Diabetology & Metabolic Syndrome

REVIEW

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Managing cardiovascular events, hyperglycemia, and obesity in type 2 diabetes through microRNA regulation linked to glucagon-like peptide-1 receptor agonists

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Abstract

Background and aims Type 2 diabetes mellitus (T2DM) is usually complicated by cardiovascular diseases, hyperglycemia, and obesity, which worsen the outcome for the patient. Since recent evidence underlines the epigenetic role of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the management of these comorbidities, this study compared the effects of these agents, namely liraglutide, semaglutide, dulaglutide, and exenatide, on miRNA regulation in the management of T2DM.

Results GLP-1RAs modify the expression of miRNAs involved in endothelial function, sugar metabolism, and adipogenesis, including but not limited to miR-27b, miR-130a, and miR-210. Baseline miR-15a-5p predict weight loss, while higher miR-378-3p and miR-126-3p levels are related to better glycemic control and lower HbA1c and FPG at one year post-treatment. miR-375-5p was also reported as a predictor of HbA1c levels. Liraglutide has a protecting effect against pancreatic β-cell apoptosis by downregulating miR-139-5p. The highly-expressed miR-375 in pancreatic islets can be considered as a biomarker for assessing the cytoprotective action of GLP-1RAs on β-cells. GLP-1RAs also enhance β-cell responsiveness by promoting GLP-1 receptor expression through the suppression of miR-204. While semaglutide, semaglutide, and dulaglutide reduce both systolic and diastolic blood pressures, lixisenatide and exenatide QW did not reveal such an effect. The long-acting exenatide-induced miR-29b-3p is required for the protection against diabetic cardiomyopathy. Liraglutide modulates critical regulators of endothelial cell function and atherosclerosis, including miR-93-5p, miR-26a-5p, and miR-181a-5p. Eventually, GLP-1RAs regulation of exosomal miRNAs, such as miR-192, implicated in the development of fibrosis and inflammation in T2DM micro-cardiovascular outcomes like DKD and DR.

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Conclusion Additional studies will be needed in the elucidation of the relations between GLP-1RA-induced miRNAs and clinical-laboratory findings concerning the diverse populations, gender, and presence of other comorbid states in treated patients with T2DM.

Keywords Diabetes Mellitus, type 2, Glucagon-like peptide-1 receptor agonists, microRNAs, Cardiovascular diseases, Hyperglycemia, Obesity

Introduction

Type 2 diabetes (T2DM) prevalence is expected to rise from 537 million people in 2021, to 643 million in 2030, and to 783 million in 2045 [1, 2]. Since about 90% of patients with T2DM are overweight, obesity is considered as one of the most consistent co-morbidities related to the disease [3]. Epidemiological studies reflect the powerful relationship between these two conditions. Indeed, T2DM can develop from combined environmental factors, such as a high-fat diet and a sedentary lifestyle, amplifying genetic predispositions. These ecological factors induce epigenetic changes, such as microRNA (miRNA) expression, to trigger some adaptive post-transcriptional modifications of DNA, which in turn play an important role in each step of the development of atherogenic dyslipidemia, hypertension, and T2DM-related cardiovascular complications [4–6]. Mechanism-wise, when these environmental factors persist, they ignite a cascade of metabolic disturbances to trigger chronic inflammation [7]. The inflammatory condition slowly overwhelms the capacity of the body to keep blood glucose within normal limits and thereby causes hyperglycemia, insulin resistance (IR), β-cell dysfunction, and ultimately T2DM [8].

Interestingly, these changes can often be ameliorated or even normalized with adequate body weight (BW) loss [9, 10]. However, even in those patients with major BW reduction, there is still a 40–50% chance that glucose tolerance impairment will progress to T2DM [11]. Moreover, subjects with diabetes with HbA1c values of > 8% had poorer overall survival compared to individuals whose HbA1c levels were < 6.5% [12]. Thus, T2DM management require comprehensive care approaches along with vigilant BW and blood glucose control for better patient outcomes and quality of life. The primary goal of oral antidiabetic drugs (OADs) is to reduce the levels of glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBS) [13]. Important categories of OADs include sulfonylureas (SUs), dipeptidyl peptidase-4 inhibitors (DPP-4Is), meglitinides, thiazolidinediones (TZDs), sodium-glucose cotransporter 2 inhibitors (SGLT-2Is), alpha-glucosidase inhibitors (αGIs), glucagon-like peptide-1 receptor agonists (GLP-1RAs), metformin, etc [14, 15]. Agents associated with varying degrees of weight loss include metformin, αGIs, SGLT-2Is, GLP-1Ra, and amylin mimetics. On the other hand, DPP-4Is are considered weight-neutral. In contrast, insulin secretagogues, TZDs, and insulin itself are commonly associated with weight gain [16]. Accordingly, the American Diabetes Association (ADA) suggests that the expected long-term weight effect of antihyperglycemic therapies should be a consideration in the provider's choice of a particular regimen for patients with T2DM. Based on NHANES 2015– 2020, metformin, associated with a modest weight reduction, represented the most common antihyperglycemic agent prescribed with a total of 43.8% of prescriptions. By contrast, the next most prevalent classes with weight gain adverse effects were insulins and sulfonylureas, prescribed for 22.0% and 23.2% of patients, respectively. Fully 5.0% of the total were GLP-1RAs. The percentage of GLP-1RA prescriptions among US commercially insured persons with type 2 diabetes has been increasing yearly, from 3.2% in 2015 to 10.7% in 2019, with a more pronounced trend in recent years. Even though there are specific benefits for Asian, Black, and Hispanic patients, as well as those with lower incomes and adult patients with atherosclerotic cardiovascular disease, the use of GLP-1 RA remains disproportionately low in these populations [17]. However, according to the new statement by the ADA and the European Association for the Study of Diabetes (EASD), GLP-1RAs are the preferred option for patients for whom major weight loss or a reduction in the risk of hypoglycemia is the key factor. In the second-line setting, GLP-1RAs are curiously effective, especially when HbA1c levels are near target [18].

In earlier studies, GLP-1RA therapy had helped T2DM patients lose an average of 2.9 kg of weight compared to placebo-treated patients [19, 20]. Mainly through its central effects on the hypothalamus, the GLP-1RAs enhance glucose uptake in muscles, reduce hepatic glucose output, and increase feelings of satiety. In addition, GLP-1RAs have been reported to have a significant reduction of around 1% in HbA1c levels and reduced all-cause mortality in T2DM patients compared to controls [21, 22]. Mechanism-wise, the incretin hormone Glucagon-like peptide-1 (GLP-1) is a thirty amino acid peptide that plays an important role in maintaining blood glucose homeostasis. It exerts its glucose homeostatic role by enhancing glucose-dependent insulin secretion, promoting the growth of the insulin-producing pancreatic β-cells, and suppressing glucagon release [18]. In T2DM, there is a reduction in incretin function, so treatments targeting this pathway, such as GLP-1RAs, can be very useful in managing blood glucose. Therefore, the artificial

forms of GLP-1 can provide added value in terms of additional gastric emptying delay, and further glucagon reduction, and also offer a protective effect on the pancreas over time [23–26]. Accordingly, GLP-1RAs are designed to last longer in the body, supporting HbA1c reduction and helping weight loss [27].

Notably, genetic differences in individuals with T2DM may immensely impact their responses to various treatments, including thiazolidinediones, sulfonylureas, metformin, and meglitinides [28–30]. In this regard, the ADA and EASD now focus more on a personalized approach to diabetes management, taking into consideration genetic etiology and precision medicine as a means of optimizing the treatment of each patient [31, 32]. In this regard, miRNAs as a class of important post-transcriptional regulators of gene expression gaining attention as genetic markers [28, 33, 34]. For instance, miRNAs can be used as predictive biomarkers for how patients might respond to various treatments like metformin, sitagliptin, TZDs, and short-term intensive insulin therapy [35–38]. Mechanism-wise, miRNAs are small, non-coding RNAs that regulate gene expression either by inducing mRNA degradation or inhibiting translation through the attachment to the 3′ UTR of target mRNAs. Here, the guide miRNA leads the RNA-induced silencing complex (RISC) to the target mRNA. Thus, through the regulation of several genes included in insulin signaling, glucose metabolism, and β-cell activity, miRNAs can modify pathophysiological processes pertinent to type 2 diabetes. This forms a base by which miRNAs might become a therapeutic avenue for T2DM treatment by modulating these pathways, as recently shown in in-vivo and in-vitro studies in which miRNA mimics or antimiRs were able to modulate glucose and lipid metabolism, and even promote β-cell regeneration [39]. Unfortunately, the exact role that GLP-1RA-related miRNAs, as epigenetic regulators, may play in managing the common comorbidities, such as obesity, hyperglycemia, and cardiovascular problems associated with T2DM, is still inadequately understood. Hence, the present narrative investigation has discussed how GLP-1RA-associated miRNAs may influence such major T2DM-related outcomes.

What effects can GLP-1RA have on the miRNA signature of patients with T2DM?

We have first carried out an extensive study of the complex molecular profile of miRNA altered by GLP-1RA therapy, as illustrated in Fig. 1 [28, 40–50]. Sprague-Dawley rats and mice, including C57BL/6J, Balb/c, and 204 knockout mice (204KO), were the animal models used in these studies. To date, in vivo studies have assessed the effects of exendin-4 (2, 4 and 8 μg/kg daily for 8 weeks; 10 μg/kg daily for 2 days; 10 nmol/kg after fasting for 16 h, being intraperitoneally injected 30 min before injecting

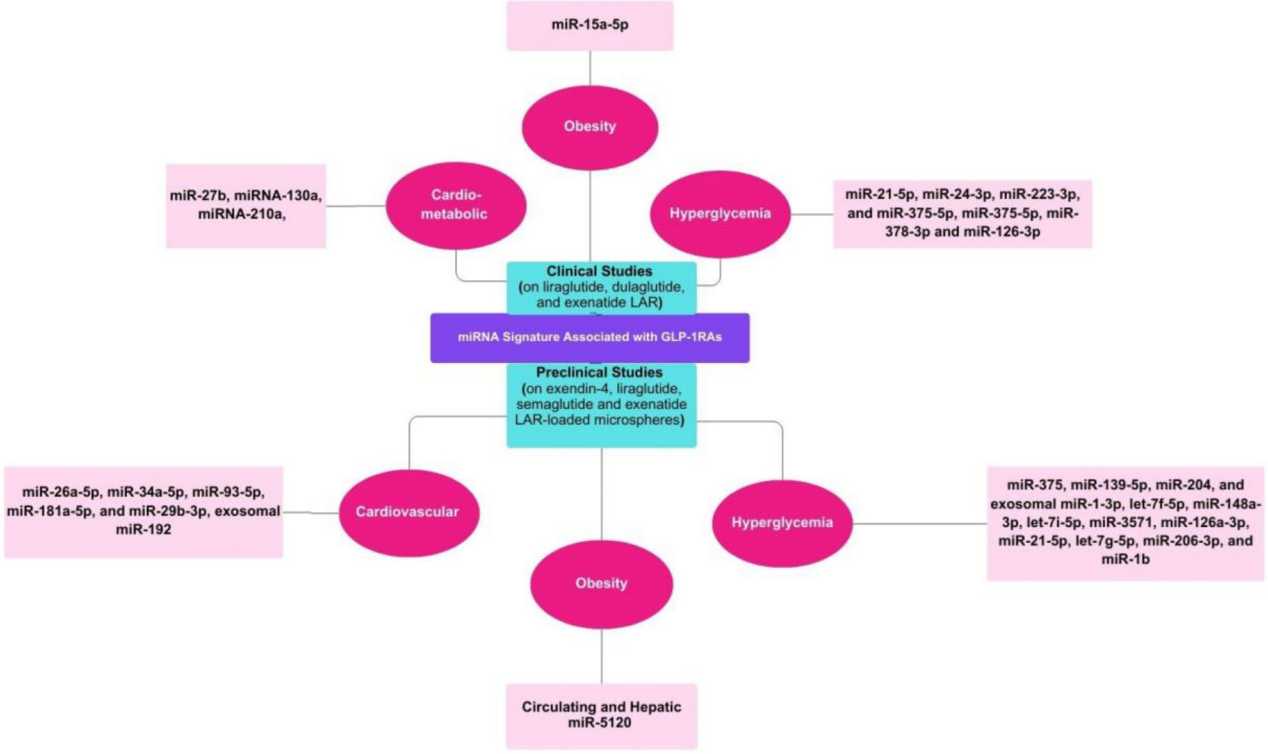

Fig. 1 miRNA signatures associated with GLP-1RAs in the management of T2DM. These miRNAs are found through a comprehensive review in the previous studies

glucose (1.5 g/kg) for measuring glucose tolerance), liraglutide (0.2 and 0.4 mg/kg/d for 12 weeks; or 200 μg/kg/d for 10 weeks; subcutaneously), semaglutide (0.42 mg/kg once a week for 12 weeks; subcutaneously), and exenatide LAR-loaded microspheres (10 mg/kg weekly for 6 weeks; intraperitoneally) on the miRNA signatures of type 2 diabetes [43–48]. Clinical research indicates that the three GLP-1RA medications whose functions have been examined in miRNA signatures in type 2 diabetes to date are liraglutide [28, 41, 42], dulaglutide [28], and exenatide long-acting release (LAR) [40]. Liraglutide was injected subcutaneously as part of the dosage. For four weeks, the dosage was 1.2 mg per day [41], then 0.6 mg per day for two weeks, and finally 1.2 mg per day for two more weeks [42]. In a different dosing plan, the dosage ranged from 0.6 to 1.2 mg in the first week and increased to 1.8 mg daily in the second week, for a total of 12 months [28]. In terms of the recommended dosing for dulaglutide, the suggested starting dose was 1.5 mg per week, to be administered consistently over 12 months [28]. Concerning the dosing of dulaglutide, one should note that the given dosage starts at 1.5 mg every week and has to be taken constantly for 12 months. A fixed dose of 2 mg/kg of exenatide LAR, also known as BYDUREON™ was injected subcutaneously once a week for 8 months [40]. In the realm of exploring exosomal miRNA patterns in individuals with T2DM after the administration of GLP-1RAs, two studies have been conducted thus far. Jia et al. (2018) conducted an in vitro experiment, while Li et al. (2017) [50] conducted an in vivo observations [49]. Our data underline the important role of GLP-1RA-associated miRNAs in regulating various T2DM complications, including control of hyperglycemia, insulin secretion, reduction of weight, and amelioration of cardiovascular outcomes. The following sections elaborate on the possible mechanisms through which GLP-1RA-related miRNAs influence the pathogenesis of cardiovascular disorders, hyperglycemia, and obesity in T2DM patients, with summarized findings presented in Table 1; Figs. 1, 2 and 3.

The correlation of GLP-1RA-linked miRNAs with obesity and lipid profiles

Previous studies have demonstrated that GLP-1 RAs tend to have a lipid-lowering effect in T2DM patients by reducing total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and free fatty acid (FFA) levels. For example, liraglutide reduces levels of non-high-density lipoprotein cholesterol (HDL-C) and TC at both 1 and 3 months, as well as LDL-C levels at 1 month [51]. However, liraglutide seems to act on subjects whose baseline LDL-C is greater than 100 mg/dL. Exenatide was further found to lower postprandial TG after high-fat meals [52]. A 6-month treatment with semaglutide reduced LDL-C and TC, whereas the decrease in TG became apparent only after 12 months [53]. Dulaglutide also resulted in an improved lipid profile, i.e., lower levels of TC and LDL-C, after 9-month treatment when compared with conventional therapy [54].

Additionally, studies on GLP-1RAs and their effects on certain miRNAs generally focus on metabolic parameters; however, the connection between these metabolic changes and alterations in the levels of miRNAs remains under-investigated. For instance, a study on 60-year-old patients receiving BYDUREON™ in combination with metformin showed reductions in anthropometric measurements, FBS, HbA1c, TC, LDL-C, and carotid intima-media thickness (CIMT), along with increases in HDL-C and flow-mediated dilation (FMD). These clinical improvements were associated with an upregulation of miR-27b, which also correlated directly with adipokines, including adiponectin, leptin, and L-selectin. However, the direct relation of miR-27b with lipid or glucose profile was not investigated in this study [40]. Moreover, 65-year-old patients who received Liraglutide combined with metformin also exhibited decreases in FBS, HbA1c, TC, triglycerides, and LDL-C but did not show any significant differences in anthropometric parameters and HDL-C levels. In this study, a significant increase in serum levels of miRNA-27b, miRNA-130a, and miRNA-210a was also reported in the treated patients [42]. MiR-15a-5p baseline levels have also been found to predict weight reduction in response to GLP-1RA therapy [28]. Notably, previous research showed that miR-15a in blood is significantly higher in subjects with T2DM and impaired glucose tolerance (IGT) than in people with normal glucose tolerance (NGT). In addition, traditional diabetes markers like fasting glucose, HbA1c, insulin levels, and HOMA-IR were inversely related to miR-15a levels, as was body mass index (BMI). Moreover, a relation between miR-15a expression and early diabetic retinal changes was demonstrated by the significant reduction of the ganglion cell complex (GCC) thickness, an early marker of retinal degeneration, in IGT and T2DM subjects compared to NGT controls [55].

Semaglutide can improve levels of miR-5120 in both blood and liver tissues while suppressing ABHD6's mRNA and protein expressions in a miR-5120-dependent manner. It has already been shown that ABHD6 is linked to several metabolic diseases, such as T2DM, obesity, insulin secretion abnormalities, and non-alcoholic fatty liver disease (NAFLD). In a prior work, mice fed a high-fat diet had lower body weights and less liver fat buildup when the expression of ABHD6 was knocked down in their peripheral tissues. These results suggest that blocking ABHD6 could be a useful therapeutic strategy for

Table 1 This table summarizes the potential mechanisms through which GLP-1RA-associated miRNAs control cardiovascular diseases, hyperglycemia, and obesity in individuals with T2DM

Type of Treatment	Clinical Outcome	MiRNA Signatures	Possible Mechanism of Actions of miRNAs	Ref
Exenatide (BYDUREON™) + Metformin	Reduced anthropometric parameters, FBS, HbA1c, TC, LDL-C, CIMT; increased HDL-C, FMD	Upregulation of miR-27b	Correlated with adipokines (adiponectin, leptin, L-selectin)	[40]
Liraglutide + Metformin	Reduced FBS, HbA1c, TC, triglycerides, and LDL-C; no significant change in anthropometric parameters and HDL-C	Upregulation of miR-27b, miR-130a, and miR-210a	Anti-adipogenic effect of miR-27b via regulating glycerol-3-phosphate acyltransferase-1 and angiopoietin-like-3 genes; Targeting the ephrin-A3 (Efna3) and protein tyrosine phosphatase-1B (Ptp1b)	[42, 96, 97]
Liraglutide or Dulaglutide	Improved blood glucose control after one year	Upregulation of miR-378-3p and miR-126-3p linked to greater reductions in both HbA1c and fasting plasma glucose over treatment; Upregulation of miR-21-5p, miR-24-3p, miR-223-3p, and miR-375-5p in patients meeting glycemic goals; miR-375-5p as a predictor of HbA1c levels;	-	[28]
Liraglutide or Dulaglutide	Higher miR-15a levels associated with BMI, fasting glucose, HbA1c, insulinemia, HOMA-IR	Baseline levels of miR-15a-5p predict weight loss response in T2DM patients	-	[28]
Exendin-4	A Potential Biomarker	Downregulating miR-375 in diabetic animal models	-	[43]
Semaglutide	Reduction in body weight	Upregulating miR-5120;	Downregulating ABHD6	[47]
Liraglutide	Reduction in β-cell apoptosis	Downregulating miR-139-5p	To reduce β-cell apoptosis; affecting caspase-3 and Bcl-2; and linking GLP-1 signaling with IRS1 inhibition	[44]
Exendin-4	Maintains β-cell function; A biomarker for evaluating the β-cell cytoprotective efficacy of various antidiabetic treatments	Upregulating miR-375	To protect β-cells; the export of miR-375-3p to HDL is inversely regulated by insulin secretion	[43, 65]
Exendin-4	Enhances GLP-1R expression in islets	Downregulation of miR-204	MiR-204 is a regulator for thioredoxin-interacting protein (TXNIP)	[45]
Liraglutide in T2DM postmenopausal animal models	Improved bone quality	Upregulating specific exosomiRNAs related to bone-protective pathways;	affecting insulin secretion and Wnt signaling pathways	[50]
BYDUREON™ or liraglutide + metformin	Improved angiogenesis; Predictors of acute myocardial infarction and early atherosclerosis	Upregulating pro-angiogenic miRNAs, such as miRNA-27b, miRNA-130a, and miRNA-210a	Epigenetically regulated T2DM	[40, 42, 73–76]
Exenatide (long-acting)	Reduces diabetic cardiomyopathy	Upregulates miR-29b-3p in the myocardium,	Regulating Sarcolemma Associated Protein (SLMAP); Reversal of miR-29b/SLMAP axis with GLP-1R inhibition	[48]
Liraglutide	Reduces endothelial cell apoptosis and promotes vascular protection; Reduces diabetic retinopathy	Downregulating miR-93-5p	To upregulate SIRT1 for protecting endothelial cells and reducing hyperglycemia	[46, 83]
Liraglutide	Reduces endothelial cell apoptosis	Under high-glucose conditions, it downregulates miR-34a-5p	To enhance the anti-apoptotic Bcl-2 protein	[46, 87]
Liraglutide	Reduces endothelial cell apoptosis in the aorta	Downregulating miR-181a-5p	To regulate the miR-181a-5p/CREB/BCL-2 pathway	[46, 91]
Exendin-4	Reduces micro-cardiovascular events induced by T2DM, such as diabetic kidney diseases and diabetic retinopathy	Inhibits the transmission of EV-miR-192 between healthy tubular epithelial cells under high-glucose stress;	To alleviate inflammation and angiogenesis in retinal cells subjected to high glucose levels by targeting ITGA1	[93–95]

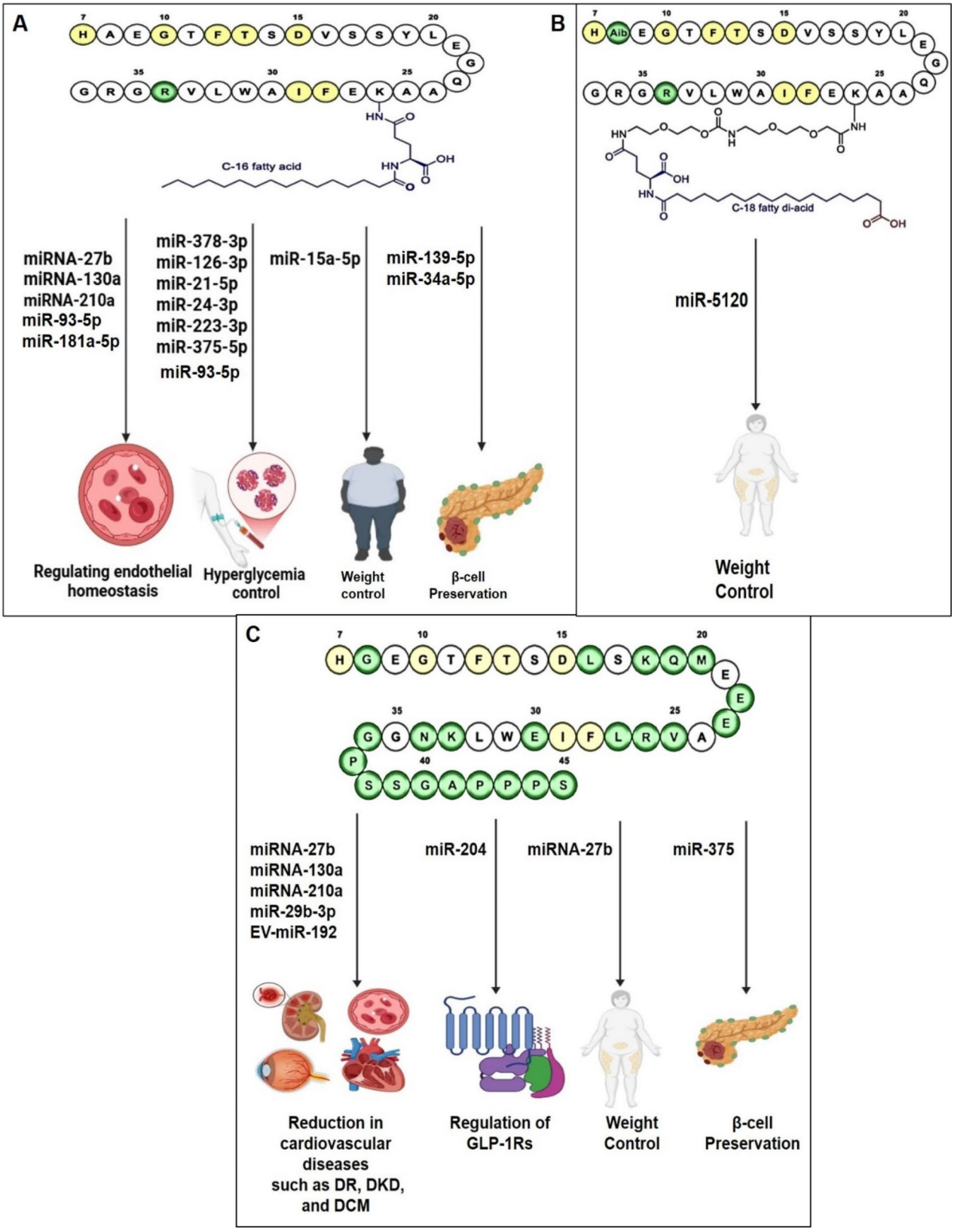

Fig. 2 It illustrates the association of each miRNA with (**A**) liraglutide, (**B**) semaglutide, and (**C**) exenatide for controlling cardiovascular diseases, hyperglycemia, and obesity in individuals with T2DM

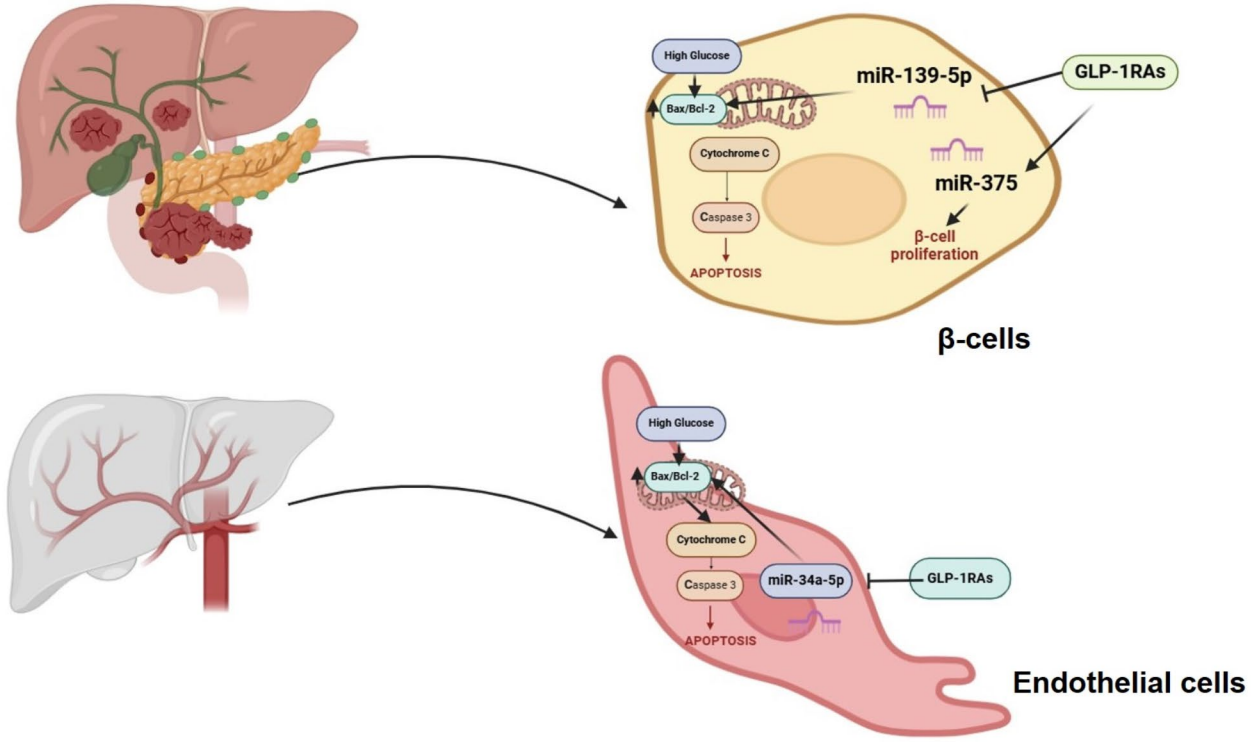

Fig. 3 It depicts the molecular interactions and cellular effects of liraglutide in controlling both hyperglycemia and cardiovascular diseases by protecting pancreatic β-cells and endothelial cells. GLP-1RAs downregulate miR-139-5p and miR-34a-5p to protect the cells against apoptosis. Additionally, they counter high glucose-induced Bcl-2 reduction and modulates miR-375 levels, essential for maintaining β-cell function and insulin signaling

the management of type 2 diabetes and other conditions linked to a high-fat diet [47].

The correlation of GLP-1RA-linked miRNAs with hypoglycemia, pancreatic beta cells, and insulin secretion

Generally, the most powerful GLP-1 RAs which have a significant reduction on HbA1c in patients with T2DM include semaglutide, dulaglutide, and liraglutide [56–58]. Semaglutide was approved for patients not reaching adequate control on at least one oral glucose-lowering medication. A 26-week, phase 2 clinical trials showed both oral semaglutide, 2.5–40 mg per day, and subcutaneous semaglutide caused a statistical difference in the reduction of HbA1c compared to placebo [59]. The phase 3 studies, including the SUSTAIN and PIONEER programs, confirmed the efficacy of semaglutide in lowering HbA1c and body weight [60, 61]. In the PIONEER 2–4 trials, oral semaglutide dose-dependently reduced HbA1c levels. Moreover, this agent was superior to empagliflozin and sitagliptin in decreasing HbA1c levels, but it showed a non-inferior response compared to liraglutide at 26 weeks [61]. Dulaglutide also lowered the levels of HbA1c and body weight more than exenatide BID and insulin glargine in AWARD-1 and 2, with notable BW reductions [62–64].

It has also been shown that 35-79-year-old patients with higher levels of miR-378-3p and miR-126-3p had better blood sugar control after one year of GLP-1RA therapy, using treatments like liraglutide and dulaglutide [28]. Higher baseline values of miR-21-5p, miR-24-3p, miR-223-3p, and miR-375-5p were commonly seen in those reaching their glycemic targets after 12 months. In particular, miR-375-5p was found to predict HbA1c levels. Interestingly, higher levels of miR-378-3p and miR-126-3p were associated with larger reductions in both HbA1c and fasting plasma glucose during the year of GLP-1RA treatment [28]. This was in agreement with studies in diabetic animal models where there was a marked increase in miR-375 about 6 to 30 h after streptozotocin (STZ) administration. Yet, there was no corresponding increase in the plasma miR-375 levels when the animals were treated with either PPAG or exendin-4 [43].

Liraglutide reduces pancreatic cell death by decreasing the levels of miR-139-5p, a marker associated with β-cell apoptosis, thereby controlling Hyperglycemia. High levels of miR-139-5p promote β-cell apoptosis through the regulation of caspase-3 activity and Bcl-2 expression, as illustrated in Fig. 3. Moreover, miR-139-5p acts as a critical intermediary between GLP-1 signaling and the inhibition of IRS1 expression, an essential component of insulin signaling pathways. Thus, it was suggested that

miR-139-5p exerts its proapoptotic function through direct targeting of Bcl-2 and the suppression of IRS1 expression affecting β-cell function [44]. Furthermore, miR-375, highly expressed in pancreatic islets, plays an important role in the maintenance of β-cell function and number. Currently, this miRNA is thought to be a biomarker to test the β-cell cytoprotective efficiency of different antidiabetic treatments including PPAG and exendin-4 (Fig. 3) [43]. Accordingly, it has recently been demonstrated that human pancreatic islets and β-cells export miR-375-3p to HDL. The export was found to be inversely regulated by glucose-stimulated insulin secretion. High glucose as well as tolbutamide, an inhibitor of ATP-sensitive potassium (K_{ATP}) channels that trigger insulin secretion, suppress the export of miR-375-3p to HDL [65].

Finally, miR-204, highly expressed in β-cells versus α-cells, directly targets the GLP-1R. This miRNA inhibits GLP-1R expression by binding to its 3′ untranslated region (UTR) in β-cells. Decreasing the levels of miR-204 or its upstream regulator such as TXNIP results in an increase in GLP-1R expression in the islets, improving responsiveness to GLP-1RAs [45]. Moreover, miR-204 is importantly involved in atherosclerosis and vascular calcification. In a study aimed at establishing the relationship between levels of circulating miR-204 and a ten-year cardiovascular disease (CVD) risk in 194 T2DM patients, the authors utilized the Framingham Risk Score (FRS) and found that lower levels of miR-204 negatively correlated with the score. Additionally, low levels of miR-204 were identified as independent predictors of a higher risk of CVD, thus indicating its potential as a specific biomarker for cardiovascular disease in diabetic patients [66].

Since the combined effects of estrogen deficiency and hyperglycemia usually lead to a significant deterioration in the bone quality of postmenopausal women with T2DM, we also incorporated this condition into our review. For instance, in an in vivo study with a focus on exosomal miRNAs derived from bone marrow, the bone-protective mechanisms of liraglutide were investigated using animal models that mimic postmenopausal women with type 2 diabetes. The exosomal miRNA expressions were evaluated in the ovariectomized (OVX), T2DM + OVX, and T2DM + OVX treated with liraglutide experimental groups. In total, 39 exosomal miRNAs were differentially expressed between the T2DM and liraglutide groups. In this, the upregulated miRNAs in the liraglutide-treated group included miR-1-3p, let-7f-5p, miR-148a-3p, let-7i-5p, miR-3571, miR-126a-3p, miR-21-5p, let-7 g-5p, miR-206-3p, and miR-1b. In addition, when compared with the OVX group, let-7c-2-3p and miR-322-3p, related to the Wnt signaling pathway, were found upregulated in the OVX group. Moreover, comparisons between liraglutide and T2DM resulted in the upregulation of miR-335 and miR-322-3p in the T2DM group, targeting insulin secretion and the Wnt signaling pathway, respectively [50].

The correlation of GLP-1RA-linked miRNAs with cardiovascular events

In individuals with T2DM, GLP-1 RAs have been demonstrated to lower both systolic blood pressure (SBP) and diastolic blood pressure (DBP). When compared to a placebo or insulin glargine, exenatide BID significantly reduced SBP and DBP, according to a meta-analysis of 16 randomized controlled trials (RCTs) [67]. Liraglutide similarly reduced SBP and DBP by 1–5 mmHg compared to glimepiride and placebo [67]. In the AWARD program, dulaglutide lowered SBP and pulse pressure, partly through weight loss, but mainly independently of weight loss [68]. Similarly, a 6-month post-intervention with semaglutide has been reported to exert beneficial effects on both SBP and DBP in subjects with overweight/obesity [69]. These observations, therefore, point toward GLP-1 RAs, with particular reference to exenatide, liraglutide, dulaglutide, and semaglutide, having a statistically significant and clinically beneficial effect on blood pressure in patients with T2D. Not only that, but several available long-acting GLP-1RAs including liraglutide, dulaglutide, and subcutaneously administered semaglutide were shown to lower cardiovascular manifestations in people with T2DM [8]. Not all GLP-1 RAs did, however, demonstrate overall cardiovascular benefit. For example, in the ELIXA and EXSCEL trials, lixisenatide and exenatide QW did not significantly lower the risk for cardiovascular outcomes [70, 71]. It is especially advantageous for GLP-1RAs to reduce visceral adipose tissue (VAT) because its buildup is associated with higher risks of T2DM, hypertension, hyperlipidemia, heart failure, and cardiovascular deaths. Another important metric for assessing the degree of atherosclerosis and cardiovascular risk is the VAT-to-subcutaneous adipose tissue (SAT) ratio. Since GLP-1 receptors are more present in VAT, which may explain the higher VAT reduction, GLP-1RAs might have different effects on VAT compared with SAT [8, 72].

More specifically, research has highlighted the predictive and diagnostic significance of miR-27b, miRNA-130a, and miRNA-210 in both acute myocardial infarction and early atherosclerosis [73–76]. Interestingly, one study has evaluated the impact of liraglutide on the serum levels of miRNA-27b, miRNA-130a, and miRNA-210 of patients with T2DM aged ≥ 18 years receiving metformin medication without any prior use of incretin-based or obesity treatments. They reported that, upon comparing the miRNAs' serum levels at baseline and after a 4-month therapy with the GLP-1RA,

there was a significant increase in levels of miRNA-27b, miRNA-130a, and miRNA-210a, independently of metabolic parameters. Thus, the levels of miRNAs seem to be altered for the regulation of endothelial cell homeostasis in T2DM using a direct epigenetic mechanism [40, 42]. Basically, miR-27b is a repressor of beige and brown adipogenesis, which are crucial in metabolic disorders determining obesity and its associated cardiovascular diseases [77, 78]. On the other hand, the down-expression of miRNA-130a contributes to endothelial dysfunction in T2DM and can be used as a biomarker for cardiovascular events [79]. Finally, miRNA-210 controls oxidative stress and acts as a hypoxia-inducible factor (HIF) [80].

In vivo studies have identified several GLP-1RA-associated miRNAs implicated in cardiovascular events, including miR-29b-3p, miR-26a-5p, miR-34a-5p, miR-93-5p, and miR-181a-5p [46, 48]. For example, long-acting exenatide increases the expression of miR-29b-3p in the ventricular myocardium. Mechanistically, long-acting exenatide regulates the expression of Sarcolemma Associated Protein (SLMAP) through miR-29b-3p. Such inhibiting of GLP-1Rs in cardiomyocytes reversed the effects of GLP-1RAs on the miR-29b/SLMAP axis. SLMAP has been implicated in the development of diabetic cardiomyopathy (DCM) in mice. Thus, the interventions with GLP-1RAs may provide protective benefits against DCM and its complications, including heart failure and microvascular damage [48]. It was further shown that, in human retinal microvascular endothelial cells exposed to high glucose and hypoxia (HG-CoCl2), the levels of miR-29b-3p were significantly upregulated. This was associated with a higher Bax/Bcl-2 ratio, reflective of an increased rate of apoptosis. Modulating the levels of miR-29b-3p showed an inverse effect on the expression of sirtuin 1 (SIRT1) and the rates of apoptosis. Importantly, SIRT1 agonists, including SRT1720, were able to counteract the pro-apoptotic impact of increased miR-29b-3p levels. These findings emphasize the important role of the miR-29b-3p/SIRT1 axis in the promotion of human retinal microvascular endothelial cells (HRMECs) apoptosis, especially under diabetic retinopathy (DR), as a micro-cardiovascular complication related to T2DM [81]. Nevertheless, the role of GLP-1RAs in this pathway has not been explored yet. Notably, miR-29b-3p expressed in bone marrow mesenchymal stem cells (BMMSCs) has been associated with age-dependent insulin resistance and may thus serve as a therapeutic target to ameliorate age-related insulin resistance in T2DM [82].

Eventually, liraglutide has been demonstrated to reduce miR-93-5p expression in the aortas of diabetic rats, leading to increased SIRT1 expression [46, 83]. SIRT1 exerts vascular protective effects by deacetylating targets such as forkhead box O3 (FOXO3) and p53 [84, 85]. Inhibition of miR-93-5p by liraglutide upregulates SIRT1 expression, which preserves endothelial cell function and protects against stress induced by hyperglycemia [46]. One study investigated the role of a long non-coding RNA (lncRNA), i.e., KCNQ1OT1, in diabetic nephropathy. Using high glucose-treated human glomerular mesangial cells (HGMCs) and human renal glomerular endothelial cells (HRGECs) treated with high glucose (as cellular models for diabetic nephropathy), it was found that KCNQ1OT1 was upregulated in these conditions. Knockdown of KCNQ1OT1 inhibited cell proliferation and fibrosis and induced apoptosis in these models. miR-93-5p was identified as a direct target of KCNQ1OT1. The effects caused by the knockdown of KCNQ1OT1 were reversed by the inhibition of miR-93-5p, which increased cell proliferation and fibrosis while decreasing apoptosis. Furthermore, Rho-associated protein kinase 2 (ROCK2) was identified as a target of miR-93-5p. Notably, KCNQ1OT1 modulated ROCK2 expression by binding with miR-93-5p. Therefore, KCNQ1OT1 knockdown mitigates the progression of diabetic nephropathy by modulating the miR-93-5p/ROCK2 axis, suggesting its potential as a therapeutic target [86]. However, the role of GLP-1RAs in this axis has not yet been evaluated.

Moreover, high-dose liraglutide treatment has been associated with an upregulation of miR-26a-5p, which is a critical player in endothelial function, and simultaneously downregulated several other miRNAs, including miR-34a-5p, miR-93-5p, and miR-181a-5p [46]. Indeed, patients treated with liraglutide showed increased expression of Bcl-2 compared to nontreated diabetic subjects. This indicated an inverse correlation between miR-34a-5p and Bcl-2. Notably, while high glucose generally suppresses the expression of Bcl-2, an anti-apoptotic protein, in endothelial cells, liraglutide significantly counteracted this process, even under high-glucose conditions (see Fig. 3) [87]. It suggests that liraglutide might confer protection against endothelial dysfunction through the activation of the PI3K-AKT pathway, which follows previous findings that exendin-4 upregulates Bcl-2 protein expression [88]. Liraglutide upregulating miR-26a-5p, which targets PTEN (an important regulator of the PI3K-AKT pathway), would suggest a possible mechanism for liraglutide to downregulate PTEN expression under hyperglycemic conditions, affecting downstream targets such as Bcl-2 [46, 89]. Of interest, two meta-analyses have reported that the downregulation of miR-26a-5p was associated with diabetic nephropathy [90]; however, no GLP-1RA intervention in such a relation has been investigated.

Moreover, liraglutide therapy has been demonstrated to downregulate the levels of miR-181a-5p, which negatively relates to the increased expression of cyclic AMP-responsive element binding protein (CREB) in the aorta. It indicates that this miRNA may be involved in

the regulation of the miR-181a-5p/CREB pathway with subsequent effects on Bcl-2 phosphorylation [91]. Both miR-181a-5p and miR-181a-3p have been reported to regulate the genes involved in the etiology of coronary artery disease (CAD). Recent studies investigating their role in atherogenesis found that the expressions of these miRNAs were significantly downregulated in the plasma and aortic plaques of CAD patients and apoE−/− mice with hyperlipidemia. The restoration of miR-181a-5p and miR-181a-3p has been associated with reduced atherosclerotic plaque formation in mice, primarily due to the downregulation of pro-inflammatory gene expression and decreased immune cell infiltration rather than through any direct effects on lipid metabolism. They were found to suppress the expression of adhesion molecules and endothelial cell activation through a similar pathway that involves TGF-β-activated kinase 1-binding protein 2 (TAB2) and the NF-κB essential modulator (NEMO) to interference with NF-κB signaling. These data put miR-181a-5p and miR-181a-3p in an excellent position as anti-atherogenic agents. Additionally, this data highlights the significance of the miR-181a-3p restoration as a novel strategy against atherosclerosis, possibly in combination with GLP-1RAs [92].

It showed that regarding exosomal miRNAs, exendin-4 p53-dependently modulated the expression of miR-192 in response to high glucose levels. The exendin-4 treated group inhibited the transmission of extracellular vesicles(EVs)-miR-192 between healthy tubular epithelial cells and those exposed to high glucose levels, preventing damage caused by elevated glucose levels. Although GLP-1R is known to play a role in regulating miR-192-induced fibrosis, the influence of this miRNA on GLP-1R may be broader than that of simple direct targeting, with indirect interactions with other proteins such as SLC39A6 and TGF-β [93, 94]. This downregulation of GLP-1R contributes to the development of diabetic kidney disease (DKD), as a T2DM- associated cardiovascular events. Notably, mesenchymal stem cell (MSC)-derived EVs containing miR-192 have been shown to alleviate inflammation and angiogenesis in retinal cells subjected to high glucose levels by targeting integrin subunit α1 (ITGA1). This contributes to the mitigation of diabetic retinopathy as well [95].

Conclusion

This narrative review underlines the important roles of miRNAs targeting GLP-1RAs in the management of comorbidities from T2DM, mainly regarding cardiovascular health, weight control, and hyperglycemia (Fig. 2; Table 1). The combination of liraglutide or BYDUREONTM, together with metformin, exerts a profound epigenetic regulatory effect in T2DM through the upregulation of protective miRNAs such as miR-27b, miR-130a, and miR-210, which are linked to improved lipid profiles, endothelial function and, predictive of improved cardiovascular outcomes. Among GLP-1RAs, semaglutide, dulaglutide, and liraglutide are the most active in the reduction of HbA1c levels in T2DM patients. Semaglutide causes the most significant effects with respect to HbA1c reduction and body weight loss. At the level of miRNA expression, higher levels of miR-378-3p and miR-126-3p were related to better glycemic control after one year of treatment with liraglutide and dulaglutide. Importantly, miR-375-5p was characterized as a predictor of HbA1c levels, whereas higher miR-378-3p and miR-126-3p levels were associated with significant reductions in both HbA1c and fasting plasma glucose. Liraglutide exerts a protective effect against pancreatic β-cell apoptosis by downregulating miR-139-5p involved in β-cell death via caspase-3 and Bcl-2.

Besides, miR-139-5p represses IRS1 expression, a critical component of insulin signaling. In particular, miR-375, highly expressed in pancreatic islets, has been considered important for maintaining β-cell function and as a biomarker for evaluating the cytoprotective action of GLP-1RAs on β-cells. Also, suppression of miR-204 increases the expression of the GLP-1 receptor on β-cells, leading to an increase in responsiveness to GLP-1RAs. Interestingly, lower levels of miR-204 are independently associated with higher CVD risk in T2DM patients.

Regarding lipid control, all GLP-1RAs, including liraglutide, exenatide, semaglutide, and dulaglutide, showed some lipid-lowering benefits; however, these varied in terms of both the extent and the duration. For example, liraglutide significantly reduced TC, LDL-C, and non-HDL-C, mainly in subjects with high baseline LDL-C values. Exenatide also decreases postprandial triglycerides, while semaglutide and dulaglutide have longer-term benefits on the lipid profile. GLP-1RAs also affect the expression levels of miRNAs such as miR-27b, miR-130a, and miR-210a, implicated in the regulation of lipid metabolism, glucose homeostasis, and adipokines, which further supports their biomarker potential for treatment response. Apart from its potent effects on weight management and non-alcoholic fatty liver disease, semaglutide uniquely inhibited ABHD6 expression and modified miR-5120. Baseline levels of miR-15a-5p have also been reported to predict weight reduction following GLP-1RA therapy in T2DM patients with IGT.

GLP-1RA administration has been associated with reductions in both systolic and diastolic blood pressure. This is more pronounced in some agents such as exenatide, liraglutide, dulaglutide, and semaglutide, lending further support to their cardiovascular benefits beyond effects on weight loss. These effects are not uniform among GLP-1RAs, though, and large trials with

lixisenatide and exenatide QW failed to show substantial effects on cardiovascular outcomes.

Additionally, a few miRNAs have emerged as important mediators of the cardiovascular actions of GLP-1RAs. For example, miR-29b-3p, induced by long-acting exenatide, is required for the protection against DCM and its complications, including heart failure and microvascular damage. The protective effects of GLP-1RAs on the miR-29b-3p/SLMAP axis are reversed by the inhibition of GLP-1 receptors in cardiomyocytes, thus pointing toward a therapeutic role of GLP-1RAs in mitigating diabetic cardiac complications. Liraglutide modulates miRNAs such as miR-93-5p, miR-26a-5p, and miR-181a-5p, which are critical regulators of endothelial cell function and atherosclerosis. Liraglutide downregulates miR-93-5p by targeting SIRT1, which may be an important mechanism by which GLP-1 analogs promote vascular health through the preservation of endothelial cell function in hyperglycemic conditions. Moreover, liraglutide upregulates miR-26a-5p, which might modulate the PI3K-AKT signaling pathway, increasing the expression of anti-apoptotic proteins such as Bcl-2. These effects may thus contribute to the protection against endothelial dysfunction, a key factor in the development of cardiovascular disease in T2DM. Furthermore, liraglutide's downregulation of miR-181a-5p, by modulating the miR-181a-5p/CREB pathway, reduces the formation of atherosclerotic plaques. Evidence of miR-181a-5p participation in atherogenesis and of its potential as an anti-atherogenic agent suggests that GLP-1RAs can exert additional cardiovascular benefits through modulation of miRNA-regulated pathways.

GLP-1RAs also regulate exosomal miRNAs, such as miR-192, implicated in the development of fibrosis and inflammation in micro-cardiovascular outcomes like DKD and DR. For example, exendin-4 might alter high glucose-induced miR-192 expression towards less inflammation, which would reduce the severity of DR. These data show that miRNAs may also be biomarkers of efficacy in the use of GLP-1RAs for the treatment of diabetic microvascular complications. In animal models mimicking postmenopausal T2DM, liraglutide resulted in significant changes in exosomal miRNA profiles by upregulating such miRNAs as miR-1-3p, let-7f-5p, and miR-148a-3p that contribute to bone quality in hyperglycemic and estrogen-depleted states in females. This represents a wide spectrum of GLP-1RA activities in many tissues beyond metabolic benefits.

Further research is required to establish the correlation between miRNAs induced by GLP-1RA and laboratory outcomes in treated T2DM patients, especially across different demographics, genders, and comorbidities. Longitudinal studies that monitor changes in miRNA and key markers of diabetes management, such as fasting glucose and HbA1c, will provide more information on the longer-term effects of GLP-1RAs. A second avenue that will be important in fleshing out how these relationships affect miRNA expression and subsequent cardiometabolic outcomes is research into the various ways in which GLP-1RAs interact with other medications for diabetes, such as metformin, especially as GLP-1RAs are the second-line treatment of T2DM. Lastly, further studies considering lifestyle factors of food and exercise will complete the picture in terms of how these factors interact with the GLP-1RA medication and miRNA expression. Finally, investigating the effect of the GLP-1RA treatment in patients having comorbid conditions such as hypertension and dyslipidemia might reveal wider cardiovascular benefits, with a more personalized approach toward treatments. We therefore will be in a better position to address the many-sided challenges in managing T2DM and improve outcomes across various patient populations.

Abbreviations

T2DM	Type 2 diabetes mellitus
OADs	Oral antidiabetic drugs
HbA1c	Glycosylated hemoglobin
FBS	Fasting blood glucose
SUs	Sulfonylureas
DPP-4Is	Dipeptidyl peptidase-4 inhibitors
TZDs	Thiazolidinediones
SGLT-2Is	Sodium-glucose cotransporter 2 inhibitors
αGIs	Alpha-glucosidase inhibitors
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
ADA	The american diabetes association
EASD	The european association for the study of diabetes
GLP-1	Glucagon-like peptide-1
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
CIMT	Carotid intima-media thickness
HDL-C	High-density lipoprotein cholesterol
FMD	Flow-mediated dilation
STZ	Streptozotocin
IGT	Impaired glucose tolerance
NGT	Normal glucose tolerance
BMI	Body mass index
GCC	The ganglion cell complex
NAFLD	Non-alcoholic fatty liver disease
UTR	Untranslated region
CVD	Cardiovascular disease
FRS	The framingham risk score
OVX	Ovariectomized
HIF	Hypoxia-inducible factor
DCM	Diabetic cardiomyopathy
SIRT1	Sirtuin 1
HRMECs	Human retinal microvascular endothelial cells
DR	Diabetic retinopathy
BM-MSCs	Bone marrow mesenchymal stem cells
FOXO3	Forkhead box O3
lncRNA	Long non-coding RNA
HGMCs	Human glomerular mesangial cells
HRGECs	Human renal glomerular endothelial cells
ROCK2	Rho-associated protein kinase 2
CREB	Cyclic AMP-responsive element binding protein
CAD	Coronary artery disease
TAB2	TGF-β-activated kinase 1-binding protein 2
NEMO	The NF-κB essential modulator
EVs	Extracellular vesicles

DKD	Diabetic kidney disease
MSC	Mesenchymal stem cell
ITGA1	Integrin subunit α1
SNAC	N-(8-(2-hydroxybenzoyl)amino) caprylate

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Competing interests
The authors declare no competing interests.

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References

1. Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front Endocrinol. 2023;14:1161521.
2. Cavan D, da Rocha Fernandes J, Makaroff L, Ogurtsova K, Webber S. IDF diabetes atlas, Brussels: International Diabetes Federation. ISBN 978-2-930229-81-2; 2015.
3. Blüher M. Obesity: global epidemiology and pathogenesis. Nat Reviews Endocrinol. 2019;15(5):288–98.
4. Arpón A, Milagro FI, Santos JL, García-Granero M, Riezu-Boj J-I, Martínez JA. Interaction among sex, aging, and epigenetic processes concerning visceral fat, insulin resistance, and dyslipidaemia. Front Endocrinol. 2019;10:496.
5. Chambers JC, Loh M, Lehne B, Drong A, Kriebel J, Motta V, et al. Epigenome-wide association of DNA methylation markers in peripheral blood from Indian asians and europeans with incident type 2 diabetes: a nested case-control study. Lancet Diabetes Endocrinol. 2015;3(7):526–34.
6. Mansour A, Mousa M, Abdelmannan D, Tay G, Hassoun A, Alsafar H. Microvascular and macrovascular complications of type 2 diabetes mellitus: Exome wide association analyses. Front Endocrinol. 2023;14:1143067.
7. Ramos-Lopez O, Milagro FI, Riezu-Boj JI, Martinez JA. Epigenetic signatures underlying inflammation: an interplay of nutrition, physical activity, metabolic diseases, and environmental factors for personalized nutrition. Inflamm Res. 2021;70:29–49.
8. Janez A, Muzurovic E, Bogdanski P, Czupryniak L, Fabryova L, Fras Z, et al. Modern management of cardiometabolic continuum: from overweight/obesity to prediabetes/type 2 diabetes mellitus. Recommendations from the Eastern and Southern Europe diabetes and obesity expert group. Diabetes Therapy. 2024;15(9):1865–92.
9. Sarma S, Sockalingam S, Dash S. Obesity as a multisystem disease: Trends in obesity rates and obesity-related complications. Diabetes Obes Metabolism. 2021;23:3–16.
10. Blüher M, Ceriello A, Davies M, Rodbard H, Sattar N, Schnell O, et al. Managing weight and glycaemic targets in people with type 2 diabetes—how far have we come? Endocrinology. Diabetes Metab. 2022;5(3):e00330.
11. Weerakiet S, Srisombut C, Bunnag P, Sangtong S, Chuangsoongnoen N, Rojanasakul A. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in Asian women with polycystic ovary syndrome. Int J Gynecol Obstet. 2001;75(2):177–84.
12. Palta P, Huang ES, Kalyani RR, Golden SH, Yeh H-C. Hemoglobin A1c and mortality in older adults with and without diabetes: results from the National Health and Nutrition examination surveys (1988–2011). Diabetes Care. 2017;40(4):453–60.
13. Slouha E, Ibrahim F, Rezazadah A, Esposito S, Clunes LA, Kollias TF. Anti-diabetics and the Prevention of Dementia: a systematic review. Cureus. 2023;15(11).
14. Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J. 2000;348(3):607–14.
15. Malboosbaf R, Hatami N. Treatment Approaches and Challenges. Nanoscience Applications in Diabetes Treatment. 2023:31.
16. American Diabetes A. 8. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Supplement1):S100–10.
17. Rothberg AE, Ard JD, Gudzune KA, Herman WH. Obesity management for the treatment of type 2 diabetes. Diabetes in America. 2024.
18. Miller L-A, Burudpakdee C, Zagar A, Bhosle M, Reaney M, Schabert VF, et al. Exenatide BID and liraglutide QD treatment patterns among type 2 diabetes patients in Germany. J Med Econ. 2012;15(4):746–57.
19. Zheng SL, Roddick AJ, Aghar-Jaffar R, Shun-Shin MJ, Francis D, Oliver N, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA. 2018;319(15):1580–91.
20. Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. Eur J Endocrinol. 2009;160(6):909–17.
21. Seufert J, Gallwitz B. The extra-pancreatic effects of GLP-1 receptor agonists: a focus on the cardiovascular, gastrointestinal and central nervous systems. Diabetes Obes Metabolism. 2014;16(8):673–88.
22. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. Diabetes Spectr. 2017;30(3):202–10.
23. Capuani B, Pacifici F, Della-Morte D, Lauro D. Glucagon like peptide 1 and MicroRNA in metabolic diseases: focusing on GLP1 action on miRNAs. Front Endocrinol. 2018;9:719.
24. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. Diabetes Care. 2011;34(Suppl 2):S279.
25. Gallwitz B. GLP-1 agonists and dipeptidyl-peptidase IV inhibitors. Diabetes-Perspectives Drug Therapy. 2011:53–74.
26. Okerson T, Chilton RJ. The cardiovascular effects of GLP-1 receptor agonists. Cardiovasc Ther. 2012;30(3):e146–55.
27. Collins L, Costello RA. Glucagon-like peptide-1 receptor agonists. 2019.
28. Formichi C, Fignani D, Nigi L, Grieco GE, Brusco N, Licata G, et al. Circulating microRNAs signature for predicting response to GLP1-RA therapy in type 2 diabetic patients: a pilot study. Int J Mol Sci. 2021;22(17):9454.
29. Dawed AY, Donnelly L, Tavendale R, Carr F, Leese G, Palmer CN, et al. CYP2C8 and SLCO1B1 variants and therapeutic response to thiazolidinediones in patients with type 2 diabetes. Diabetes Care. 2016;39(11):1902–8.
30. Rathmann W, Bongaerts B. Pharmacogenetics of novel glucose-lowering drugs. Diabetologia. 2021;64:1201–12.
31. Association AD. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Supplement1):S15–33.
32. Chung WK, Erion K, Florez JC, Hattersley AT, Hivert M-F, Lee CG, et al. Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(7):1617–35.
33. Lu F, Gong H, Duan L, Yan Y, Chen L, Peng P, et al. miR-29 regulates metabolism by inhibiting JNK-1 expression in non-obese patients with type 2 diabetes mellitus and NAFLD. Open Med. 2023;18(1):20230873.

34. Joglekar MV, Januszewski AS, Jenkins AJ, Hardikar AA. Circulating microRNA biomarkers of diabetic retinopathy. Diabetes. 2016;65(1):22–4.
35. Demirsoy İH, Ertural DY, Balci Ş, Çınkır Ü, Sezer K, Tamer L, et al. Profiles of circulating miRNAs following metformin treatment in patients with type 2 diabetes. J Med Biochem. 2018;37(4):499.
36. Catanzaro G, Besharat ZM, Chiacchiarini M, Abballe L, Sabato C, Vacca A et al. Circulating microRNAs in elderly type 2 diabetic patients. International Journal of Endocrinology. 2018;2018.
37. Flowers E, Aouizerat BE, Abbasi F, Lamendola C, Grove KM, Fukuoka Y, et al. Circulating microRNA-320a and microRNA-486 predict thiazolidinedione response: moving towards precision health for diabetes prevention. Metabolism. 2015;64(9):1051–9.
38. Lopez YON, Retnakaran R, Zinman B, Pratley RE, Seyhan AA. Predicting and understanding the response to short-term intensive insulin therapy in people with early type 2 diabetes. Mol Metabolism. 2019;20:63–78.
39. Palihaderu P, Mendis B, Premarathne J, Dias W, Yeap SK, Ho WY, et al. Therapeutic potential of miRNAs for type 2 diabetes mellitus: an overview. Epigenetics Insights. 2022;15:25168657221130041.
40. Nikolic D, Giglio R, Chianetta R, Castracani CC, Sardo V, Castellino G, et al. editors. The GLP-1RA exenatide LAR increases circulating miR-27b in patients with type 2 diabetes: an 8-month prospective study of cardiometabolic and epigenetic response. DIABETOLOGIA; 2017: SPRINGER 233 SPRING ST, NEW YORK, NY 10013 USA.
41. Gaborit B, Julla J-B, Besbes S, Proust M, Vincentelli C, Alos B, et al. Glucagon-like peptide 1 receptor agonists, diabetic retinopathy and angiogenesis: the AngioSafe type 2 diabetes study. J Clin Endocrinol Metabolism. 2020;105(4):e1549–60.
42. Rosaria Vincenza Giglio DN, Giovanni Li AA, Rizvi. Giorgio Sesti, and Manfredi Rizzo. Liraglutide Increases Serum Levels of MicroRNA-27b, -130a and – 210 in Patients with Type 2 Diabetes Mellitus: A Novel Epigenetic Effect. Metabolites. 2020;10(10):391.
43. Song I, Roels S, Martens GA, Bouwens L. Circulating microRNA-375 as biomarker of pancreatic beta cell death and protection of beta cell mass by cytoprotective compounds. PLoS ONE. 2017;12(10):e0186480.
44. Li J, Su L, Gong Y-y, Ding M-l, Hong S-b, Yu S, et al. Downregulation of mir-139-5p contributes to the antiapoptotic effect of liraglutide on the diabetic rat pancreas and INS-1 cells by targeting IRS1. PLoS ONE. 2017;12(3):e0173576.
45. Jo S, Chen J, Xu G, Grayson TB, Thielen LA, Shalev A. miR-204 controls glucagon-like peptide 1 receptor expression and agonist function. Diabetes. 2018;67(2):256–64.
46. Zhang Q, Xiao X, Zheng J, Li M. A glucagon-like peptide-1 analog, liraglutide, ameliorates endothelial dysfunction through miRNAs to inhibit apoptosis in rats. PeerJ. 2019;7:e6567.
47. Li R, Ye Z, She D, Fang P, Zong G, Hu K et al. Semaglutide may alleviate hepatic steatosis in T2DM combined with NFALD mice via miR-5120/ABHD6. Drug Design, Development and Therapy. 2023:3557-72.
48. Fang P, Ye Z, Li R, She D, Zong G, Zhang L et al. Glucagon-like peptide-1 receptor agonist protects against diabetic cardiomyopathy by modulating microRNA-29b-3p/SLMAP. Drug Design, Development and Therapy. 2023:791–806.
49. Jia Y, Zheng Z, Guan M, Zhang Q, Li Y, Wang L, et al. Exendin-4 ameliorates high glucose-induced fibrosis by inhibiting the secretion of miR-192 from injured renal tubular epithelial cells. Exp Mol Med. 2018;50(5):1–13.
50. Li J, Fu L-Z, Liu L, Xie F, Dai R-C. Glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide alters bone marrow exosome-mediated miRNA signal pathways in ovariectomized rats with type 2 diabetes. Med Sci Monitor: Int Med J Experimental Clin Res. 2017;23:5410.
51. Aoki K, Kamiyama H, Takihata M, Taguri M, Shibata E, Shinoda K, et al. Effect of liraglutide on lipids in patients with type 2 diabetes: a pilot study. Endocr J. 2020;67(9):957–62.
52. Koska J, Schwartz EA, Mullin MP, Schwenke DC, Reaven PD. Improvement of postprandial endothelial function after a single dose of exenatide in individuals with impaired glucose tolerance and recent-onset type 2 diabetes. Diabetes Care. 2010;33(5):1028–30.
53. Berra CC, Rossi MC, Mirani M, Ceccarelli Ceccarelli D, Romano C, Sassi L, et al. Real world effectiveness of subcutaneous semaglutide in type 2 diabetes: a retrospective, cohort study (Sema-MiDiab01). Front Endocrinol. 2023;13:1099451.
54. Tuttolomondo A, Cirrincione A, Casuccio A, Del Cuore A, Daidone M, Di Chiara T, et al. Efficacy of dulaglutide on vascular health indexes in subjects with type 2 diabetes: a randomized trial. Cardiovasc Diabetol. 2021;20:1–14.
55. Sangalli E, Tagliabue E, La S. Circulating MicroRNA-15a associates with retinal damage in patients with early stage type 2 diabetes. Front Endocrinol (Lausanne). 2020;11:254.
56. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, 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):275–86.
57. Frias JP, Wynne AG, Matyjaszek-Matuszek B, Bartaskova D, Cox D, Woodward B et al. Efficacy and safety of an expanded Dulaglutide Dose Range—A phase 2, placebo-controlled trial in T2D patients on Metformin. Diabetes. 2018;21(9):2048-2057.
58. 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 Metabolism. 2017;19(4):524–36.
59. Davies M, Pieber TR, Hartoft-Nielsen M-L, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. JAMA. 2017;318(15):1460–70.
60. Aroda VR, Ahmann A, Cariou B, Chow F, Davies MJ, Jódar E, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: insights from the SUSTAIN 1–7 trials. Diabetes Metab. 2019;45(5):409–18.
61. Thethi TK, Pratley R, Meier JJ. Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: the PIONEER programme. Diabetes Obes Metabolism. 2020;22(8):1263–77.
62. Giorgino F, Benroubi M, Sun J-H, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Diabetes Care. 2015;38(12):2241–9.
63. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care. 2014;37(8):2159–67.
64. Salmen T, Serbanoiu L-I, Bica I-C, Serafinceanu C, Muzurović E, Janez A, et al. A critical view over the newest antidiabetic molecules in light of Efficacy—A systematic review and Meta-analysis. Int J Mol Sci. 2023;24(11):9760.
65. Sedgeman LR, Beysen C, Ramirez Solano MA, Michell DL, Sheng Q, Zhao S, et al. Beta cell secretion of miR-375 to HDL is inversely associated with insulin secretion. Sci Rep. 2019;9(1):3803.
66. Wang R, Ding Y-D, Gao W, Pei Y-Q, Yang J-X, Zhao Y-X, et al. Serum microRNA-204 levels are associated with long-term cardiovascular disease risk based on the Framingham risk score in patients with type 2 diabetes: results from an observational study. J Geriatric Cardiology: JGC. 2020;17(6):330.
67. Wang B, Zhong J, Lin H, Zhao Z, Yan Z, He H, et al. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. Diabetes Obes Metabolism. 2013;15(8):737–49.
68. Ferdinand KC, Dunn J, Nicolay C, Sam F, Blue EK, Wang H. Weight-dependent and weight-independent effects of dulaglutide on blood pressure in patients with type 2 diabetes. Cardiovasc Diabetol. 2023;22(1):49.
69. Ruseva A, Michalak W, Zhao Z, Fabricatore A, Hartaigh BÓ, Umashanker D. Semaglutide 2.4 mg clinical outcomes in patients with obesity or overweight in a real-world setting: a 6-month retrospective study in the United States (SCOPE). Obes Sci Pract. 2024;10(1):e737.
70. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–39.
71. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373(23):2247–57.
72. Liu F, Yang Q, Zhang H, Zhang Y, Yang G, Ban B, et al. The effects of glucagon-like peptide-1 receptor agonists on adipose tissues in patients with type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS ONE. 2022;17(7):e0270899.
73. Wang J, Song Y, Zhang Y, Xiao H, Sun Q, Hou N, et al. Cardiomyocyte overexpression of miR-27b induces cardiac hypertrophy and dysfunction in mice. Cell Res. 2012;22(3):516–27.
74. Li T, Cao H, Zhuang J, Wan J, Guan M, Yu B, et al. Identification of miR-130a, miR-27b and miR-210 as serum biomarkers for atherosclerosis obliterans. Clin Chim Acta. 2011;412(1–2):66–70.

75. Boštjančič E, Zidar N, Glavač D. MicroRNA microarray expression profiling in human myocardial infarction. Dis Markers. 2009;27(6):255–68.
76. Signorelli SS, Volsi GL, Pitruzzella A, Fiore V, Mangiafico M, Vanella L, et al. Circulating miR-130a, miR-27b, and miR-210 in patients with peripheral artery disease and their potential relationship with oxidative stress: a pilot study. Angiology. 2016;67(10):945–50.
77. Sun L, Trajkovski M. MiR-27 orchestrates the transcriptional regulation of brown adipogenesis. Metabolism. 2014;63(2):272–82.
78. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med. 2013;19(10):1252–63.
79. Jia Q-W, Chen Z-H, Ding X-Q, Liu J-Y, Ge P-C, An F-H, et al. Predictive effects of circulating miR-221, miR-130a and miR-155 for coronary heart disease: a multi-ethnic study in China. Cell Physiol Biochem. 2017;42(2):808–23.
80. Devlin C, Greco S, Martelli F, Ivan M. miR-210: more than a silent player in hypoxia. IUBMB Life. 2011;63(2):94–100.
81. Zeng Y, Cui Z, Liu J, Chen J, Tang S. MicroRNA-29b-3p promotes human retinal microvascular endothelial cell apoptosis via blocking SIRT1 in diabetic retinopathy. Front Physiol. 2020;10:1621.
82. Su T, Xiao Y, Xiao Y, Guo Q, Li C, Huang Y, et al. Bone marrow mesenchymal stem cells-derived exosomal MiR-29b-3p regulates Aging-Associated insulin resistance. ACS Nano. 2019;13(2):2450–62.
83. Li N, Muthusamy S, Liang R, Sarojini H, Wang E. Increased expression of miR-34a and miR-93 in rat liver during aging, and their impact on the expression of Mgst1 and Sirt1. Mech Ageing Dev. 2011;132(3):75–85.
84. Hwang J-w, Yao H, Caito S, Sundar IK, Rahman I. Redox regulation of SIRT1 in inflammation and cellular senescence. Free Radic Biol Med. 2013;61:95–110.
85. Nadtochiy SM, Redman E, Rahman I, Brookes PS. Lysine deacetylation in ischaemic preconditioning: the role of SIRT1. Cardiovascular Res. 2011;89(3):643–9.
86. Zhao L, Chen H, Wu L, Li Z, Zhang R, Zeng Y, et al. LncRNA KCNQ1OT1 promotes the development of diabetic nephropathy by regulating miR-93-5p/ROCK2 axis. Diabetol Metab Syndr. 2021;13:1–13.
87. Qin W, Ren B, Wang S, Liang S, He B, Shi X, et al. Apigenin and naringenin ameliorate PKCβII-associated endothelial dysfunction via regulating ROS/caspase-3 and NO pathway in endothelial cells exposed to high glucose. Vascul Pharmacol. 2016;85:39–49.
88. Wang L, Tang L, Wang Y, Wang L, Liu X, Liu X, et al. Exendin-4 protects HUVECs from t-BHP-induced apoptosis via PI3K/Akt-Bcl-2-caspase-3 signaling. Endocr Res. 2016;41(3):229–35.
89. Kang KH, Lemke G, Kim JW. The PI3K–PTEN tug-of-war, oxidative stress and retinal degeneration. Trends Mol Med. 2009;15(5):191–8.
90. Gholaminejad A, Abdul Tehrani H, Gholami Fesharaki M. Identification of candidate microRNA biomarkers in diabetic nephropathy: a meta-analysis of profiling studies. J Nephrol. 2018;31:813–31.
91. Das S, Cordis GA, Maulik N, Das DK. Pharmacological preconditioning with resveratrol: role of CREB-dependent Bcl-2 signaling via adenosine A3 receptor activation. Am J Physiol Heart Circ Physiol. 2005;288(1):H328–35.
92. Su Y, Yuan J, Zhang F, Lei Q, Zhang T, Li K, et al. MicroRNA-181a-5p and microRNA-181a-3p cooperatively restrict vascular inflammation and atherosclerosis. Cell Death Dis. 2019;10(5):365.
93. Liu Y, Batchuluun B, Ho L, Zhu D, Prentice KJ, Bhattacharjee A, et al. Characterization of zinc influx transporters (ZIPs) in pancreatic β cells: roles in regulating cytosolic zinc homeostasis and insulin secretion. J Biol Chem. 2015;290(30):18757–69.
94. Kim JH, Lee CH, Lee S-W. Hepatitis C virus infection stimulates transforming growth factor-β1 expression through up-regulating miR-192. J Microbiol. 2016;54:520–6.
95. Gu C, Zhang H, Gao Y. Adipose mesenchymal stem cells-secreted extracellular vesicles containing microRNA-192 delays diabetic retinopathy by targeting ITGA1. J Cell Physiol. 2021;236(7):5036–51.
96. Vickers KC, Shoucri BM, Levin MG, Wu H, Pearson DS, Osei-Hwedieh D, et al. MicroRNA-27b is a regulatory hub in lipid metabolism and is altered in dyslipidemia. Hepatology. 2013;57(2):533–42.
97. Hu S, Huang M, Li Z, Jia F, Ghosh Z, Lijkwan MA, et al. MicroRNA-210 as a novel therapy for treatment of ischemic heart disease. Circulation. 2010;122(11suppl1):S124–31.

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