.* 2020;23(5):556-568. doi:10.22038/ijbms.2020.41638.9832
31. Stonehouse A, Okerson T, Kendall D, Maggs D. Emerging incretin based therapies for type 2 diabetes: incretin mimetics and DPP-4 inhibitors. *Curr Diabetes Rev.* 2008;4(2):101-109. doi:10.2174/157339908784220705
32. Drucker DJ. Glucagon-like peptide-1 and the islet beta-cell: augmentation of cell proliferation and inhibition of apoptosis. *Endocrinology.* 2003;144(12):5145-5148. doi:10.1210/en.2003-1147

33. Hare KJ, Vilsbøll T, Asmar M, Deacon CF, Knop FK, Holst JJ. The glucagonostatic and insulinotropic effects of glucagon-like peptide 1 contribute equally to its glucose-lowering action. *Diabetes*. 2010;59(7):1765-1770. doi:10.2337/db09-1414
34. Gupta NA, Kolachala VL, Jiang R, et al. The glucagon-like peptide-1 receptor agonist Exendin 4 has a protective role in ischemic injury of lean and steatotic liver by inhibiting cell death and stimulating lipolysis. *Am J Pathol*. 2012;181(5):1693-1701. doi:10.1016/j.ajpath.2012.07.015
35. Vilsbøll T. On the role of the incretin hormones GIP and GLP-1 in the pathogenesis of type 2 diabetes mellitus. *Dan Med Bull*. 2004; 51(4):364-370.
36. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157): 1519-1529. doi:10.1016/S0140-6736(18)32261-X
37. Kadouh H, Chedid V, Halawi H, et al. GLP-1 analog modulates appetite, taste preference, gut hormones, and regional body fat stores in adults with obesity. *J Clin Endocrinol Metab*. 2020; 105(5):dgz140. doi:10.1210/clinem/dgz140
38. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab*. 2016;24(1):15-30. doi:10.1016/j.cmet.2016.06.009
39. Blundell J, Finlayson G, Axelsen M, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes Obes Metab*. 2017;19(9):1242-1251. doi:10.1111/dom.12932
40. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. *Mol Metab*. 2022;57:101351. doi:10.1016/j.molmet.2021.101351
41. Crajoiinas RO, Oricchio FT, Pessoa TD, et al. Mechanisms mediating the diuretic and natriuretic actions of the incretin hormone glucagon-like peptide-1. *Am J Physiol Renal Physiol*. 2011; 301(2):F355-363. doi:10.1152/ajprenal.00729.2010
42. Patel VJ, Joharapurkar AA, Shah GB, Jain MR. Effect of GLP-1 based therapies on diabetic dyslipidemia. *Curr Diabetes Rev*. 2014;10(4):238-250. doi:10.2174/1573399810666140707092506
43. Vekic J, Zeljkovic A, Al Rasadi K, et al. A new look at novel cardiovascular risk biomarkers: the role of atherogenic lipoproteins and innovative antidiabetic therapies. *Metabolites*. 2022; 12(2):108. doi:10.3390/metabo12020108
44. Nikolic D, Giglio RV, Rizvi AA, et al. Liraglutide reduces carotid intima-media thickness by reducing small dense low-density lipoproteins in a real-world setting of patients with type 2 diabetes: a novel anti-atherogenic effect. *Diabetes Ther*. 2021;12(1): 261-274. doi:10.1007/s13300-020-00962-3
45. Anholm C, Kumarathurai P, Pedersen LR, et al. Liraglutide in combination with metformin may improve the atherogenic lipid profile and decrease C-reactive protein level in statin treated obese patients with coronary artery disease and newly diagnosed type 2 diabetes: a randomized trial. *Atherosclerosis*. 2019;288: 60-66. doi:10.1016/j.atherosclerosis.2019.07.007
46. Mikhailidis DP, Elisaf M, Rizzo M, et al. "European panel on low density lipoprotein (LDL) subclasses": a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. *Curr Vasc Pharmacol*. 2011;9(5):533-571. doi:10.2174/157016111796642661
47. Kieffer TJ, Habener JF. The glucagon-like peptides. *Endocr Rev*. 1999;20(6):876-913. doi:10.1210/edrv.20.6.0385
48. Jin T, Weng J. Hepatic functions of GLP-1 and its based drugs: current disputes and perspectives. *Am J Physiol Endocrinol Metab*. 2016;311(3):E620-E627. doi:10.1152/ajpendo.00069.2016
49. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019; 7(10):776-785. doi:10.1016/S2213-8587(19)30249-9
50. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022; 65(12):1925-1966. doi:10.1007/s00125-022-05787-2
51. Ma X, Liu Z, Ilyas I, et al. GLP-1 receptor agonists (GLP-1Ras): cardiovascular actions and therapeutic potential. *Int J Biol Sci*. 2021;17(8):2050-2068. doi:10.7150/ijbs.59965
52. Rizzo M, Nikolic D, Patti AM, et al. GLP-1 receptor agonists and reduction of cardiometabolic risk: potential underlying mechanisms. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864(9 Pt B): 2814-2821. doi:10.1016/j.bbdis.2018.05.012
53. Hussein H, Zaccardi F, Khunti K, et al. Efficacy and tolerability of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a systematic review and network meta-analysis. *Diabetes Obes Metab*. 2020;22(7):1035-1046. doi:10.1111/dom.14008
54. Usdin TB, Mezey E, Button DC, Brownstein MJ, Bonner TI. Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. *Endocrinology*. 1993;133(6):2861-2870. doi:10.1210/endo.133.6.8243312
55. Meier JJ, Gallwitz B, Siepmann N, et al. Gastric inhibitory polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at euglycaemia. *Diabetologia*. 2003; 46(6):798-801. doi:10.1007/s00125-003-1103-y
56. Seghieri M, Christensen AS, Andersen A, Solini A, Knop FK, Vilsbøll T. Future perspectives on GLP-1 receptor agonists and GLP-1/glucagon receptor co-agonists in the treatment of NAFLD. *Front Endocrinol (Lausanne)*. 2018;9:649. doi:10.3389/fendo.2018.00649
57. Thondam SK, Daousi C, Wilding JPH, et al. Glucose-dependent insulinotropic polypeptide promotes lipid deposition in subcutaneous adipocytes in obese type 2 diabetes patients: a maladaptive response. *Am J Physiol Endocrinol Metab*. 2017;312(3): E224-E233. doi:10.1152/ajpendo.00347.2016
58. Bergmann NC, Lund A, Gasbjerg LS, et al. Effects of combined GIP and GLP-1 infusion on energy intake, appetite and energy expenditure in overweight/obese individuals: a randomised, crossover study. *Diabetologia*. 2019;62(4):665-675. doi:10.1007/s00125-018-4810-0
59. Meier JJ, Goetze O, Anstipp J, et al. Gastric inhibitory polypeptide does not inhibit gastric emptying in humans. *Am J Physiol*

- Endocrinol Metab.* 2004;286(4):E621-E625. doi:10.1152/ajpendo.00499.2003
60. Gögebakan Ö, Osterhoff MA, Schüler R, et al. GIP increases adipose tissue expression and blood levels of MCP-1 in humans and links high energy diets to inflammation: a randomised trial. *Diabetologia.* 2015;58(8):1759-1768. doi:10.1007/s00125-015-3618-4
61. Asmar M, Simonsen L, Arnglim N, Holst JJ, Dela F, Bülow J. Glucose-dependent insulinotropic polypeptide has impaired effect on abdominal, subcutaneous adipose tissue metabolism in obese subjects. *Int J Obes (Lond).* 2014;38(2):259-265. doi:10.1038/ijo.2013.73
62. Asmar M, Arnglim N, Simonsen L, et al. The blunted effect of glucose-dependent insulinotropic polypeptide in subcutaneous abdominal adipose tissue in obese subjects is partly reversed by weight loss. *Nutr Diabetes.* 2016;6(5):e208. doi:10.1038/nutd.2016.15
63. Kaneko K, Fu Y, Lin HY, et al. Gut-derived GIP activates central Rap1 to impair neural leptin sensitivity during overnutrition. *J Clin Invest.* 2019;129(9):3786-3791. doi:10.1172/JCI1126107
64. Thondam SK, Cuthbertson DJ, Wilding JPH. The influence of glucose-dependent insulinotropic polypeptide (GIP) on human adipose tissue and fat metabolism: implications for obesity, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). *Peptides.* 2020;125:170208. doi:10.1016/j.peptides.2019.170208
65. Campbell JE. Targeting the GIPR for obesity: to agonize or antagonize? Potential mechanisms. *Mol Metab.* 2021;46:101139. doi:10.1016/j.molmet.2020.101139
66. Sánchez-Garrido MA, Brandt SJ, Clemmensen C, Müller TD, DiMarchi RD, Tschöp MH. GLP-1/glucagon receptor co-agonism for treatment of obesity. *Diabetologia.* 2017;60(10):1851-1861. doi:10.1007/s00125-017-4354-8
67. Finan B, Yang B, Ottaway N, et al. A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nat Med.* 2015;21(1):27-36. doi:10.1038/nm.3761
68. Jall S, Sachs S, Clemmensen C, et al. Monomeric GLP-1/GIP/glucagon triagonism corrects obesity, hepatosteatosis, and dyslipidemia in female mice. *Mol Metab.* 2017;6(5):440-446. doi:10.1016/j.molmet.2017.02.002
69. Kahles F, Liberman A, Halim C, et al. The incretin hormone GIP is upregulated in patients with atherosclerosis and stabilizes plaques in ApoE^{-/-} mice by blocking monocyte/macrophage activation. *Mol Metab.* 2018;14:150-157. doi:10.1016/j.molmet.2018.05.014
70. Yip RG, Boylan MO, Kieffer TJ, Wolfe MM. Functional GIP receptors are present on adipocytes. *Endocrinology.* 1998;139(9):4004-4007. doi:10.1210/endo.139.9.6288
71. Weaver RE, Donnelly D, Wabitsch M, Grant PJ, Balmforth AJ. Functional expression of glucose-dependent insulinotropic polypeptide receptors is coupled to differentiation in a human adipocyte model. *Int J Obes (Lond).* 2008;32(11):1705-1711. doi:10.1038/ijo.2008.148
72. Falko JM, Crockett SE, Cataland S, Mazzaferri EL. Gastric inhibitory polypeptide (GIP) stimulated by fat ingestion in man. *J Clin Endocrinol Metab.* 1975;41(2):260-265. doi:10.1210/jcem-41-2-260
73. Sirinek KR, Crockett SE, Mazzaferri EL, Cataland S, Thomford NR. Release of gastric inhibitory polypeptide: comparison of glucose and fat as stimuli. *Surg Forum.* 1974;25(0):361-363.
74. Eckel RH, Fujimoto WY, Brunzell JD. Gastric inhibitory polypeptide enhanced lipoprotein lipase activity in cultured preadipocytes. *Diabetes.* 1979;28(12):1141-1142. doi:10.2337/diab.28.12.1141
75. Flatt PR. Dorothy Hodgkin lecture 2008. Gastric inhibitory polypeptide (GIP) revisited: a new therapeutic target for obesity-diabetes? *Diabet Med.* 2008;25(7):759-764. doi:10.1111/j.1464-5491.2008.02455.x
76. McClean PL, Irwin N, Cassidy RS, Holst JJ, Gault VA, Flatt PR. GIP receptor antagonism reverses obesity, insulin resistance, and associated metabolic disturbances induced in mice by prolonged consumption of high-fat diet. *Am J Physiol Endocrinol Metab.* 2007;293(6):E1746-E1755. doi:10.1152/ajpendo.00460.2007
77. Pfeiffer AFH, Keyhani-Nejad F. High glycemic index metabolic damage—a pivotal role of GIP and GLP-1. *Trends Endocrinol Metab.* 2018;29(5):289-299. doi:10.1016/j.tem.2018.03.003
78. Keyhani-Nejad F, Irmeler M, Isken F, et al. Nutritional strategy to prevent fatty liver and insulin resistance independent of obesity by reducing glucose-dependent insulinotropic polypeptide responses in mice. *Diabetologia.* 2015;58(2):374-383. doi:10.1007/s00125-014-3423-5
79. Ussher JR, Campbell JE, Mulvihill EE, et al. Inactivation of the glucose-dependent insulinotropic polypeptide receptor improves outcomes following experimental myocardial infarction. *Cell Metab.* 2018;27(2):450-460.e6. doi:10.1016/j.cmet.2017.11.003
80. Hirano T, Mori Y. Anti-atherogenic and anti-inflammatory properties of glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and dipeptidyl peptidase-4 inhibitors in experimental animals. *J Diabetes Investig.* 2016;7(Suppl 1):80-86. doi:10.1111/jdi.12446
81. Mori Y, Matsui T, Hirano T, Yamagishi SI. GIP as a potential therapeutic target for atherosclerotic cardiovascular disease—a systematic review. *Int J Mol Sci.* 2020;21(4):E1509. doi:10.3390/ijms21041509
82. Muzurović E, Čojić M, Stanković Z, Janež A. Epicardial adipocyte-derived TNF- α modulates local inflammation in patients with advanced coronary artery disease. *Curr Vasc Pharmacol.* 2022;20(1):94-95. doi:10.2174/157016112001211228145754
83. Muzurović E, Stanković Z, Kovačević Z, Škrijelj BŠ, Mikhailidis DP. Inflammatory markers associated with diabetes mellitus—old and new players. *Curr Pharm Des.* 2021;27(27):3020-3035. doi:10.2174/1381612826666201125103047
84. Christensen MB, Lund A, Calanna S, et al. Glucose-dependent insulinotropic polypeptide (GIP) inhibits bone resorption independently of insulin and glycemia. *J Clin Endocrinol Metab.* 2018;103(1):288-294. doi:10.1210/jc.2017-01949
85. Christensen M, Calanna S, Sparre-Ulrich AH, et al. Glucose-dependent insulinotropic polypeptide augments glucagon responses to hypoglycemia in type 1 diabetes. *Diabetes.* 2015;64(1):72-78. doi:10.2337/db14-0440
86. Skov-Jepesen K, Svane MS, Martinussen C, et al. GLP-2 and GIP exert separate effects on bone turnover: a randomized,

- placebo-controlled, crossover study in healthy young men. *Bone*. 2019;125:178-185. doi:10.1016/j.bone.2019.05.014
87. Wice BM, Reeds DN, Tran HD, et al. Xenin-25 amplifies GIP-mediated insulin secretion in humans with normal and impaired glucose tolerance but not type 2 diabetes. *Diabetes*. 2012;61(7):1793-1800. doi:10.2337/db11-1451
 88. Ding X, Saxena NK, Lin S, Gupta NA, Gupta N, Anania FA. Exendin-4, a glucagon-like protein-1 (GLP-1) receptor agonist, reverses hepatic steatosis in *ob/ob* mice. *Hepatology*. 2006;43(1):173-181. doi:10.1002/hep.21006
 89. Mori Y, Kushima H, Koshihara M, et al. Glucose-dependent insulinotropic polypeptide suppresses peripheral arterial remodeling in male mice. *Endocrinology*. 2018;159(7):2717-2732. doi:10.1210/en.2018-00336
 90. Timper K, Grisouard J, Sauter NS, et al. Glucose-dependent insulinotropic polypeptide induces cytokine expression, lipolysis, and insulin resistance in human adipocytes. *Am J Physiol Endocrinol Metab*. 2013;304(1): E1-13. doi:10.1152/ajpendo.00100.2012
 91. Góralska J, Rażny U, Polus A, et al. Pro-inflammatory gene expression profile in obese adults with high plasma GIP levels. *Int J Obes (Lond)*. 2018;42(4):826-834. doi:10.1038/ijo.2017.305
 92. Berglund LM, Lyssenko V, Ladenvall C, et al. Glucose-dependent insulinotropic polypeptide stimulates osteopontin expression in the vasculature via endothelin-1 and CREB. *Diabetes*. 2016;65(1):239-254. doi:10.2337/db15-0122
 93. Nogi Y, Nagashima M, Terasaki M, Nohtomi K, Watanabe T, Hirano T. Glucose-dependent insulinotropic polypeptide prevents the progression of macrophage-driven atherosclerosis in diabetic apolipoprotein E-null mice. *PLoS One*. 2012;7(4):e35683. doi:10.1371/journal.pone.0035683
 94. Nagashima M, Watanabe T, Terasaki M, et al. Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice. *Diabetologia*. 2011;54(10):2649-2659. doi:10.1007/s00125-011-2241-2
 95. April-Sanders AK, Rodriguez CJ. Metabolically healthy obesity redefined. *JAMA Network Open*. 2021;4(5):e218860. doi:10.1001/jamanetworkopen.2021.8860
 96. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol*. 2018;17(1):122. doi:10.1186/s12933-018-0762-4
 97. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet*. 2022;399(10322):394-405. doi:10.1016/S0140-6736(21)01919-X
 98. American Diabetes Association Professional Practice Committee. 3. Prevention or delay of type 2 diabetes and associated comorbidities: standards of medical care in diabetes—2022. *Diabetes Care*. 2021;45(suppl 1):S39-S45. doi:10.2337/dc22-S003
 99. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391(10120):541-551. doi:10.1016/S0140-6736(17)33102-1
 100. Jensterle M, Janež A. Glucagon like peptide 1 receptor agonists in the treatment of obesity. *Horm Res Paediatr*. 2021. doi:10.1159/000521264
 101. Rosenstock J, Klaff LJ, Schwartz S, et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. *Diabetes Care*. 2010;33(6):1173-1175. doi:10.2337/dc09-1203
 102. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
 103. Muzurović E, Rizzo M, Mikhailidis DP. Obesity and nonalcoholic fatty liver disease in type 1 diabetes mellitus patients. *J Diabetes Complications*. 2022;36(12):108359.
 104. Guyton J, Jeon M, Brooks A. Glucagon-like peptide 1 receptor agonists in type 1 diabetes mellitus. *Am J Health Syst Pharm*. 2019;76(21):1739-1748. doi:10.1093/ajhp/zxz179
 105. Rizvi AA, Rizzo M. The emerging role of dual GLP-1 and GIP receptor agonists in glycemic management and cardiovascular risk reduction. *Diabetes Metab Syndr Obes*. 2022;15:1023-1030. doi:10.2147/DMSO.S351982
 106. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
 107. Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? *Trends Endocrinol Metab*. 2020;31(6):410-421. doi:10.1016/j.tem.2020.02.006
 108. Patti AM, Nikolic D, Magan-Fernandez A, et al. Exenatide once-weekly improves metabolic parameters, endothelial dysfunction and carotid intima-media thickness in patients with type-2 diabetes: an 8-month prospective study. *Diabetes Res Clin Pract*. 2019;149:163-169. doi:10.1016/j.diabres.2019.02.006
 109. Dushay J, Gao C, Gopalakrishnan GS, et al. Short-term exenatide treatment leads to significant weight loss in a subset of obese women without diabetes. *Diabetes Care*. 2012;35(1):4-11. doi:10.2337/dc11-0931
 110. Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. 2016;315(22):2424-2434. doi:10.1001/jama.2016.7602
 111. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med*. 2015;373(1):11-22. doi:10.1056/NEJMoa1411892
 112. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399-1409. doi:10.1016/S0140-6736(17)30069-7
 113. Kim SH, Abbasi F, Lamendola C, et al. Benefits of liraglutide treatment in overweight and obese older individuals with prediabetes. *Diabetes Care*. 2013;36(10):3276-3282. doi:10.2337/dc13-0354
 114. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637-649. doi:10.1016/S0140-6736(18)31773-2
 115. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss

- maintenance in adults with overweight or obesity: the step 4 randomized clinical trial. *JAMA*. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224
116. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. 2021;325(14):1403-1413. doi:10.1001/jama.2021.1831
117. Perreault L, Davies M, Frias JP, et al. Changes in glucose metabolism and glycemic status with once-weekly subcutaneous semaglutide 2.4 mg among participants with prediabetes in the STEP program. *Diabetes Care*. 2022;45(10):2396-2405. doi:10.2337/dc21-1785
118. Commissioner O of the. FDA approves novel, dual-targeted treatment for type 2 diabetes. FDA. Published May 13, 2022. Accessed November 18, 2022. <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes>
119. Lilly receives U.S. FDA Fast Track designation for tirzepatide for the treatment of adults with obesity, or overweight with weight-related comorbidities | Eli Lilly and Company. Published October 6, 2022. Accessed November 18, 2022. <https://investor.lilly.com/news-releases/news-release-details/lilly-receives-us-fda-fast-track-designation-tirzepatide>
120. Thomas MK, Nikooienejad A, Bray R, et al. Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes. *J Clin Endocrinol Metab*. 2020;106(2):388-396. doi:10.1210/clinem/dgaa863
121. Garvey WT, Birkenfeld AL, Dicker D, et al. Efficacy and safety of liraglutide 3.0 mg in individuals with overweight or obesity and type 2 diabetes treated with basal insulin: the scale insulin randomized controlled trial. *Diabetes Care*. 2020;43(5):1085-1093. doi:10.2337/dc19-1745
122. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA*. 2015;314(7):687-699. doi:10.1001/jama.2015.9676
123. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403. doi:10.1056/NEJMoa012512
124. Haw JS, Galaviz KI, Straus AN, et al. Long-term sustainability of diabetes prevention approaches: a systematic review and meta-analysis of randomized clinical trials. *JAMA Internal Medicine*. 2017;177(12):1808-1817. doi:10.1001/jamainternmed.2017.6040
125. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359(9323):2072-2077. doi:10.1016/S0140-6736(02)08905-5
126. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;368(9541):1096-1105. doi:10.1016/S0140-6736(06)69420-8
127. ORIGIN Trial Investigators, Gerstein HC, Bosch J, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319-328. doi:10.1056/NEJMoa1203858
128. Wittert G, Bracken K, Robledo KP, et al. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *Lancet Diabetes Endocrinol*. 2021;9(1):32-45. doi:10.1016/S2213-8587(20)30367-3
129. Hemmingsen B, Sonne DP, Metzendorf MI, Richter B. Dipeptidyl-peptidase (DPP)-4 inhibitors and glucagon-like peptide (GLP)-1 analogues for prevention or delay of type 2 diabetes mellitus and its associated complications in people at increased risk for the development of type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2017;5(5):CD012204. doi:10.1002/14651858.CD012204.pub2
130. Galaviz KI, Weber MB, Straus A, Haw JS, Narayan KMV, Ali MK. Global diabetes prevention interventions: a systematic review and network meta-analysis of the real-world impact on incidence, weight, and glucose. *Diabetes Care*. 2018;41(7):1526-1534. doi:10.2337/dc17-2222
131. Popovic DS, Rizzo M, Stokic E, Papanas N. New subphenotyping of subjects at high risk of type 2 diabetes: what are the potential clinical implications? *Diabetes Ther*. 2021;12(6):1605-1611. doi:10.1007/s13300-021-01065-3
132. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19(4):524-536. doi:10.1111/dom.12849
133. Jensterle M, Rizzo M, Haluzik M, Janež A. Efficacy of GLP-1 RA approved for weight management in patients with or without diabetes: a narrative review. *Adv Ther*. 2022;39(6):2452-2467. doi:10.1007/s12325-022-02153-x
134. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Ther Adv Endocrinol Metab*. 2021;12:2042018821997320. doi:10.1177/2042018821997320
135. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Obes Metab*. 2021;23(9):2116-2124. doi:10.1111/dom.14451
136. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10278):971-984. doi:10.1016/S0140-6736(21)00213-0
137. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6(4):275-286. doi:10.1016/S2213-8587(18)30024-X
138. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5

- randomized clinical trial. *JAMA*. 2022;327(6):534-545. doi:10.1001/jama.2022.0078
139. Friás JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503-515. doi:10.1056/NEJMoa2107519
 140. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313(6):603-615. doi:10.1001/jama.2014.18574
 141. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5
 142. Dalsgaard NB, Vilsbøll T, Knop FK. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk factors: a narrative review of head-to-head comparisons. *Diabetes Obes Metab*. 2018;20(3):508-519. doi:10.1111/dom.13128
 143. Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y, Imaoka T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. *Diabetes Obes Metab*. 2015;17(10):974-983. doi:10.1111/dom.12534
 144. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care*. 2018;41(2):258-266. doi:10.2337/dc17-0417
 145. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care*. 2019;42(9):1724-1732. doi:10.2337/dc19-0749
 146. Berberich AJ, Hegele RA. Lipid effects of glucagon-like peptide 1 receptor analogs. *Curr Opin Lipidol*. 2021;32(3):191-199. doi:10.1097/MOL.0000000000000750
 147. Kolovou GD, Watts GF, Mikhailidis DP, et al. Postprandial hypertriglyceridaemia revisited in the era of non-fasting lipid profile testing: a 2019 expert panel statement, main text. *Curr Vasc Pharmacol*. 2019;17(5):498-514. doi:10.2174/1570161117666190507110519
 148. Kolovou GD, Watts GF, Mikhailidis DP, et al. Postprandial hypertriglyceridaemia revisited in the era of non-fasting lipid profile testing: a 2019 expert panel statement, narrative review. *Curr Vasc Pharmacol*. 2019;17(5):515-537. doi:10.2174/1570161117666190503123911
 149. Nikolic D, Patti AM, Giglio RV, et al. Liraglutide improved cardiometabolic parameters more in obese than in non-obese patients with type 2 diabetes: a real-world 18-month prospective study. *Diabetes Ther*. 2022;13(3):453-464. doi:10.1007/s13300-022-01217-z
 150. Schwartz EA, Koska J, Mullin MP, Syoufi I, Schwenke DC, Reaven PD. Exenatide suppresses postprandial elevations in lipids and lipoproteins in individuals with impaired glucose tolerance and recent onset type 2 diabetes mellitus. *Atherosclerosis*. 2010;212(1):217-222. doi:10.1016/j.atherosclerosis.2010.05.028
 151. Tuttolomondo A, Cirrincione A, Casuccio A, et al. Efficacy of dulaglutide on vascular health indexes in subjects with type 2 diabetes: a randomized trial. *Cardiovasc Diabetol*. 2021;20(1):1. doi:10.1186/s12933-020-01183-5
 152. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet*. 2019;394(10192):39-50. doi:10.1016/S0140-6736(19)31271-1
 153. Janić M, Rizzo M, Cosentino F, et al. Effect of oral semaglutide on cardiovascular parameters and their mechanisms in patients with type 2 diabetes: rationale and design of the semaglutide anti-atherosclerotic mechanisms of action study (SAMAS). *Diabetes Ther*. 2022;13(4):795-810. doi:10.1007/s13300-022-01226-y
 154. Wilson JM, Nikooienejad A, Robins DA, et al. The dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist, tirzepatide, improves lipoprotein biomarkers associated with insulin resistance and cardiovascular risk in patients with type 2 diabetes. *Diabetes Obes Metab*. 2020;22(12):2451-2459. doi:10.1111/dom.14174
 155. Sattar N, McGuire DK, Pavo I, et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. *Nat Med*. 2022;28(3):1-8. doi:10.1038/s41591-022-01707-4
 156. Rakipovski G, Rolin B, Nøhr J, et al. The GLP-1 analogs liraglutide and semaglutide reduce atherosclerosis in ApoE^{-/-} and LDLr^{-/-} mice by a mechanism that includes inflammatory pathways. *JACC Basic Transl Sci*. 2018;3(6):844-857. doi:10.1016/j.jacbs.2018.09.004
 157. Muzurović E, Mikhailidis DP, Mantzoros C. Commentary: From mice to men: in search for dietary interventions to form the background on which pharmacotherapy for non-alcoholic fatty liver disease should be based. *Metabolism*. 2020;109:154305. doi:10.1016/j.metabol.2020.154305
 158. Dhir G, Cusi K. Glucagon like peptide-1 receptor agonists for the management of obesity and non-alcoholic fatty liver disease: a novel therapeutic option. *J Investig Med*. 2018;66(1):7-10. doi:10.1136/jim-2017-000554
 159. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the study of liver diseases. *Hepatology*. 2018;67(1):328-357. doi:10.1002/hep.29367
 160. Gupta NA, Mells J, Dunham RM, et al. Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. *Hepatology*. 2010;51(5):1584-1592. doi:10.1002/hep.23569
 161. Svegliati-Baroni G, Saccomanno S, Rychlicki C, et al. Glucagon-like peptide-1 receptor activation stimulates hepatic lipid oxidation and restores hepatic signalling alteration induced by a high-fat diet in nonalcoholic steatohepatitis. *Liver Int*. 2011;31(9):1285-1297. doi:10.1111/j.1478-3231.2011.02462.x
 162. Bernsmeier C, Meyer-Gerspach AC, Blaser LS, et al. Glucose-induced glucagon-like peptide 1 secretion is deficient in patients

- with non-alcoholic fatty liver disease. *PLoS One*. 2014;9(1): e87488. doi:10.1371/journal.pone.0087488
163. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. *Metabolites*. 2021;11(2):73. doi:10.3390/metabo11020073
164. Valenzuela-Vallejo L, Guatibonza-García V, Mantzoros CS. Recent guidelines for non-alcoholic fatty liver disease (NAFLD)/fatty liver disease (FLD): are they already outdated and in need of supplementation? *Metabolism*. 2022;136:155248. doi:10.1016/j.metabol.2022.155248
165. Panjwani N, Mulvihill EE, Longuet C, et al. GLP-1 receptor activation indirectly reduces hepatic lipid accumulation but does not attenuate development of atherosclerosis in diabetic male ApoE(-/-) mice. *Endocrinology*. 2013;154(1):127-139. doi:10.1210/en.2012-1937
166. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014;155(4):1280-1290. doi:10.1210/en.2013-1934
167. Ao N, Yang J, Wang X, Du J. Glucagon-like peptide-1 preserves non-alcoholic fatty liver disease through inhibition of the endoplasmic reticulum stress-associated pathway. *Hepatol Res*. 2016;46(4):343-353. doi:10.1111/hepr.12551
168. Lee J, Hong SW, Chae SW, et al. Exendin-4 improves steatohepatitis by increasing Sirt1 expression in high-fat diet-induced obese C57BL/6J mice. *PLoS One*. 2012;7(2): e31394. doi:10.1371/journal.pone.0031394
169. Dutour A, Abdesselam I, Ancel P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. *Diabetes Obes Metab*. 2016;18(9):882-891. doi:10.1111/dom.12680
170. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387(10019):679-690. doi:10.1016/S0140-6736(15)00803-X
171. Frøssing S, Nylander M, Chabanova E, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: a randomized clinical trial. *Diabetes Obes Metab*. 2018;20(1):215-218. doi:10.1111/dom.13053
172. Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP. Semaglutide, lipid-lowering drugs, and NAFLD. *Lancet Diabetes Endocrinol*. 2017;5(5):329-330. doi:10.1016/S2213-8587(17)30109-2
173. Flint A, Andersen G, Hockings P, et al. Randomised clinical trial: semaglutide versus placebo reduced liver steatosis but not liver stiffness in subjects with non-alcoholic fatty liver disease assessed by magnetic resonance imaging. *Aliment Pharmacol Ther*. 2021;54(9):1150-1161. doi:10.1111/apt.16608
174. Newsome P, Francque S, Harrison S, et al. Effect of semaglutide on liver enzymes and markers of inflammation in subjects with type 2 diabetes and/or obesity. *Aliment Pharmacol Ther*. 2019;50(2):193-203. doi:10.1111/apt.15316
175. Luo Q, Wei R, Cai Y, Zhao Q, Liu Y, Liu WJ. Efficacy of off-label therapy for non-alcoholic fatty liver disease in improving non-invasive and invasive biomarkers: a systematic review and network meta-analysis of randomized controlled trials. *Front Med (Lausanne)*. 2022;9:793203. doi:10.3389/fmed.2022.793203
176. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med*. 2021;384(12):1113-1124. doi:10.1056/NEJMoa2028395
177. Cusi K, Sattar N, García-Pérez LE, et al. Dulaglutide decreases plasma aminotransferases in people with type 2 diabetes in a pattern consistent with liver fat reduction: a post hoc analysis of the AWARD programme. *Diabet Med*. 2018;35(10):1434-1439. doi:10.1111/dme.13697
178. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). *Diabetologia*. 2020;63(11):2434-2445. doi:10.1007/s00125-020-05265-7
179. Ghosal S, Datta D, Sinha B. A meta-analysis of the effects of glucagon-like-peptide 1 receptor agonist (GLP1-RA) in non-alcoholic fatty liver disease (NAFLD) with type 2 diabetes (T2D). *Sci Rep*. 2021;11(1):22063. doi:10.1038/s41598-021-01663-y
180. Wong C, Lee MH, Yaow CYL, et al. Glucagon-like peptide-1 receptor agonists for non-alcoholic fatty liver disease in type 2 diabetes: a meta-analysis. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/fendo.2021.609110
181. Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. *Lancet Gastroenterol Hepatol*. 2022;7(4):367-378. doi:10.1016/S2468-1253(21)00261-2
182. Feng W, Gao C, Bi Y, et al. Randomized trial comparing the effects of gliclazide, liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. *J Diabetes*. 2017;9(8):800-809. doi:10.1111/1753-0407.12555
183. Yan J, Yao B, Kuang H, et al. Liraglutide, sitagliptin, and insulin glargine added to metformin: the effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. *Hepatology*. 2019;69(6):2414-2426. doi:10.1002/hep.30320
184. Rizvi AA, Patti AM, Giglio RV, et al. Liraglutide improves carotid intima-media thickness in patients with type 2 diabetes and non-alcoholic fatty liver disease: an 8-month prospective pilot study. *Expert Opin Biol Ther*. 2015;15(10):1391-1397. doi:10.1517/14712598.2015.1067299
185. Majzoub AM, Nayfeh T, Barnard A, et al. Systematic review with network meta-analysis: comparative efficacy of pharmacologic therapies for fibrosis improvement and resolution of NASH. *Aliment Pharmacol Ther*. 2021;54(7):880-889. doi:10.1111/apt.16583
186. Dickson I. Semaglutide is safe and efficacious for NASH resolution. *Nat Rev Gastroenterol Hepatol*. 2021;18(1):6. doi:10.1038/s41575-020-00396-z

187. Musso G, Gambino R, Pacini G, De Michieli F, Cassader M. Prolonged saturated fat-induced, glucose-dependent insulinotropic polypeptide elevation is associated with adipokine imbalance and liver injury in nonalcoholic steatohepatitis: dysregulated enteroadipocyte axis as a novel feature of fatty liver. *Am J Clin Nutr*. 2009;89(2):558-567. doi:10.3945/ajcn.2008.26720
188. Møller CL, Vistisen D, Færch K, et al. Glucose-dependent insulinotropic polypeptide is associated with lower low-density lipoprotein but unhealthy fat distribution, independent of insulin: The ADDITION-PRO study. *J Clin Endocrinol Metab*. 2016;101(2):485-493. doi:10.1210/jc.2015-3133
189. Adriaenssens AE, Biggs EK, Darwish T, et al. Glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake. *Cell Metab*. 2019;30(5):987-996.e6. doi:10.1016/j.cmet.2019.07.013
190. Baggio LL, Drucker DJ. Glucagon-like peptide-1 receptor agonists for treating metabolic disease. *Molecular Metabolism*. 2021;46(6):101090. doi:10.1016/j.molmet.2020.101090
191. Hartman ML, Sanyal A, Loomba R, et al. 134-OR: Effects of tirzepatide (TZP), a novel dual GIP and GLP-1 receptor agonist, on biomarkers of nonalcoholic steatohepatitis (NASH) in patients with T2D. *Diabetes*. 2019;68(Supplement 1):134-OR. doi:10.2337/db19-134-OR
192. Hartman ML, Sanyal AJ, Loomba R, et al. Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of nonalcoholic steatohepatitis in patients with type 2 diabetes. *Diabetes Care*. 2020;43(6):1352-1355. doi:10.2337/dc19-1892
193. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol*. 2022;10(6):393-406. doi:10.1016/S2213-8587(22)00070-5
194. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215-2222. doi:10.1016/S0140-6736(10)60484-9
195. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373(23):2247-2257. doi:10.1056/NEJMoa1509225
196. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917
197. Rizzo M, Nauck MA, Mantzoros CS. Incretin-based therapies in 2021—current status and perspectives for the future. *Metabolism*. 2021;122:154843. doi:10.1016/j.metabol.2021.154843
198. Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with efglenatide in type 2 diabetes. *N Engl J Med*. 2021;385(10):896-907. doi:10.1056/NEJMoa2108269
199. Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. *Nat Med*. 2022;28(1):89-95. doi:10.1038/s41591-021-01584-3
200. Marsico F, Paolillo S, Gargiulo P, et al. Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with type 2 diabetes mellitus with or without established cardiovascular disease: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2020;41(35):3346-3358. doi:10.1093/eurheartj/ehaa082
201. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. *Diabetes Care*. 2016;39(9):1501-1509. doi:10.2337/dc15-2479
202. Janez A, Muzurovic E, Stoian AP, et al. Translating results from the cardiovascular outcomes trials with glucagon-like peptide-1 receptor agonists into clinical practice: recommendations from an Eastern and Southern Europe diabetes expert group. *Int J Cardiol*. 2022;365:8-18. doi:10.1016/j.ijcard.2022.07.017