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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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REVIEW

MicroRNA 375 and diabetes: A key regulator of β cell function and a promising non-invasive biomarker

Marina Pierantoni, Marcello Dell'Aira, Silvia Grassilli, Federica Brugnoli, Valeria Bertagnolo

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Abstract

Diabetes is a growing global health concern, calling for improved diagnostic and therapeutic strategies. Of the emerging possible biomarkers, microRNA 375 (miR-375) has gained attention for its pivotal role in pancreatic β cell development and function, and its altered blood levels following β cell injury. This review summarizes the current knowledge on the role of miR-375 in insulin regulation, its correlation with diabetes, and its clinical potential. Despite its well-known role in β cell biology, literature analyses have failed to reveal a consistent correlation between the circulating levels of miR-375 and diabetes. A key limitation lies in the lack of β cell specificity of miR-375, along with its modulation by diabetes-related complications, which influences circulating levels of the miRNA. Moreover, the absence of large-scale, standardized clinical studies undermines the comparability of existing data. Despite these limits, the literature analysis clearly indicates the need to expand research into miR-375 modulation strategies in humans, as integrating miR-375 with other diagnostic and therapeutic technologies could enhance its clinical relevance. Such strategies may support more personalized and timely interventions for treating diabetes and its complications, ultimately benefiting patient outcomes and contributing to the sustainability of global healthcare systems.

Key Words: Pancreatic β cells; MicroRNA 375; Type 1 diabetes; Type 2 diabetes; Gestational diabetes mellitus

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Core Tip: Diabetes mellitus is strongly linked to microRNA 375 (miR-375), the most abundant miRNA in pancreatic β cells, where it plays an essential role in cell development and insulin production. MiR-375 is detectable in blood, making it a promising non-invasive biomarker, but the exact relationship between circulating miR-375 levels and both type 1 diabetes and type 2 diabetes remains unclear. This review provides a comprehensive overview of the current understanding of how miR-375 contributes to the onset and progression of diabetes mellitus and its potential use as a tool for the management of this complex pathology.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that includes a heterogeneous group of metabolic disorders characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both[1]. Prolonged hyperglycemia is associated with long-term damage, dysfunction, and the failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels[2]. DM is traditionally classified into distinct categories, including type 1 diabetes (T1D), type 2 diabetes (T2D), gestational DM (GDM), and other less common forms such as monogenic diabetes. Recent advances in genetics, immunology, and metabolomics are promoting a shift toward a more integrated and mechanistic classification of the disease[3,4].

T1D is primarily caused by autoimmune-mediated destruction of pancreatic β cells, resulting in an absolute deficiency of insulin that typically manifests during childhood or adolescence[5,6]. In contrast, T2D is characterized by its gradual onset, resulting from a combination of insulin resistance and inadequate compensatory insulin secretion. T2D pathogenesis is multifactorial, with obesity, aging, and a sedentary lifestyle each making important contributions to its development[7,8]. The condition of glucose intolerance associated with GDM, on the other hand, emerges or is first recognized during pregnancy. Women diagnosed with GDM also have an elevated risk of developing T2D in the years following delivery. From a pathophysiological standpoint, GDM arises when pancreatic β cells fail to compensate adequately for the progressive increase in insulin resistance associated with pregnancy, which is largely due to the secretion of placental hormones. This imbalance between insulin demand and β cell function can negatively impact fetal development and long-term metabolic programming[4,9]. By contrast, monogenic diabetes typically appears early in life and is caused by rare genetic mutations that prevent the normal functioning of pancreatic β cells, representing about 1%-5% of diabetes cases in children[10].

From an epidemiological perspective, the global prevalence of diabetes is increasing at a worrying rate. As reported by the World Health Organization in 2022, an estimated 14% of adults were living with diabetes, compared with 7% in 1990 [11]. Another alarming finding is that more than 50% of diabetic adults aged 30 or over are not receiving any pharmacological treatment for their condition, leaving them at risk of serious complications, with the lowest therapeutic coverage observed in low-income and middle-income countries[2]. In 2021, diabetes directly accounted for approximately 1.6 million deaths, with 47% of these occurring before the age of 70[11]. Moreover, the disease also contributed to around 530000 deaths from kidney disease, and approximately 11% of deaths from cardiovascular causes were also associated with diabetes[2]. This trend highlights the urgent need for more effective strategies in the prevention of diabetes, early detection, and long-term management. Innovative approaches are essential not only to improve patient outcomes but also to mitigate the significant economic impact of the disease, 75% of which can be attributed to avoidable complications[12].

Of the most promising lines of investigation in diabetes research, regarding the role of microRNAs (miRNAs) has garnered great interest over recent years, and is considered to hold great promise[13]. MiRNAs are non-coding RNAs, ranging from 18 to 25 nucleotides in length, and their main action is to regulate gene expression at the post-transcriptional level, by influencing the stability and translation of messenger RNAs[14]. A number of these small RNAs have been implicated in various aspects of diabetes pathogenesis, including β cell dysfunction, insulin resistance, and inflammation, making them ideal markers for early diagnosis, disease progression, and as therapeutic targets in precision-based strategies. Furthermore, the analysis of miRNAs could hold promise for the identification of individuals at a high risk of developing diabetes, thereby enabling earlier interventions and more personalized care[13].

Given the high specificity of miRNA 375 (miR-375) to pancreatic islets, its central role in β cell biology, and its involvement in immune modulation, inflammation, and even tumorigenesis, this miRNA emerges as a multifaceted regulatory molecule with significant implications for diseases of the endocrine pancreas. The present article summarizes our findings from a narrative literature review conducted to appraise evidence addressing the role of miR-375 in DM. We included studies investigating the involvement of miR-375 in endocrine pancreas development, insulin productions and secretion, and in circulating levels of the miRNA in β cell disfunctions, to ensure a comprehensive overview and deepen our understanding of the actual potential role of this molecule in the management of diabetes.

MIR-375 IN β CELL DEVELOPMENT AND FUNCTION

MiR-375, initially identified by Poy *et al*[15] in mouse insulinoma 6 murine pancreatic β cells, is one of the most abundant miRNAs within human pancreatic islet, and it is specific for this pancreatic compartment[15,16]. MiR-375 also shows high expression in other tissues, including brain, lung, stomach, small intestine, and colon, in which several studies have highlighted its involvement in multiple regulatory functions[17]. This miRNA is also essential for modulating immune system responses, particularly that of macrophages and T helper cells, and it plays a role in autoimmune thyroid diseases and rheumatoid arthritis, as well as in inflammation[18-22]. Finally, miR-375 has frequently been shown to be dysregulated in cancer cells, and both *in vitro* and *in vivo* evidence reveals it to exhibit tumor suppressor activity[23-28].

MiR-375 participates in the development of various cell types, including neurons, adipocytes, and bone cells, and it is essential for the normal development of the pancreas, where it is regulated by several key transcription factors, in turn involved in complex feedback loops that often determine their own modulation by the miRNA. Specifically, the miR-375 promoter region contains conserved binding sites for hepatocyte nuclear factor 6 and insulinoma-associated protein 1, two essential regulators within the transcriptional cascade that drives neurogenin 3 (NGN3)-dependent differentiation of endocrine progenitors[29]. In addition, enhancer regions critical for achieving full transcriptional activation of the *miR-375* gene include binding elements for pancreatic and duodenal homeobox-1 (PDX1), NGN3, and neurogenic differentiation 1 (NEUROD1), which are key transcription factors involved in β cell specification and maturation[29]. The proper functioning of miR-375 in pancreatic β cells also depends on the fine regulation of proteins involved in the miRNA-mediated gene silencing pathway. One of these is Argonaute 2 (AGO2), the dysregulation of which prevents the assembly of the RNA-induced silencing complex and impairs miR-375 activity, resulting in reduced repression of several miR-375 target genes[30]. In the endocrine pancreas, miR-375 controls various aspects of β cell biology, including development, proliferation, apoptosis, and insulin secretion in response to glucose (Figure 1).

The role of miR-375 in pancreatic β cell maturation

Pancreatic β cells are specialized endocrine cells located in the islets of Langerhans, and their primary function is the synthesis and secretion of insulin. During embryonic development, multipotent pancreatic progenitor cells give rise to β cells through a tightly regulated process involving the sequential expression of key transcription factors[31,32]. Any impairment in β cell development, mass, or insulin-secreting ability can result in dysregulated blood glucose levels, contributing to the onset of DM[31,32]. In this context, miRNAs have emerged as critical post-transcriptional regulators of gene expression, and much evidence points to miR-375 as one of the most enriched and functionally relevant in β cell development and physiology[15,33]. MiR-375 plays an essential role in β cell generation during pancreatic development by modulating key genes involved in endocrine cell maturation and hormone production (Figure 1).

In the differentiation of human embryonic stem cell to insulin-producing cells, miR-375 regulates C-X-C chemokine receptor type 4, a gene implicated in pancreatic progenitor cell migration and endocrine lineage specification during early pancreatic development. The modulation is positive or negative depending on the differentiation stage, and it acts by influencing the responsiveness of progenitor cells to stromal-derived factor-1[34,35]. During the differentiation of pancreatic progenitors into endocrine cells, miR-375 regulates the expression of critical transcription factors such as forkhead box A2, NGN3, NEUROD1, and PDX1, which coordinate a tightly regulated gene network that governs pancreatic organogenesis and β cell identity. The regulatory action of the miRNA may be positive or negative, depending on the maturation stage of stem precursor cells. Not surprisingly, evidence points to a feedback mechanism whereby transcription factors, in turn, modulate the expression of miR-375[34,36]. Forkhead box A2 acts early in development by enabling chromatin accessibility for downstream factors, including PDX1[37], a master regulator in pancreas organogenesis, maturation, and β cell identity preservation, as well as normal insulin function[38]. NGN3 serves as a master regulator of endocrine lineage commitment, initiating the differentiation of progenitor cells into all endocrine subtypes. NEUROD1, acting downstream of NGN3, further promotes β cell maturation and insulin expression[39]. The interplay between miR-375 and these transcription factors underscores the importance of a regulatory feedback loop to ensure proper timing and balance during β cell development and functional maintenance.

The crucial role of miR-375 in the maturation of β cells through the regulation of critical genes was definitively confirmed when it was demonstrated that the overexpression of this miRNA *in vitro* not only promoted but directly induced the differentiation of various stem precursors into insulin producing cells in the absence of any additional extrinsic factors[40,41]. Furthermore, overexpression of miR-375 in human *in vitro* cultures of islet cells, in which proliferation is associated with dedifferentiation and loss of β cell phenotype, induced redifferentiation, which was in turn associated with the induction of PDX1, v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog a, NK6 homeobox 1, NEUROD1, and paired box 4 transcription factors[42]. The same study also found increased levels of insulin 1 and islet amyloid polypeptide transcription and an elevated secretion of C-peptide[43]. These findings indicate that miR-375 upregulation may facilitate the generation of functional insulin-producing cells following the *ex-vivo* expansion of human islet cells.

MiR-375 maintains β cell mass

Several studies have demonstrated the role of miR-375 in maintaining β cell mass in animal models. Poy *et al*[43] were the first to demonstrate that pancreatic β cells were significantly reduced in miR-375 knock-out mice due to impaired proliferation. Accordingly, the same study showed the pancreatic islets in obese mice (ob/ob), a model of increased β cell mass, to exhibit increased expression of miR-375. Thereafter, Latreille *et al*[44] investigated the effects of both the loss and overexpression of miR-375, and revealed that selective upregulation of miR-375 levels in mouse pancreatic islets reduced levels of gephyrin, chondroitin sulfate synthase 1, insulin-induced gene 2, myotrophin (MTPN), and eukaryotic tran-

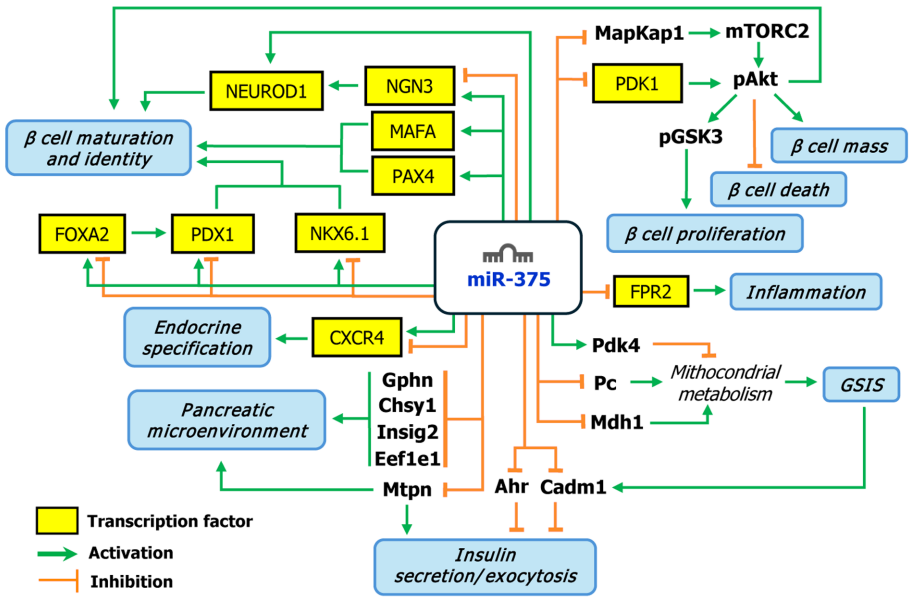

Figure 1 Schematic representation of the molecular pathways regulated by microRNA 375 in pancreatic β cells. Green arrows indicate positive regulation (activation), while orange lines ending with a T bar represent negative regulation (inhibition). NEURPD1: Neurogenic differentiation 1; NGN3: Neurogenin 3; MAFA: V-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A; PAX4: Paired box 4; FOXA2: Forkhead box A2; PDX1: Pancreatic and duodenal homeobox-1; NKX6.1: NK6 homeobox 1; CXCR4: C-X-C chemokine receptor type 4; Gphn: Gephyrin; Chsy1: Chondroitin sulfate synthase 1; Insig2: Insulin induced gene 2; Eef1e1: Eukaryotic translation elongation factor 1 epsilon 1; Mtpn: Myotrophin; miR-375: MicroRNA 375; MAPKAP1: Mitogen-activated protein kinase associated protein 1; mTORC2: Mammalian target of rapamycin complex 2; PDK1: 3-phosphoinositide-dependent protein kinase 1; pAkt: Phosphorylated protein kinase B; pGSK3: Phosphorylated glycogen synthase kinase 3; FPR2: Formyl peptide receptor 2; Pdk4: Pyruvate dehydrogenase kinase 4; Pc: Pyruvate carboxylase; Mdh1: Malate dehydrogenase 1; GSIS: Glucose - stimulated insulin secretion; Ahr: Aryl hydrocarbon receptor; Cadm1: Cell adhesion molecule 1.

slation elongation factor 1 epsilon 1, which are mainly involved in the regulation of β cell function and the pancreatic microenvironment, without a significant impact on metabolic homeostasis. By contrast, the complete deletion of miR-375 resulted in pronounced metabolic dysfunction, including reduced β cell mass, increased α-cell mass, and hyperglucagonemia.

MiR-375 is essential for maintaining β cell mass in humans[14], which it achieves by acting on both β cell proliferation and apoptosis. However, concerning the potential mechanism involved, no data is available to date demonstrating a direct effect of miR-375 on the levels of B-cell lymphoma 2 (BCL2) and BCL2-associated X protein (BAX), the two regulators of β cell survival and apoptosis known to play a central role in determining β cell mass. Increasing the expression of BAX, or reducing that of BCL2, promotes β cell death, contributing to the progression of diabetes[45]. On the other hand, miR-375 modulates the expression of BCL2/BAX in other cell contexts, including models of colon cancer and congenital heart disease, leading to enhanced cellular apoptosis through BCL2 suppression and/or BAX activation[46-48]. These findings support the need for further investigations to establish whether miR-375 also regulates pancreatic β cell mass through the BCL2/BAX-mediated apoptotic pathways.

Evidence indicates miR-375 to regulate β cell growth through targeting the gene for 3-phosphoinositide-dependent protein kinase 1 (PDK1), whose 3′ untranslated region contains a conserved binding site for this miRNA[49]. Studies in porcine pancreatic stem cells demonstrated the overexpression of miR-375 to suppress PDK1 levels directly, thereby reducing protein kinase B (Akt) phosphorylation, a key downstream effector of PDK1 in the phosphatidylinositol 3-kinase/Akt signaling pathway[49]. This event impairs β cell proliferation, promotes apoptosis, and hinders differentiation toward insulin-producing cells[49]. In rat pancreatic insulinomas and pancreatic β cells, miR-375 was shown to lead to a decrease in the phosphorylation of the downstream Akt effector glycogen synthase kinase 3, thereby attenuating β cell survival and proliferation[50]. In humans, the role of miR-375 in inhibiting proliferation and inducing apoptosis by targeting PDK1 was only demonstrated in various cancers[25,51,52].

Another relevant mechanism through which miR-375 may modulate Akt-related β cell function involves the mitogen-activated protein kinase associated protein 1 (MAPKAP1)-mediated signaling pathway. MAPKAP1 is an essential component of the mammalian target of rapamycin complex 2 (mTORC2) complex, which is involved in the activation of Akt and plays a crucial role in regulating pancreatic β cell proliferation, survival, and insulin secretion[53]. MiR-375 directly binds to the 3′ untranslated region of MAPKAP1 mRNA, inhibiting its expression and thereby negatively impacting the activity of mTORC2/Akt signaling. This regulation has been implicated in the cellular response to angiotensin II (Ang II), a factor known to impair β cell function. In a mouse model of diabetes, Ang II increases the expression of miR-375, which in turn represses MAPKAP1, contributing to reduced β cell proliferation, increased apoptosis, and impaired insulin signaling. These findings suggest that miR-375 mediates Ang II-induced β cell dysfunction by targeting the MAPKAP1/mTORC2/Akt pathway, thus highlighting another important route through which miR-375 influences β cell mass and insulin homeostasis[54]. Finally, the induction of miR-375 expression in a mouse model of β cells through exposure to fatty acids, such as palmitic acid, was shown to increase apoptosis, sug-

gesting a role for the miRNA in β cell lipotoxicity[55].

MiR-375 regulates insulin secretion

While it is recognized that miR-375 is essential for endocrine pancreas development, its inhibitory action on insulin secretion reveals multiple facets of this miRNA in β cell physiology (Figure 1). MiR-375 knockout mice exhibit severe metabolic impairments, including hyperglycemia and severely reduced glucose tolerance, accompanied by a marked reduction in insulin production[44]. Moreover, one of the miR-375 targets downregulated following miR-375 overexpression is MTPN, a known regulator of insulin exocytosis. The re-expression of miR-375 in β cells not only restored glycemic control but it is also likely that it contributed to the recovery of insulin secretory capacity[44]. In this context, Poy *et al*[14] demonstrated that miR-375 acts as a negative regulator of insulin secretion in mature β cells. This effect is mediated through its direct targeting of the *MTPN* gene, which is involved in insulin granule exocytosis[56].

Gain-function and loss-of-function studies have shown that overexpression of miR-375 in both rat and human pancreatic islets significantly reduces glucose-stimulated insulin secretion without altering total insulin content, suggesting a defect in the secretion process rather than in insulin production[57]. This inhibitory effect seems to be correlated with reduced glucose-induced cytosolic Ca^{2+}, oxygen consumption, and adenosine triphosphate production, all of which occur due to miR-375 overexpression, rather than by hampering late steps in the regulation of the exocytosis apparatus[57]. While glucose uptake is not compromised, mitochondrial metabolism is significantly altered, with a shift toward anaerobic glycolysis, as evidenced by increased lactate release. Accordingly, transcriptomic analyses revealed that overexpression of miR-375 represses genes involved in mitochondrial function, including those encoding pyruvate carboxylase and malate dehydrogenase 1, while upregulating pyruvate dehydrogenase kinase 4, a known inhibitor of pyruvate oxidation, which would diminish mitochondrial energy metabolism and the glucose response, and in turn insulin secretion. Conversely, silencing endogenous miR-375 enhances glucose-stimulated insulin secretion and increases glucose-induced oxygen consumption, further confirming its inhibitory role on mitochondrial related insulin release[57].

Another miR-375 target gene is the one encoding cell adhesion molecule 1 (*CADM1*, the predominant isoform of the CADM family in human pancreatic islets), the expression of which is inversely correlated with insulin secretion[30]. Specifically, experiments demonstrated *CADM1* expression to decrease in response to glucose stimulation, suggesting an adaptive regulatory role of this gene. Functional studies further demonstrated CADM1 to interact with key components of the β cell secretory machinery, contributing to the limitation of secretory activity. Its downregulation following prolonged glucose stimulation may reflect a compensatory mechanism aimed at enhancing insulin release under conditions of increased metabolic demand[58]. In murine models, the depletion of AGO2 led to elevated fasting blood glucose levels and a significant reduction in plasma insulin levels. Conversely, increased AGO2 expression is associated with a reduction in the transcript levels of several miR-375 targets, including CADM1. Protein analyses further confirmed that the loss of AGO2 results in elevated CADM1 protein levels, indicating that AGO2 is essential to ensure the full repressive activity of miR-375 *in vivo*[30].

MIR-375 IN DIABETES INSURGENCE

As a key miRNA with a broad range of targets influencing many β cell functions, it is not surprising that the levels of miR-375 in islets from human individuals with T2D are not different to those in non-diabetic controls[59]. Moreover, epigenetic regulation adds an additional layer of complexity to the control of miR-375 expression. Notably, differential expression and cytosine-phosphate-guanine methylation of the *miR-375* gene have been proposed as ethnicity-related factors that may contribute to the varying incidence of T2D across populations[60]. Several studies have reported that hypomethylation of the miR-375 promoter region correlates with the upregulation of the miRNA in individuals with T2D, supporting the hypothesis that epigenetic modifications may drive its dysregulation in pathological conditions[60,61].

At variance with T2D, T1D is characterized by β cell destruction, even if with a largely enigmatic kinetics induced by infectious, nutritional, or environmental stressors in individuals with unfavorable human leukocyte antigen backgrounds, and with a more aggressive course in younger subjects[62].

In the context of GDM, a growing body of evidence suggests that miR-375 dysregulation contributes significantly to disease pathogenesis, particularly through its interaction with inflammatory mediators[63]. One of its direct targets is formyl peptide receptor 2 (FPR2), a G protein-coupled receptor involved in inflammatory signaling and placental function, and which is significantly upregulated in the blood and placental tissues of women with GDM, contributing to disease pathogenesis. Studies show that high glucose levels induce FPR2 expression, which is suppressed by miR-375 overexpression, and enhanced by its silencing. This regulatory axis is further influenced by circular RNA ADAM9 (circ-ADAM9), acting as a miR-375 sponge and promoting FPR2 upregulation and placental damage[63]. Silencing circ-ADAM9 restores miR-375 levels, reduces FPR2 expression, and alleviates inflammation through modulation of the mitogen-activated protein kinase signaling pathway. These findings underscore the importance of the circ-ADAM9/miR-375/FPR2 axis in GDM and its potential as a therapeutic target[63].

In recent years, miR-375 was demonstrated to prevent high-fat diet-induced insulin resistance and obesity. Feeding mice a high-fat diet was shown to downregulate miR-375 expression, accompanied by upregulation of the aryl hydrocarbon receptor (AHR) and a reduction in vesicle-associated membrane protein 7 levels, two critical mediators of insulin secretion[64]. The authors also demonstrated that the oral administration of ginger-derived nanoparticles was able to restore miR-375 and vesicle-associated membrane protein 7 expression suppressed by a high-fat diet, thereby improving insulin sensitivity. At the molecular level, induction of intracellular miR-375 inhibited AHR expression and regulated the export of miR-375 into intestinal epithelial exosomes. These exosomes were shown to interact with gut

microbiota to suppress the production of AHR ligands, such as indoles, and they are taken up by hepatocytes, where miR-375 attenuates hepatic AHR overexpression and promotes the expression of genes associated with insulin responsiveness. These findings highlight how the loss of miR-375 disrupts β cell function and systemic insulin signaling, while ginger-derived nanoparticles-based restoration of miR-375 offers a promising therapeutic strategy against diet-induced insulin resistance[64].

CIRCULATING MIR-375 IN DIABETES

The presence and stability of miRNAs in biological fluids such as blood, plasma, serum, urine, saliva, and cerebrospinal fluids make them ideal candidates for diagnostic applications. Of the miRNAs implicated in the pathogenesis of both T1D and T2D and their associated complications[65,66], miR-375 has also caught the attention of researchers due its presence in biological fluids including blood, plasma, serum, and urine, highlighting its potential use as a non-invasive biomarker in DM, both for disease diagnosis and monitoring[44,67].

Exosomal miR-375 as an early marker of β cell injury

MiRNAs are actively released into circulation through extracellular vesicles, such as exosomes, released by most cell types, including pancreatic islets. Exosomes carry molecular cargo, including miRNAs, reflecting the physiological or pathological state of their cell of origin[68,69], and offering an important "window" into the cellular health of an individual. Indeed, this secretion mechanism is often altered in pathological conditions, making miRNAs sensitive indicators of diseases such as cancer, neurological disorders, and cardiovascular diseases[70].

In a recent study, pancreatic islets isolated from mice were exposed *in vitro* to diabetogenic insults, including pro-inflammatory cytokines and streptozotocin (STZ), a β cell cytotoxin. Exosomes released into the culture medium under these conditions exhibited distinct miRNA profiles, with miR-375 consistently enriched in response to both stimuli. Subsequent *in vivo* analyses revealed that serum exosomal miR-375 levels increased significantly in STZ-treated mice before the onset of hyperglycemia and hypoinsulinemia, suggesting that its release may precede marked metabolic dysfunction[71]. Interestingly, in human subjects, elevated levels of exosomal miR-375 were detected in newly diagnosed T1D or T2D patients, indicating a conserved role for this miRNA as an early biomarker of islet injury. However, discrepancies were found between the miRNA profiles of exosomes from islet culture supernatants and those from serum, suggesting that exosomal miRNA analysis in blood may not fully reflect islet-specific damage[71]. Indeed, multiple tissues contribute to the exosome pool in plasma, with adipose tissues being a major source[72]. Thus, while exosomal miR-375 shows promise as a non-invasive marker of β cell injury, further methodological advances are needed to isolate islet-specific exosomes to improve diagnostic precision for this miRNA.

Circulating miR-375 is modified in cell damage in mouse models

Mice models of acute β cell destruction showed elevated circulating levels of miR-375[73]. Similarly, increased plasma miR-375 levels were observed in a model of chronic β cell dysfunction and hyperglycemia[44]. Conversely, in compensatory models of insulin resistance with β cell hyperplasia, intra-pancreatic miR-375 levels were reduced without a corresponding increase in circulating levels[44]. In the same model, *in vivo* experiments conducted by Erener *et al*[73] demonstrated that circulating levels of miR-375 were significantly increased in multiple models of β cell damage, including STZ-treated mice and non-obese diabetic mice, as well as in *in vitro* models of cytokine-induced islet apoptosis, models that represent β cell injury and reflect the dynamic nature of β cell destruction in T1D. The authors demonstrated that the rise in plasma miR-375 observed in STZ-diabetic mice had already occurred in presymptomatic stages, with higher expression levels compared with those detected for other tissue miRNAs, such as miR-16. A similar increase was observed in non-obese diabetic mice approximately two weeks before the diagnosis of diabetes, reinforcing the hypothesis that the release of miR-375 into the bloodstream constitutes an early event associated with autoimmune β cell destruction[73]. *In vitro* experiments conducted on murine pancreatic islets confirmed that miR-375 release is induced by treatment with STZ or pro-inflammatory cytokines, such as tumor necrosis factor-α, interferon-γ, and interleukin-1β, while inhibition of cell death with Z-Val-Ala-Asp(Ome)-fluoromethylketone significantly reduced miRNA release[73].

Several studies have reported elevated levels of circulating miR-375, reflecting acute β cell destruction and activation of autoimmune mechanisms[44,74]. For instance, high plasma levels of miR-375 have been observed during episodes of acute β cell death, suggesting its potential as an early biomarker for β cell damage[44]. A pilot study conducted by Seyhan *et al*[74], which looked at the plasma levels of miRNA from subjects with prediabetes, T2D, latent autoimmune diabetes in adults, or T1D, identified miRNAs associated with β cell injury and islet inflammation. Among these, miR-375 levels were significantly elevated in individuals with diabetes, and correlated with glucose tolerance, glycated hemoglobin A1c (HbA1c), β cell function, and insulin resistance[74]. The finding that miR-375 levels were significantly elevated in individuals with diabetes suggested that this miRNA might serve as a non-invasive biomarker for identifying diabetes subtypes, particularly when combined with autoantibody detection, predicting disease progression, guiding therapeutic strategies, and monitoring treatment responses[74]. The main studies reporting the levels of circulating miR-375 in T1D and T2D are summarized in Table 1.

MiR-375 in T1D patients: Biomarker of disease onset and progression?

Despite the low number of examined subjects, Seyhan *et al*[74] showed that miR-375 was significantly elevated in the plasma of subjects with autoimmune-mediated T1D, although the increase in the miRNA had not been associated with β cell injury or the inflammatory process, *per se*. Samandari *et al*[75] found that in a cohort of 123 children with newly

Table 1 Main evidence of the modulation of circulating miR-375 in diabetes

Type	Extraction method	Source	Level	Ref.
T1D	miRNeasy serum/plasma kit	Plasma	Up	[73]
	miRCURY RNA isolation kit	Plasma	Up	[74]
	NA	Serum	Up	[75]
	miRNeasy mini kit	Exosome	Up	[70]
	TRIzol	Serum	Down	[76]
	miRNeasy mini kit	Blood	Down	[66]
T2D	miRNeasy serum/plasma kit	Plasma	Up	[59]
	miRNeasy mini kit	Plasma	Up	[60]
	QIAzol and miRNeasy kit	Plasma	Up	[80]
	miRNeasy mini kit	Exosome	Up	[70]
	QIAamp circulating nucleic acid kit	Serum	Up	[78]
	TRIzol	Serum	Up/down[1]	[79]
	mirVana™ miRNA isolation kit	Plasma	Down	[83]
	miRCURY RNA isolation kit	Urinary EVs	Down	[84]
Pre-T2D	miRNeasy mini kit	Plasma	Down	[81]
	mirVana™ miRNA isolation kit	Plasma	Down	[83]
	Rneasy serum/plasma advanced kit	Serum	Down	[82]

[1]Down: In the presence of nephropathy and diabetic foot.
T1D: Type 1 diabetes; T2D: Type 2 diabetes; NA: Not available; miRNA: MicroRNA; EVs: Extracellular vesicles.

diagnosed T1D, blood levels of miR-375, along with five other miRNAs (miR-24-3p, miR-146a-5p, miR-194-5p, miR-197-3p, and miR-301a-3p), were significantly correlated with residual β cell function assessed between six and twelve months after disease onset. Multiple linear regression analysis further demonstrated that circulating levels of miR-375 could predict clinically relevant markers such as stimulated C-peptide, HbA1c, and insulin dose-adjusted A1c in the months following diagnosis[75]. Increased serum levels of miR-375 were also revealed in patients with Wolfram syndrome (WFS) who developed T1D, indicating that this miRNA can be used as an indicator of WFS progression[76]. In T1D patients, serum exosomal miR-375-3p was found to be significantly elevated in newly diagnosed patients, indicating the potential utility of exosomal miRNAs in detecting islets damage[71].

By contrast, significantly reduced serum levels of miR-375 have also been reported in children with newly diagnosed T1D[77], rendering the interpretation of circulating levels of miR-375 levels in T1D controversial. In the study by Marchand *et al*[77], sera were obtained from 22 children with newly diagnosed T1D, before they started subcutaneous insulin therapy, and compared with 10 age-matched nondiabetic controls. Despite the lower serum levels of miR-375 in the T1D children compared with controls, no significant correlations were observed between miR-375 and HbA1c, blood glucose, or the number of autoantibodies[77]. A more recent study also found miR-375 to be significantly downregulated in children with T1D compared with their siblings or healthy controls, as well as inversely correlated with HbA1c levels, and positively correlated with other biochemical parameters such as low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, mean corpuscular volume, and aspartate aminotransferase. These findings support the hypothesis that the under-expression of miR-375 plays a potential role in β cell function and glycemic control[67].

The discrepancies in results concerning miR-375 levels in children with T1D could be attributed to various factors. T1D is a progressive disease, and the rate of β cell destruction varies between patients[78], which may in turn influence circulating miR-375 levels. Furthermore, the increase in plasma miR-375 was generally not observed in response to normal postprandial glycemic peaks, but only under sustained hyperglycemic conditions, suggesting that its release is specifically associated with chronic β cell stress. Interestingly, insulin administration reduced plasma levels of miR-375 in mice, indicating that metabolic improvement may modulate this biomarker[73]. Moreover, methodological differences between studies, such as sample collection and analysis methods, the sensitivity of the tools used to quantify miR-375, and the characteristics of the control groups, could contribute to the observed discrepancies (Table 1).

Can circulating miR-375 levels play a predictive role in T2D?

In the context of T2D, the evidence correlating circulating miR-375 levels with the disease's pathology is inconsistent. On the one hand, elevated plasma levels of miR-375 have been found in patients with T2D compared with individuals with normal glucose tolerance[61,79], providing promise for miR-375 as a potential predictive biomarker for disease onset. On the other hand, García-Jacobo *et al*[80] while revealing higher miR-375 in the serum of T2D patients with poor glycemic

control, found reduced levels in T2D patients with nephropathy and diabetic foot. A more recent study again found the expression of miR-375 to be significantly upregulated in T2D patients compared with controls, but the authors also claimed that reduction in miR-375 may be implicated in the pathogenesis of nephropathy correlated with the progression stage[81]. Increased miR-375 levels were also revealed in serum exosomes of newly diagnosed T2D patients, again indicating the potential utility of exosomes in the management of diabetes[71].

At variance with the above, Seyhan *et al*[74] found no significant differences in miR-375 levels between T2D patients and control subjects, while a study conducted by Jiménez-Lucena *et al*[82] demonstrated that individuals who later developed T2D exhibited significantly lower baseline levels of circulating miR-375 compared with those who remained disease-free. Notably, participants with higher baseline plasma levels of miR-375 experienced a significant reduction in the hepatic insulin resistance index over the follow-up period, suggesting a protective metabolic role of the miRNA. These findings imply that decreased circulating miR-375 may precede overt metabolic dysfunction and identify individuals at a higher risk for T2D development, supporting its utility in early risk stratification and preventive strategies[82]. Still in the context of prediabetes, miR-375 appears to play a significant role as an indicator of health-promoting metabolic adaptations. Heianza *et al*[83] demonstrated that circulating miR-375-3p is dynamically regulated in response to lifestyle interventions and is associated with metabolic improvements in individuals at risk of T2D. In participants with prediabetes, circulating levels of miR-375-3p were positively associated with fasting insulin and insulin resistance at baseline. Following an 18-month lifestyle intervention, a significant increase in miR-375-3p was observed, which correlated with reductions in visceral and deep subcutaneous adipose tissues, as well as intrahepatic fat content. These associations suggest that rising circulating levels of miR-375-3p may reflect improvements in diabetogenic fat depots, independently of glucose and insulin levels. Although the study was not designed to establish a cause-and-effect relationship, the consistent associations between miR-375 levels, insulin metabolism, and ectopic fat distribution support its potential use as a biomarker for tracking metabolic improvements during lifestyle interventions aimed at preventing T2D[83]. A more recent study reported that circulating miR-375 is downregulated in T2D patients and further reduced in T2D-susceptible individuals compared with healthy controls and inversely correlated with HbA1c levels[84]. Furthermore, a study investigating the role of urine-derived extracellular vesicles in T2D patients with kidney diseases revealed the downregulation of miR-375, indicating that urine-derived extracellular vesicle-related miRNAs may also be valuable biomarkers for complementary diagnosis[85].

In the pathogenesis of T2D, epigenetic modifications have emerged as a central driving force and may be at the basis of discrepancies between circulating levels of miR-375. In a study by Chang *et al*[60], the plasma level of miR-375 was significantly lower in Kazak T2D samples compared with Han T2D samples, highlighting the presence of ethnic differences in the expressions and cytosine-phosphate-guanine methylation of the miR-375 promoter regions, contributing to the different patterns of T2D.

Circulating miR-375 and diabetes complications

Beyond diabetes onset and progression, miR-375 is also being investigated as a potential marker for diabetes complications[80]. In this context, patients with T2D who go on to develop chronic complications exhibit lower circulating levels of miR-375 compared with patients with uncomplicated T2D, suggesting a disruption of its regulatory functions under pathological conditions. A significant reduction in miR-375 levels has also been observed in individuals with diabetic nephropathy[80,81]. In a study comparing newly diagnosed T2D patients, T2D-susceptible individuals, and healthy controls, Raza *et al*[84] demonstrated that circulating levels of miR-375 were significantly reduced in both T2D patients and the T2D-susceptible individuals compared with healthy controls, with the lowest levels observed in the latter group. Moreover, miR-375 expression showed an inverse correlation with HbA1c and fasting blood glucose levels, suggesting its potential involvement in glycemia regulation[84]. In the context of vascular complications, significantly lower levels of miR-375 were associated with the progression of critical limb ischemia, a severe manifestation of peripheral artery disease in diabetic subjects[86]. Intramuscular administration of miR-375 in diabetic mice improved perfusion and promoted arteriogenesis through its inhibitory action on Kruppel-like factor 5, identifying the miR-375/Kruppel-like factor 5/nuclear factor-kappa B axis as a potential therapeutic target[86].

The presence of diabetes complications could be one of the reasons behind the discrepancies in miR-375 levels in T2D. In fact, miR-375 is one of the miRNAs upregulated in the T2D patients who also develop coronary artery disease (CAD), a major cause of death in the world[87]. Indeed, a recent study conducted by Sangali *et al*[87] revealed that miR-375 and miR-541, both known to play a role in cardiac cell injury and cardiac hypertrophy, were significantly up-modulated in T2D patients with CAD compared with those without CAD, suggesting a possible protective role for these miRNAs. The application of receiver operating characteristic curves to evaluate the diagnostic accuracy of miRNAs as potential biomarkers revealed that only the circulating levels of miR-375, and not miR-541, could potentially serve as a non-invasive biomarker for the diagnosis of CAD in T2D patients[88]. The association of miR-375 with T2D complications, such as cardiovascular diseases, may increase the clinical possibility to predict and manage these complications more effectively and to reduce healthcare costs, thereby exerting a positive socio-economic impact.

MiR-375 also represents a promising marker for assessing diabetes progression in the context of WFS, a rare disease characterized by insulin-dependent DM and progressive neurodegeneration. Zmyslowska *et al*[76] found miR-375 to be significantly increased in the serum of patients with WFS, both when compared with individuals with T1D and in association with the progression of neurodegeneration. These findings reinforce the role of miR-375 not only as an indicator of β cell loss, but also as a potential dynamic biomarker of neurodegeneration[76]. Further sustaining the notion that miR-375 could serve as a marker of diabetes severity and complication, Zapała *et al*[85] recently demonstrated decreased urinary levels of miR-375 in patients with diabetic kidney disease, suggesting its potential as a non-invasive tool to monitor renal complications.

CIRCULATING MIR-375 IN PANCREATIC ISLET TRANSPLANTATION

Current therapeutic approaches for managing T1D, such as insulin therapy and glucose monitoring, often fail to replicate physiological insulin secretion, exposing patients to glycemic variability and complications. Pancreatic islet transplantation has emerged as a promising strategy to restore endogenous insulin secretion in selected patients[89]. While this approach may improve metabolic stability, reduce severe hypoglycemia, and achieve temporary insulin independence[90], its long-term success remains limited by several challenges. Transplanted islet viability is also compromised by isolation stress, and immune-mediated rejection necessitates lifelong immunosuppression, which in turn has a negative impact on graft functioning, leading many patients back to insulin therapy[91].

To address the poor results of islet transplantation, also due to the shortage in donor pancreases and the limitations of allogeneic transplantation, stem cell-derived insulin-producing cells have emerged as a compelling alternative[36], constituting a potentially unlimited source for cell replacement therapy. However, current differentiation protocols produce heterogeneous, immature β cell populations with suboptimal glucose responsiveness, and their long-term safety also remains a concern due to risks such as teratoma formation and inadequate metabolic control[92]. In this context, increasing attention has been directed toward the identification of molecular biomarkers that could support the evaluation and prediction of graft function. Of the various hypothetical biomarkers being considered, circulating miRNAs have emerged as promising non-invasive indicators of β cell health and differentiation[93,36]. The potential of miR-375 has been demonstrated in experimental transplantation models, where it shows efficacy in quantifying early graft destruction and predicting long-term transplant outcomes. Specifically, Roels *et al*[94] demonstrated miR-375 plasma levels to increase in proportion to the number of transplanted β cells within the first hour post-infusion, and they found a similar prognostic value for assessing graft outcome at two months. These results support the use of miR-375 for monitoring early β cell loss, a critical indicator of long-term graft survival and function[94].

Saravanan *et al*[93] observed that the concentration of miR-375 released during the enzymatic digestion and islet purification phases correlated with post-transplant endocrine function. Specifically, elevated miR-375 levels during the isolation process were associated with poorer post-transplant glycemic control, reflecting islet damage and a higher insulin requirement. In contrast, lower levels of miR-375 correlated with lower insulin requirement and lower HbA1c levels, indicating better functioning of the transplanted islets[93]. Additional evidence highlighted the relevance of miR-375 as a circulating biomarker for evaluating donor pancreas quality in allogeneic transplantation settings. High pre-transplant levels of circulating miR-375 were shown to correlate with poorer graft function and lower β cell viability, reflecting underlying cellular damage and reduced functional islet mass[95]. Moreover, in a humanized mouse model of transplant rejection, elevated circulating miR-375 levels preceded the onset of hyperglycemia, supporting its role as an early indicator of β cell death during immune-mediated rejection[96].

In addition to diagnostic applications, emerging strategies have explored the therapeutic modulation of miR-375 to improve graft outcomes. Wen *et al*[97] demonstrated that exosomes from human bone marrow-derived mesenchymal stem cells engineered with a pshFas-anti-miR-375 construct exhibited immunosuppressive properties when co-administered with islet grafts, promoting graft survival by inhibiting islet apoptosis. In a more recent study conducted by Mattke *et al*[98], the authors observed that elevated plasma levels of miR-375 and miR-200c correlated with poor graft function following total pancreatectomy with islet auto transplantation. Similarly, levels of circulating miR-375 and miR-200c were shown to correlate with the effectiveness of the islet isolation process in total pancreatectomy with islet auto transplantation[99].

MIR-375 *vs* OTHER DIABETES BIOMARKERS: IMPROVEMENTS AND LIMITATIONS

Early diagnosis of DM could prevent the progression of numerous specific complications associated with the disease. However, the current biomarkers of diabetes have several limitations, and between 24% and 62% of people with diabetes presently remain undiagnosed and untreated, highlighting a significant gap in current diagnostic practices[100]. To better contextualize the clinical utility of miR-375 in diabetes management, it is essential to compare its performance with both conventional biomarkers and other circulating miRNAs. Currently, HbA1c and fasting plasma glucose remain the standard diagnostic and monitoring tools for diabetes. HbA1c reflects long-term glycemic control and represents a strong predictor of disease progression, but it may be influenced by conditions affecting red blood cells turnover, and it does not provide any insight into glycemic variability[101]. Furthermore, while useful for diagnosis, fasting plasma glucose is subject to fluctuations due to stress, diet, and circadian rhythm[102]. In a recent study, Yu *et al*[103] demonstrated that patients with higher baseline circulating levels of miR-21-5p, miR-24-3p, miR-223-3p, and miR-375-5p have a considerably greater chance of attaining glycemic control following a 12-month administration of glucagon-like peptide-1 receptor agonists. Furthermore, using receiver operating characteristic curve analysis, miR-375-5p emerged as a predictor of reductions in HbA1c induced by treatment[103].

Of the other diabetes-related miRNAs, miR-29 and miR-122 have also been extensively studied. MiR-29 is involved in insulin signaling and glucose metabolism, and its elevated serum levels have been associated with insulin resistance and T2D[104]. MiR-122 has been correlated with metabolic syndrome and non-alcoholic fatty liver disease, both of which are common comorbidities in T2D[105]. However, their direct association with β cell injury is less specific compared with that for miR-375. In a study conducted by Vasu *et al*[106], in which the authors compared different T2D patient cohorts, circulating levels of miR-28-3p, miR-142, miR-486, miR-122, miR-15a, miR-320a, miR-126, and miR-375, were significantly altered even before the onset of any clinical symptoms. This large-scale analysis highlights the concept that miR-375 stands to be more useful when assessed in combination with other miRNAs, rather than as a standalone biomarker. The

high heterogeneity of T2D, with multiple subtypes highlighting the complexity of the disease and the need for personalized approaches to treatment, could underly some of the discrepancies on the reported roles of miR-375. In this context, a recent study by Sulaiman *et al*[107] found that each T2D subtype is associated with a specific miRNA profile, not including miR-375 and miR-126. Notably, the various techniques used to detect circulating miRNAs may have a non-negligible role in defining profiles of T2D subtypes. Therefore, it is essential that future studies control for technical and biological variables by adopting standardized protocols. A very recent work by Alum *et al*[108] proposes the use of point-of-care testing with RNA biosensors in order to integrate RNA diagnostics into clinical routine practice. Once again, this highlights the need to improve standardization and clinical validation of miR-375 and other specific pancreatic miRNAs in the management of diabetes. Overall, improvements in the diagnostic efficacy and predictive potential of miRNAs, and particularly of miR-375, for therapeutic intervention strategies will stem from increasing the data samples, standardizing detection technologies, and tracking and validating correlations with disease progression in patients.

Although several studies have highlighted the potential of miR-375 as a biomarker in diabetes, its translation into clinical practice still faces several limitations, especially in T2D. One of the main issues arises from the fact that miR-375, like other circulating miRNA, can be modified by the various physiological or pathological conditions, including complications associated with diabetes, which are patient specific. Furthermore, the lack of large, well-designed clinical studies makes it difficult to define clear cut-off values and to fully assess its usefulness for diagnosis and prognosis in real-world settings. Moreover, miR-375 is not exclusively expressed in pancreatic β cells, raising concerns about its specificity, especially when considered as a single biomarker.

CONCLUSION

This literature analysis clearly supports the need for the development of miR-375 modulation strategies to improve our knowledge of the downstream targets of this miRNA. Such a tool might provide an important step towards developing new therapeutic approaches to restoring pancreatic β cell functions and glucose homeostasis. Furthermore, integration of miR-375 with other diagnostic and therapeutic technologies could help contribute to a more personalized and timely approach to treating diabetes and its complications, to the benefit of patient health and the sustainability of global healthcare systems.

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