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REVIEW ARTICLE

The role of miR-143/miR-145 in the development, diagnosis, and treatment of diabetes

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Abstract

Objectives Diabetes mellitus [DM], is a multifaceted metabolic disease, which has become a worldwide threat to human wellness. Over the past decades, an enormous amount of attention has been devoted to understanding how microRNAs [miRNAs], a class of small non-coding RNA regulators of gene expression at the post-transcriptional level, are tied to DM pathology. It has been demonstrated that miRNAs control insulin synthesis, secretion, and activity. This review aims to provide an evaluation of the use of miR-143 and miR-145 as biomarkers for the diagnosis and prognosis of diabetes.

Methods The use of miR-143 and miR-145 as biomarkers for the diagnosis and prognosis of diabetes has been studied, and research that examined this link was sought after in the literature. In addition, we will discuss the cellular and molecular pathways of insulin secretion regulation by miR-143/145 expression and finally their role in diabetes.

Results In the current review, we emphasize recent findings on the miR-143/145 expression profiles as novel DM biomarkers in clinical studies and animal models and highlight recent discoveries on the complex regulatory effect and functional role of miR-143/145 expression in DM.

Conclusion A novel clinical treatment that alters the expression and activity of miR-143/miR-145 may be able to return cells to their natural state of glucose homeostasis, demonstrating the value of using comprehensive miRNA profiles to predict the beginning of diabetes.

Keywords Diabetes mellitus [DM] · miR-143/145 · Biomarkers · T2DM

Introduction

Diabetes is a chronic metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion, insulin action, or both. The disease affects millions of people worldwide and is associated with various complications such as cardiovascular disease, nephropathy, retinopathy, and neuropathy. MicroRNAs [miRNAs] are small non-coding RNA molecules that play important roles in the post-transcriptional regulation of gene expression. Recent studies have revealed that miRNAs are implicated in diabetes pathogenesis and its complications such as insulin resistance, beta-cell dysfunction, and vascular dysfunction [1, 2]. Among the miRNAs studied concerning diabetes, miR-143 and miR-145 have received particular attention.

MiR-143 and miR-145 are members of the miR-143/145 cluster, highly expressed in smooth muscle cells and involved in vascular development and homeostasis [3]. Studies suggest that miR-143 and miR-145 may play crucial roles in developing, diagnosing, and treating diabetes [1, 3]. In terms of development, studies have revealed that miR-143 and miR-145 are implicated in the regulation of insulin signaling pathways and glucose homeostasis. Dysregulation of these miRNAs may contribute to the development of two key features of type 2 diabetes [T2DM] including insulin resistance and beta-cell dysfunction [4, 5].

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In terms of diagnostics, research has suggested that miR-143 and miR-145 have the potential to be used as biomarkers for the diagnosis of diabetes. For instance, several studies have shown that miR-143 and miR-145 are deregulated in the serum of patients with T2DM compared with healthy controls. These results suggest that these miRNAs can be used as non-invasive biomarkers for the diagnosis of diabetes [6, 7]. Regarding therapy, studies have shown that modulation of miR-143 and miR-145 expression may be a potential therapeutic strategy for diabetes and its complications. Several researches in animal models of diabetes have revealed that overexpression of miR-143 and miR-145 improves insulin sensitivity and glucose tolerance [8, 9].

In conclusion, miR-143 and miR-145 may play important roles in developing, diagnosing, and treating of diabetes. Further studies are needed to fully understand the mechanisms underlying the effects of these miRNAs on diabetes and to determine their potential as diagnostic and therapeutic targets for this disease. This review can aid in our knowledge of the promising role that miR-143 and miR-145 may play in the early detection and management of diabetes.

miRNAs and major signaling pathways in diabetes

Numerous signaling pathways, including the insulin signaling system, the AMP-activated protein kinase [AMPK] pathway, the peroxisome proliferators-activated receptors [PPARs] regulation pathway, and the chromatin modification pathway, have been linked to the pathophysiology of diabetes, according to an increasing number of research. To treat metabolic disorders including diabetes, these signaling pathways have therefore emerged as the main source of new therapeutic targets that show promise.

miRNAs and insulin signaling system

Recent data suggest that miRNAs play a direct role in insulin secretion, also they regulate insulin signaling in the target tissues of insulin action [10]. Insulin signaling is complicated because it comprises a network of signaling cascades that are highly linked. The receptor is phosphorylated by insulin, and its substrate is connected to the downstream control of signaling pathways, eventually increasing glucose transport across cell membranes [11, 12].

A study suggests that miR-145-5p affects insulin signaling pathways related to T2DM [13]. The facilitative glucose transporter type 4 [GLUT4] mediates the controlled entry of glucose into the cell, which is the primary process by which insulin enhances energy storage or use. Instead of raising the intrinsic function of the transporter, insulin primarily improves glucose absorption by enhancing the concentration of GLUT4 proteins in the plasma membrane [14, 15].

In other studies related to miRNAs and [insulin resistance [IR]], IR has been defined as the diminished responsiveness of target tissues to insulin, including skeletal muscle [SM], liver, and adipocytes [16]. At the cellular level, IR is caused by delayed insulin-stimulated tyrosine phosphorylation of the insulin receptor [IRS-1/IRS-2] and related downstream signaling processes [translocation of glucose transporters to cell membranes] in glucose-metabolizing cells [17]. Because cells are unable to adequately absorb more glucose as a consequence, even in the presence of insulin, blood glucose levels rise. Almost the majority of the IR in T2DM patients is caused by abnormalities in insulin-stimulated muscle glycogen synthesis, which arise from a lack of insulin-stimulated glucose transport and phosphorylation activity. In late research, mice were given a high-fructose diet to cause insulin resistance [IR]. It was shown that numerous miRNAs, including miR-19b3p, miR-101a-3p, miR-30a-5p, miR-582-3p, and miR-378a-3p, were overexpressed, whereas IRS-1, FOXO-1, SREBP-1c, SREBP-2, SREBP-2, Insig-1, and Insig-2 [Ing-2a and − 2b], which are implicated in insulin signaling, are some of the putative target genes for these miRNAs [18].

A different research study showed that miR-143 specifically blocked insulin signaling at the level of AKT activation in livers but not in Skeletal muscles, whereas upstream receptor signaling was unaffected [19]. Similar to resistin, overexpression of miR-145 in HepG2 cells may impede glucose absorption and contribute to IR by lowering AKT and insulin receptor substrate-1 [IRS-1] phosphorylation. Overexpression of miR-145 may be induced by resistin both in vivo and in vitro [20].

Another study confirmed a strong correlation between the miR-494 and insulin resistance in a mouse model as it affected the cells' insulin signaling [21]. Likewise, miR-375 has been involved in many studies targeting diabetes and insulin pathways, as it controls insulin excretion by hindering myotrophin [MTPN]. According to this research, it blocks the fusion and exocytosis of intracellular vesicles at the cell membrane, inhibits glucose-stimulated insulin secretion [GSIS] by targeting MTPN, and may also suppress NF-B activity. Targets reducing insulin synthesis and cell proliferation [22].

miRNAs and AMPK pathway

AMPK is a heterotrimeric protein made up of three subunits. Each subunit has many isoforms, which combine to generate 12 different heterotrimer combinations. AMPK

recognizes cellular energy status by self-activation via phosphorylation and allosteric activation, which is responsible for a variety of metabolic functions [23]. Studies showed that AMPK activation increased glucose absorption into cells while decreasing intracellular glucose synthesis which plays an important role in diabetes [24].

A prior study showed that upregulated miR-451 leads to increasing AMPK phosphorylation, so they revealed that miR-451 is involved in diabetic cardiomyopathy through suppression of the AMPK pathway [24]. Another study showed that miR-141 had a negative regulatory influence on IRS2 abundance. Furthermore, knocking down miR-141 dramatically increased the expression of AKT/AMPK-related proteins which was inhibited by inhibiting IRS2 [25].

Entezari, M., et al., revealed that miRNA-148a suppresses AMPK signaling. AMPK signaling activity protects cells against oxidative stress and apoptosis in part by downregulating the forkhead box O1[FOXO1]. Furthermore, AMPK is essential for reducing endoplasmic reticulum [ER] stress in cells and increasing their survival and viability. According to these findings, activating AMPK signaling is useful in avoiding T1D formation by protecting cells. So inhibiting AMPK could lead to the development of T1DM [26]. Also, miRNA-3138 induces insulin resistance via down-regulation of the kinase suppressor of ras 2 [KSR2] to prevent AMPK signaling activation, leading to GLUT4 inhibition [27].

miRNAs and PPARs regulation pathway

Peroxisome proliferator-activated receptors [PPARs] are a transcription factor family that plays an important role in glucose and lipid metabolism. Many cell types, including pancreatic beta cells and immunological cells, carry PPARs, which control insulin secretion and T-cell development [28]. Polymorphisms in the PPARα and PPAR promoter regions influence the genetic propensity to T1D and the degree of islet autoimmunity [29]. Furthermore, PPAR has been linked to the development of insulin resistance and type 2 diabetes [30].

Preclinical studies involving these microRNAs [miR-33 and miR-21] showed that it has a direct effect on PPARα. Also, miRNA-103 and miRNA-107 for type 2 diabetes [31]. A study involving a rodent model showed that activated PPARα has been shown to decrease hyperglycemia by enhancing peripheral insulin sensitivity and decreasing hepatic glucose synthesis. This study suggests that miR-27a is important in inducing insulin resistance via the PPARα mediated PI3K/AKT signaling pathway [32]. Additionally, it has been proven that these microRNAs have a role in diabetes due to their effect on the expression of PPAR-γ subunits, miRNA 34a/-34c [33], miRNA 128- 3p [34], and miRNA 130a/ miRNA 130b [35], as their upregulation led to the suppression of PPAR-γ expression.

Mechanism of action of miR- 143 and 145 in types of diabetes

Mature miRNAs have biological effects by controlling the post-transcriptional control of protein-coding mRNAs through two identified mechanisms: target transcript degradation/decay and target transcript translation inhibition [36]. Because miR-143 and miR-145 are positioned in close genomic proximity and may be transcribed in a bicistronic fashion, they are frequently studied/reported together. In 2004, miR-143 was discovered to be a positive regulator of human adipocyte development through its effects on ERK5 signaling [37]. Studies show that since IR and obesity are related, miR-143 expression was elevated in high-fat diet [HFD]-fed mice's mesenteric adipose, while tumor necrosis factor-alpha therapy lowered it. miR-143 expression suggests that obesity-related inflammation may alter miR-143 expression, influencing adipogenesis [38, 39].

While conditional overexpression of miR-143 worsens IR in diet-induced obesity, miR-143/145 cluster knockout mice are protected against IR-induced obesity. By speeding up the degradation of the positive regulator of AKT signaling, oxysterol-binding protein-like 8, miR-143 may boost IR [19].

Research was conducted to discover the molecular targets of miR-143-3p in the development of insulin resistance. Gene ontology and biological association analyses were performed. After significant research, it was discovered that IGF2R and IGFBP5 were two previously unknown targets of miR-143-3p [40]. This study confirmed that miR-143-3p therapy lowered IGF2R [52.88% reduction] and IGFBP5 [36.88% reduction] levels. IGF2R and IGFBP5 protein levels were also found to be downregulated by miR-143-3p treatment and increased by miR-143-3p therapy. Remarkably, knocking down miR-143 increased the expression of one of the anticipated targets, the mitogen-activated protein kinase ERK5/BMK1/MAPK7, suggesting that miR-143 acts via the target gene ERK5 [41, 42].

As has been reported earlier that miR-143 and miR-145 have an influence over the regulation of insulin by targeting different insulin signaling pathways, so they affect genes such as IRS1, IGF-1Rb, ORP8 [43], AKT, and ABCA1 [44]. AKT has a major role in different metabolic activities so it has an influence on diabetes [45], it has been proved that miR-145 has an indirect effect over AKT due to its effect on P53, because AKT regulates mitogenic growth and

proliferation, growth factors activate it; however, stresses and DNA-damaging substances inhibit its activity, resulting in p53 activation. As a consequence, energized p53 promotes miR-145 expression [46].

A study about [IRS-1] and colon cancer confirmed that miR-145 has a role in downregulating IRS1. As it has been shown that levels of protein decreased however it did not reduce the level of IRS-1 mRNA [38]. Thus, since the strong correlation between IRS-1 and T2DM and some cases of T1DM, the miR-145 affects diabetes as well. Also, miR-145 affects the IGF-1Rb gene as it was shown that it causes downregulation of this gene on both transcription [mRNA] level and translation [protein] level [43].

A study confirmed the correlation between [SERPINE1] and diabetes as it showed that it was highly expressed in individuals with diabetes mellitus [47]. As per a prior study, overexpression of miR-145 repressed SERPINE1 consequently, proves it affects diabetes as well [48]. Furthermore, a study suggested that potential target genes of miR-145 that influence diabetes are ADAM22, MYO5A, LOX, and GM2A [44].

Cellular and molecular targets of miR-143 and miR-145 in the diabetes

The genes encoding miR-143 and miR-145 are highly conserved and are located close to each other in human chromosome 5 [1.7 kb] [3]. Considering this, it has been determined that in the genomic organization, these genes are transcribed together, so it is shown as miR-143/miR-145 [38, 49]. Many miRNAs are of specific importance in diseases related to vascular complications such as diabetes. Perhaps we can mention miR-143/145 from this category. The results of recent studies have determined that the expression level of miR-143/145 is strongly increased in vascular smooth muscle cells and to a lesser amount by endothelial cells, and both glomerular and tubular epithelial cells [50, 51]. It has also been found that high glucose levels, stress, and TFG induce miR-143/145 levels and ultimately have a protective effect on blood vessels [52].

According to the mentioned points, it can be said that the regulation of signaling pathways of insulin secretion by microRNAs in smooth muscle cells plays a role in vascular complications related to diabetes. Two miRNAs, miR-143 and miR-145 in smooth muscle have been found to target insulin signaling pathways in non-smooth muscle cells [38, 53]. In this section, we aim to study the cellular and molecular pathways of insulin secretion regulation by miR-143/145 expression and finally their role in diabetes. Vascular disease is the most common cause of death in patients with insulin-resistant diabetes, but the mechanisms involved in diabetic vascular disease are not clearly understood. One of the proposed mechanisms for insulin resistance is decreased expression of insulin receptor substrate [IRS-1] [54]. Thus, the reduction of IRS-1 expression plays a role in changing the function of vascular smooth muscles and can also play a role in the development of diabetes [20]. The results of various studies have determined that the miR-143/145 cluster is vastly enriched in smooth muscle cells and plays an essential role in vascular smooth muscle function. It has also been found that the expression of IRS-1 is partially regulated by miRNAs including miR-145 in hepatocytes, and this mechanism may play a role in insulin resistance [55]. Insulin resistance in liver cells is also associated with increased expression of miR-143 in insulin resistance in liver cells, so it targets some factors, including proteins related to binding to oxysterol [ORP] [20]. The signaling pathway and function of this factor is such that the reduction of ORP8 expression leads to the disruption of the AKT signal as one of the insulin pathways [56].

One of the mechanisms involved in the effects of blood vessels and perhaps diabetes can be attributed to the effect of different microRNAs such as miR-145 and miR-143 on the phenotypic modulation of VSMC through the suppression of Kruppel-like factor 5 [KLF5] and [KLF4] and followed by the stimulation of their downstream signaling molecules [57]. Based on the results of various studies, the serum response factor [SRF] leads to stimulation of the expression of miR 143/145, and following the increase of miR-143/145 levels, their inhibitory effects on klf4 and Elk1 lead to regulation with the suppressive functions of several factors, including KLF4 and Elk-1 regulation. It has been reported that they play a role in regulating the proliferation of VSMC and lead to the differentiation and inhibition of the proliferation and promotion of smooth muscle cells [49]. In addition, the findings of various studies have determined that the levels of miR-143 and miR-145 in plasma have shown a relationship with various other factors, including blood pressure, coronary artery disease, diabetes, and AMI. These findings highlight the importance of miR-143/-145 as potential biomarkers for diseases with vascular involvement [cardiovascular diseases, diabetes] [6, 58, 59].

In order to understand the function of miRNAs in obesity and T2DM, more studies have been conducted. For this purpose, in some of these studies, they investigated miRNAs regulated in the liver that were related to certain nutritional conditions [20]. Increased expression of miR-143 has also been confirmed in the liver of mice with the db/db genotype [diet-induced obese mice]. miR-143 and miR-145 are located on chromosome 18, which is a small gene cluster. It has also been proven that the amount of miR-145 is positively regulated in the liver and pancreas of obese mice, while the regulation pattern of the expression of these microRNAs

was different in tissues such as adipose tissue [60]. miR-143, miR-145 deficient mice and control mice were subjected to a high-fat diet, and then these mice were compared in terms of metabolism, glucose levels, and hepatic insulin signaling pathways. The results of these studies showed that the treatment groups were significantly improved in terms of both glucose tolerance and insulin sensitivity compared to the control group. Insulin sensitivity was also found to be associated with increased insulin-stimulated AKT phosphorylation in miR-143/145-deficient compared to healthy controls, which coincided with increased miR-143 expression. The promoter region of miR-143-145 contains many sites for FOXO1 transcription factors. Therefore, there may be a regulatory loop in obesity and diabetes-induced miR-143 expression that is increased through the upregulation of miR-143 in FOXO1-dependent hepatocytes under conditions of insulin resistance/AKT inhibition. Therefore, we propose the existence of an autoregulatory loop in which insulin resistance induced by weight gain and obesity leads to a feedback mechanism through the upregulation of FOXO-dependent miR-143/145 expression which is mostly inhibited by insulin activity dependent on some microRNAs [18, 61].

Therefore, according to the results of the studies mentioned above, the different settings created by different signaling pathways for miR-143/145 can be related to obesity, and then obesity leads to disorders in blood pressure, heart diseases, vascular and even diabetes. According to what was mentioned, this pathway shown in (Fig. 1) can be discussed and researched as one of the main targets in therapeutic methods. However, altered expression of miR-143/145 has been noted in a variety of other disorders, such as a variety of cancers, such as prostate, bladder, breast, colorectal, and B-cell malignancies [62–65], suggesting the possibility of targeting these miRNAs for the treatment of metabolic disorders. As with diabetes, more caution is needed. Finally, the levels of miR-143/145 may play a role in different stages of the disease [early to final phases] of diabetes, especially type 2, and can change and disrupt insulin signaling in tissues, leading to insulin resistance and unresponsiveness to insulin.

Diagnostic role of miR-143/145 & the potential prospects in the treatment of diabetes

Due to the emerging global epidemics of T2DM, great efforts are being made to discover new biomarkers for early diagnosis of this disease. Since miRNAs play important roles in

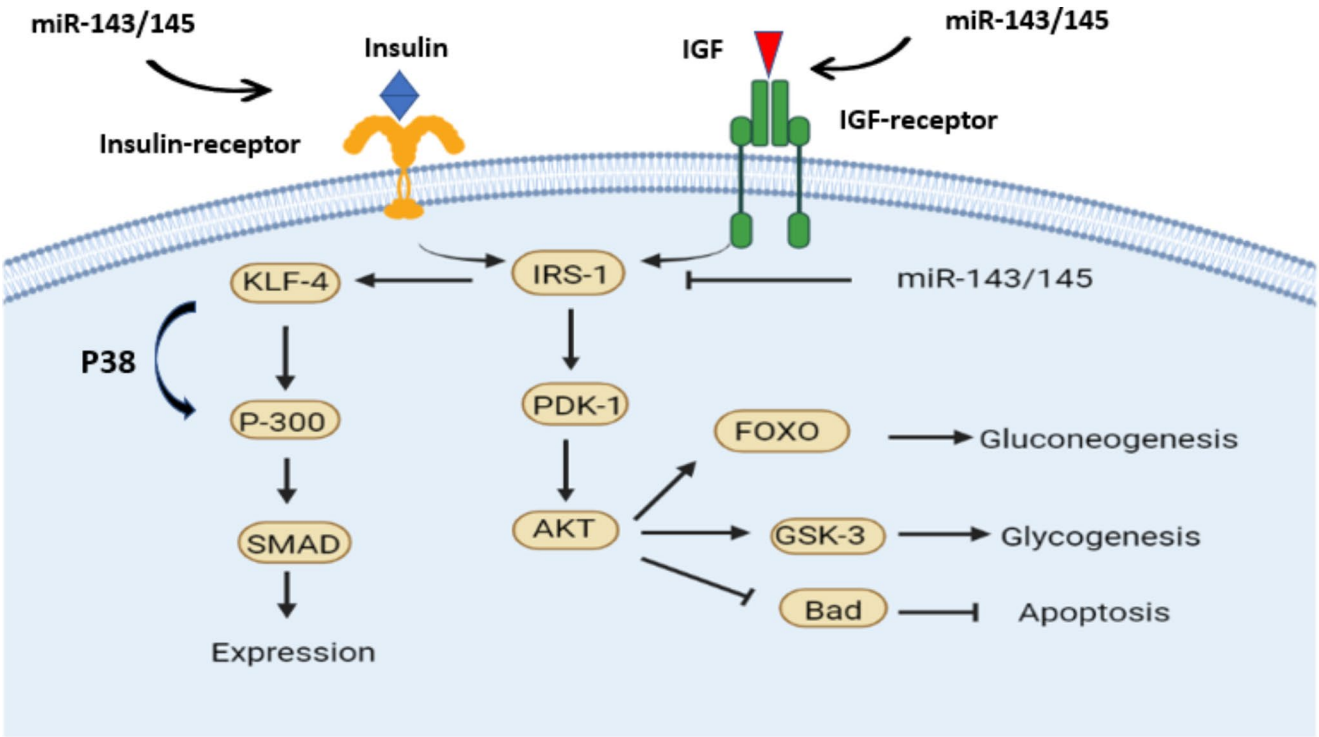

Fig. 1 miR-143/145 signaling pathway in diabetes. As shown in the figure, miR-143/145 can be effective on various factors both outside the cell and inside the cell. In the extracellular part, it affects the action of insulin on its receptor and IGF on its receptor. In addition, miR-143/145 can have an inhibitory effect on IRS-1 through the intracellular pathway and ultimately affect the expression of its downstream genes. The main downstream pathways related to IRS-1 include KLF-4 and AKT, which ultimately affect gene expression, gluconeogenesis, glycogenolysis, and apoptosis

the development and progression of diabetes, In the intervening time, a number of diabetes-related miRNAs have been discovered during diabetic tests. For instance, it has been confirmed that diabetes is associated with increased expression levels of the miRNAs; miR-28-3p and miR-143 and decreased expression levels of the plasma miRNAs; miR-20b, miR-21, miR-24, miR-15a, miR-126, miR-191, miR-197, and miR-486. This review aimed to evaluate the use of miR-143 and miR-145 as biomarkers in the diagnosis of T2DM. Mir-143 and miR-145 are two miRNAs identified as potential biomarkers for the diagnosis and prognosis of diabetes. Several studies have shown that the expression levels of miR-143 and miR-145 are dysregulated in diabetes, especially in T2DM [66, 67]. They are involved in regulating insulin signaling pathways and glucose metabolism. Studies have revealed that the downregulation of miR-143 and miR-145 in diabetic patients is associated with insulin resistance, impaired glucose tolerance, and dyslipidemia [66, 67]. Furthermore, the expression levels of miR-143 and miR-145 are altered in various tissues and body fluids, including blood, serum, plasma, and urine, in diabetic patients. Therefore, they have the potential to be used as diagnostic biomarkers for diabetes and its complications.

In a case-control study, Jahantigh et al. show those functional miR-143/145 variants might increase the risk of T2DM and suggest that studying functional miR-143/145 variants can be a novel target for researchers to use for diagnostic and therapeutic purposes [6]. In another study, Aladel et al. observed increased miR-143 and miR-145 expression and found it to be associated with hypertension, fatigue, and blurred vision among T2DM cases [66]. In the case of miR-145, Shahrokhi et al. displayed that the expression level of miR-145-5p is deregulated in diabetics and prediabetic subjects. In addition, miR-145-5p showed a significant ability to distinguish diabetics from healthy individuals. Their results show that miR-145-5p may be used as a useful biomarker in the diagnosis of T2DM [7]. Also, Barutta et al. explored the potential independent links of miR-145-5p with micro/macro-vascular complications of T1DM by evaluating miR-145-5p in individual serum samples from T1DM patients [68]. Hao et al., results suggest that rectifying macrophage function using miR-145a-5p overexpression accelerates diabetic chronic wound healing [69]. In miR-143-transgenic mice, it has been shown that miR-143 overexpression causes insulin resistance rather than islet b cell malfunction. However, after a high-fat diet [HFD], mice with a miR-143 deletion showed greater insulin sensitivity compared to wild-type animals [10].

In hepatocytes and the liver, miRNAs control insulin resistance. In research conducted on the livers of diabetic rats, it was found that miR-143 levels were elevated, which was associated with poor glucose metabolism [20]. Microarray analysis of serum and urine samples from patients with metabolic syndrome and healthy controls revealed greater levels of circulating miR-143 [70]. Further research has revealed that miR-143 suppresses oxysterol-binding protein-related proteins [Orp8], which hinders insulin's capacity to activate PKB [AKT] signaling, which is a key signaling node of insulin action to promote glucose metabolism [20].

The miR-143 gene, which belongs to the miR-143/145 cluster, is found in the fifth autosome and has a highly conserved sequence. The specific role of miR-143 in regulating and modulating lipid and energy metabolism has been reported [18]. Moreover, earlier research has shown that miR-143 overexpression may impede cellular energy metabolism, resulting in liver glycogenolysis and an increase in blood glucose. In addition, this high amount of miR-143 can prevent AKT from being phosphorylated and prevent blood glucose from being regulated by insulin, leading to insulin resistance and subsequently diabetes [20]. Moreover, precursor adipocyte differentiation and miR-143 are closely related processes. Triglyceride levels significantly reduce when miR-143 is inhibited [71], indicating that miR-143 may be extremely related to human obesity, insulin resistance, and diabetes. As a result, miR-143 may be useful as a possible biomarker for the detection, treatment, and prevention of diabetes in individuals [61].

However, it is important to note that while miR-143 and miR-145 are promising diagnostic markers, they are not currently used as definitive tests for diabetes diagnosis. Diagnosis of diabetes typically involves measuring blood glucose levels, either through a fasting plasma glucose test or an oral glucose tolerance test, as well as assessing symptoms and risk factors.

Briefly, miR-143 and miR-145 are promising biomarkers for the diagnosis and prognosis of diabetes, and further studies are needed to validate their diagnostic and prognostic value in larger patient populations.

Current limitations and future challenges

Due to their functions in the regulation of numerous physiological processes and their modulation in human disorders, miRNAs are an intriguing field of RNA biology. MiRNAs are regulatory molecules that have a role in several phases and facets of diabetes, as well as associated consequences, such as slowed wound healing. Depending on the stimuli, they can perform a variety of roles, such as activating particular signaling pathways or up or down-regulating the expression of particular genes [72]. It is now obvious that some of these molecules might offer useful information in a therapeutic setting, possibly serving as screening tools for

high-risk patients, developing into early predictive diagnostic tools, and assisting in the choice of treatment. Although the promiscuity and diversity of interactions may cause major issues and invalidate clinical applications, many of these markers still need to be verified in vivo environments. Most importantly, because most of these miRNAs exert different functions depending on the tissues and conditions where they are expressed, we still do not fully understand how many of these miRNAs exert their functions. This is either because we lack critical knowledge of the pathways involved or because we are only seeing a small portion of the "big picture". Nonetheless, after being confirmed in vivo, they might be regarded as direct therapeutic targets [69].

In a previous study which still has several restrictions. Although it looked at the cellular role of miR-143-3p and its underlying mechanism in gestational diabetes mellitus, further in vivo research is necessary to confirm these initial in vitro findings. In addition, MIN6 was the sole cell line utilized in this investigation. Thus, confirmation requires additional research using different cell lines, such as INS-1 cells [73].

Another study has several drawbacks. Although having a prospective design, the EURODIAB trial only collects samples at follow-up, making it unable to evaluate miR-145-5p levels at baseline. Establishing causal and temporal links is impossible given the study's cross-sectional nature. The lower number of controls compared to cases decreased the analysis' power. Despite the fact that miRNAs are very stable in biofluids, the likelihood of miR-145-5p degradation during storage cannot be completely ruled out [72].

Conclusion

Due to the emerging global epidemics of T2DM, great efforts are being undertaken to uncover new biomarkers for early diagnosis of this disease. Since miRNAs play important roles in the development and progression of diabetes, this review sought to evaluate the use of miR-143 and mir-145 as biomarkers. miR-143 and miR-145 are highly expressed in smooth muscle cells and are involved in vascular development and homeostasis. Dysregulation of miR-143 and miR-145 may contribute to the emergence of type 2 diabetes. In this review, we mentioned that there are numerous signaling pathways, including the insulin signaling system, the AMP-activated protein kinase [AMPK] pathway, and the PPARs regulation pathway have been linked to the pathophysiology of diabetes. To treat diabetes, these signaling pathways have been recognized as the main source of new therapeutic targets that show promise. Mature miRNAs have biological effects by controlling the post-transcriptional control of protein-coding mRNAs. MiR-143 and miR-145 are positioned in close genomic proximity and may be transcribed in a bicistronic fashion, they are frequently studied/reported together. In 2004, mir-143 was discovered to be a positive regulator of human adipocyte development through its effects on ERK5 signaling. miRNAs which are considered as types of epigenetic processes are non-coding RNAs that can negatively control gene expression. The expression level of miR-143/145 is strongly increased in vascular smooth muscle cells and to a lesser amount by endothelial cells, and both glomerular and tubular epithelial cells. Increased expression of miR-143 has also been confirmed in the liver of diabetic mice. A novel clinical therapy that modifies the expression and activity of these miRNAs can potentially restore normal glucose homeostasis and cell function, supporting the relevance of applying broad miRNA profiles to anticipate the onset of diabetes.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest regarding the publication of this article.

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