REVIEW ARTICLE

# A comprehensive overview on Micro RNA signature in type 2 diabetes Mellitus and its complications

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## Abstract

MicroRNAs (miRNAs) are small endogenous, non-coding RNA molecules that can modulate the expression of their target genes. Since its discovery, an enormous breakthrough has been established regarding its biogenesis and patho-physiological action, which has revolutionized the field of molecular biology. In addition, recent studies have identified the existence of stable extracellular/circulating miRNAs tissues and in biological fluids like blood where they are safeguarded from endogenous ribonuclease activity. Type 2 diabetes mellitus (T2DM) has emerged as a prime health issue worldwide. Incidence has increased considerably over the past decade. There are various tests that have been employed to diagnose T2DM. But for early detection and development, the establishment of biomarkers are of paramount importance. Contemporary evidence also validates the signature of a set of this epigenetic factor miRNA in the development of various diseases, including T2DM.

This article reviews the contemporary corroboration associating miRNAs and T2DM and emphasizes the potential role of miRNA as a circulatory biomarker that could alert the growing prevalence of T2DM. Also, it acknowledges the valuable compendium of information regarding biogenesis and functional role of circulating miRNA in insulin resistance which is intimately linked to T2DM.

**Keywords** Diabetes mellitus · microRNA · Insulin resistance

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## Introduction

Diabetes mellitus (DM) has been known since antiquity. India is one of the epicenters of the global diabetes pandemic. It can be speculated that the prevalence of diabetes will double in the next 2 decades in developing countries where the preponderance of vulnerable groups is between 45 and 65 years [1]. There are two major forms of DM. Type 1 DM (T1DM) results from loss of insulin deficiency whereas type 2 DM (T2DM) is delineated by insulin insensitivity in peripheral tissues due to IR [2]. Chronic elevation of blood glucose is a characteristic feature of type 2DM. Although the exact cause is not thoroughly acknowledged, T2DM may notably eventuate due to interaction between lifestyle, genetic and environmental factors [3]. As it is recognized as a risk factor for several micro, and macro-vascular complications, it has become a global threat to humans worldwide with high morbidity and mortality. It has been observed that delayed diagnosis often brings about the above-mentioned chronic complications. Thus, the establishment of a definitive circulating biomarker, that can alert the incidence and growing prevalence and progression of T2DM is crucial. Interestingly, according to recent studies, miRNAs emerged as an alluring perspective for clinical implementation in T2DM [4, 5]. In addition, its potential value in insulin

resistance (IR) and dysregulated metabolism is connected with diabetes development and prognosis.

MicroRNAs [miRNAs] are a novel class of naturally occurring short, single-stranded, endogenous, non-protein-coding RNA molecules within 19–25 nucleotides in length [6]. Since its discovery in the early 1990s, there is considerable attentiveness regarding its association with various diseases. Of note, the landscape of miRNAs has revolutionized the field of molecular biology by the noteworthy paragon change in central dogma that RNA transcripts outnumber protein-encoding genes [7]. Plausibly, miRNAs are one of the most predominantly represented non-coding RNA groups in clinical research. They are presumed to be indispensable for an extensive range of biological activity comprising cell proliferation, differentiation, development metabolism, stress response, apoptosis, and carcinogenesis by regulating gene expression at the post-transcriptional level either by targeting specific cleavage of homologous messenger RNA or by targeting specific inhibition of protein synthesis [6, 8]. Recent studies have identified the existence of extracellular/circulating miRNAs in biological fluids like plasma, serum, CSF, saliva, and urine, which validate the role of this epigenetic factor in a variety of diseases [9]. It is noteworthy to mention here that miRNAs have been extensively studied in diabetes and distinctive revelation of miRNAs has been documented in diabetes and its chronic complications [4]. Besides, the existence of circulating miRNAs and their stability may collectively account for the role as a novel diagnostic marker for T2DN. To date, there is a dearth of published evidence concerning the association between miRNA and T2DM. Appropriate comprehension might confer prompt identification and establishment of preventive therapy for persons at risk of diabetes. This review comes up with a brief update on miRNA biogenesis as well as the expression of miRNA signature accompanying diabetes and associated chronic complications of T2DM. It also overviews the contributory role of miRNA in insulin resistance as a part of the underlying mechanism to the development of diabetes and associated clinical complications.

## miRNA Biogenesis:

The recent advances in molecular technology provide new sight of miRNA, which helps to understand the cellular behavior of these molecules. miRNAs are usually generated through either canonical pathway or non-canonical pathway, out of which the former one is the predominant pathway [6]. Recent advances have led to a more detailed understanding of the canonical pathway of miRNA biogenesis, which comprises transcription, nuclear processing, nuclear export, and cytoplasmic processing. Of note, miRNA can be found between the genes (intergenic miRNA) or in the

region of an intron in a gene (intronic miRNA). Evidence accumulated over recent years has indicated that Canonical miRNA biogenesis commences with the formation of pri-miRNA transcript by RNA polymerase II (RNA Pol II) within the nucleus from its promoter or promoter of the host genes in which it is contained [10]. Pri-miRNA holds a hairpin structure with variable base pairs in length. Moreover, these are 5' capped and 3'polyadenylated. This process is reported to be regulated by RNA pol II-associated transcription factors and epigenetic regulators [11]. Drosha (initially described in Drosophila), a member of RNAse III endonuclease and its cofactor DGCR8 (Di George Syndrome critical region 8), together known as microprocessor complex is involved in nuclear processing [12]. It intervenes in the first cropping step and cleaves the stem of the hair-spin structure of miRNA to liberate 60–70 nucleotide precursors (pre-miRNA). Subsequently, pre-miRNA with a mini hairpin structure is exported from the nucleus to cytoplasm by exportin-5 (member of karyopherin family) [6]. This nucleocytoplasmic shuttle is energy-dependent via RAN-GTP (Ras-related nuclear protein guanosine triphosphate). Finally, cytoplasmic processing occurs by removal of the terminal loop of pre-miRNA by Dicer (RNAse III enzyme) and its cofactor TRBP (transactivation responsive RNA binding protein) [13]. This is considered as the final step of mature miRNA duplex formation, after which it is untwisted by RNA helicase enzyme to form mature miRNA strand and passenger strand [14]. Subsequently, mature miRNA gets loaded into Argonaute family protein (AGO 1–4 in humans) in an ATP-dependent manner to form RISC (RNA induced silencing complex) and the passenger strand is degraded by cellular machinery. It should be noted that the strand with lower 5' stability is preferentially loaded into AGO which is called the guide strand, which forms the mature miRNA [15]. In addition to the above predominant canonical pathway, numerous non-canonical pathways can also facilitate miRNA generation. In terms of mechanism, these can be categorized into Drosha/DGCR8 independent pathways or Dicer-independent pathways [6]. Intriguingly, Mirtons are the specific group of miRNAs that can be generated from the introns of mRNA during splicing by the Drosha independent pathway [16]. Similarly, 7-methyl guanosine capped pre-miRNA bypass Drosha cleavage and proceed to the cytoplasm by Exportin-1. During the process, the 7-methyl guanosine cap inhibits Argonaute loading. Contrastingly, Dicer-independent miRNAs are stepped by Drosha from shRNA (short hairpin) transcript, which requires Argonaut loading [17].

Briefing the mechanism of action of miRNAs, these are non-coding RNAs with uridine residue at 5'-end, which may act complementary to target messenger RNAs [mRNAs] [14]. Consequently, miRNAs are thought to impede

translation and downregulate gene expression by deadenylation of said mRNAs [18]. Moreover, recent studies have also expressed that miRNAs may amend the expression of 20–30% of mammalian protein-encoding genes at the post-translational level [6, 10]. In a mechanistic term, "seed site" (2–8 nucleotide from 5' end of miRNA) within 3'UTR is reviewed as miRNA recognition element (MREs)[19]. This promotes base pairing between 3'segment of miRNA and mRNA target. Thus, it could restrain the translation of mRNA. Based on this molecular basis, it could be summarised that miRNA-induced silencing complex plays part in gene regulation either by degradation of mRNA or blocking mRNA translation [8]. The latest techniques furnish the scope to investigate and explore the advancement of genetic revolution at the miRNA level.

## miRNA signature in type 2 diabetes Mellitus:

It is already known that DM is a complex metabolic disorder that is the cause of serious concern worldwide due to consequential complications such as neuropathy, retinopathy, nephropathy, and cardiovascular diseases [20]. The contemporary interpretation of the diagnosis of T2DM as per ADA (American diabetes association): Fasting plasma glucose (FPG) ≥ 126 mg/dl, 2 h postprandial plasma glucose ≥ 200 mg/dl, and HbA1c ≥ 6.5% [21]. The term prediabetes is applied to individuals with FPG between 100 and 125 mg/dl (also known as impaired fasting glucose: IFG) and 2 h glucose level between 140 and 199 mg/dl (also known as impaired glucose tolerance: IGT) [21]. Usually, prediabetic individuals with IFG, IGT, and very high HbA1c are likely to develop T2DM. Although HbA1c is a preferable and dependable diagnostic marker, it is beneficial only after the inception of diabetes. Even with the improvement in acknowledging the disease development, course, and drug therapy, there has been a persistent rise in diabetes prevalence. There is a pending necessity for a prompt and timely acknowledgment of type 2 diabetes patients. Apt diagnosis and effective intervention might impede advancement to overt disease and thus it helps in significant relative risk curtailment. Thus neoteric, specified, non-invasive markers are essential for the diagnosis of initiation and advancement of T2DM. In recent years, several studies have suggested that circulating miRNAs are connected with both physiological processes as well as several chronic diseases [7, 14]. Additionally, they can be quickly quantitated from biological fluids plasma, serum, saliva, cerebrospinal fluid, and urine, which validate their omnipresence throughout the body [7]. This non-coding RNA can be recommended as a prospective circulating biomarker for various metabolic diseases due to its stability in biological specimens. Notably, an increasing number of research articles have highlighted

**Table I** Summary of MicroRNA expression

| miRNA | Expression | Target | References |
| --- | --- | --- | --- |
| miR-7a | Up | IRS-2 | [23, 24] |
| miR-375 | Up/down | PI3-Akt | [23, 24] |
| miR-34a | Down | Sirtuin-1, PPAR alpha | [5, 24] |
| miR-146a | Down | Fibronectin | [5, 25] |
| miR-144 | UP | IRS-1 | [5, 6] |
| miR-29 | UP | AKT3 | [23, 25] |
| miR-192 | Up | SIP 1 | [5] |
| miR-21 | Up | PTEN, AKT, PPAR alpha | [25] |
| miR-223 | Up | GLUT 4 | [5] |
| miR-320 | Up | IGF-1 | [5] |
| miR-182 | Up | NOX4 | [5] |
| miR-130 | Up | PPAR alpha | [25] |
| miR-184 | Down | AMPK | [5] |
| miR-24 | Up/down | PIK3R3 | [6, 25] |
| miR-486 | Down | AMPK, TGF-β, MAPK | [25] |
| miR-204 | Down | TXNIP, GLP1R | [24, 25] |
| miR-122 | Up | HNF6 | [24, 25] |
| miR-377 | Up | PAK/SOD | [5, 6] |
| miR-223 | Up/down | STAT3/GLUT 4 | [5] |
| miR-33a | UP | IRS-2, STRT6,,AMPKα | [6, 25] |
| miR-204 | Up | GRB 10, GLP1 R | [25] |
| miR-378 | Up | P 110α, SIRT-7 | [23, 24] |
| miR-103 | Up | CAV-1, SFRP4 | [5, 25] |
| miR-143 | Up | ORP 8 | [5, 23] |
| Let-7 | Up | IGF1R, INSR, IRS-2 | [23, 24] |

IRS-2, Insulin receptor substrate-2; PI3-Akt, phosphatidyl inositol 3 kinase, protein kinase B; PPAR alpha, Peroxisome proliferator- activated receptor; AKT, Ak strain transforming; SIP1, SMAD interacting Protein; PTEN, Phosphatase and tensin homolog; GLUT, Glucose transporter; IGF, Insulin like growth factor; NOX, NADPH oxidase; AMPK, AMP activated protein Kinase; PIK3R3, Phosphoinositide-3-Kinase Regulatory Subunit 3;TGF- β, Transforming Growth Factor β; MAPK, Mitogen Activated Protein Kinase; TXNIP, thioredoxin interacting Protein;GLP1R, Glucagon like peptide1 receptor;HNF6, Hepatocyte Nuclear Factor 6;PAK/SOD, p-21 Activated Kinase and Superoxide Dismutase;STAT3, Signal Transducer and Activator of Transcription 3; GRB 10, Growth Factor Receptor bound Protein 10; GLP1R, Glucagon like peptide receptor 1;P110 α, Phosphatidylinositol-4,5-bisphosphate 3 -Kinase; SIRT7, Sirtuin7;CAV1, caveolin 1;SFRP4, Secreted Frizzled Related Protein 4;ORP8, Oxysterol Binding Protein-related Proteins; INSR, Insulin receptor gene.

the prospective role of miRNA in metabolic diseases such as T2DM [4, 22]. Of note, a change in miRNA expression has been demonstrated in T2DM and specific miRNA profiling has been explored copiously in serum, pancreatic islet, and skeletal muscle (Table-I) [5, 6, 23–25]. Thus, it could exemplify the signature potential of miRNA in respect to T2DM. In this sense, positioning the correct and on-target miRNA will facilitate the assessment of the progress and intensity of T2DM.
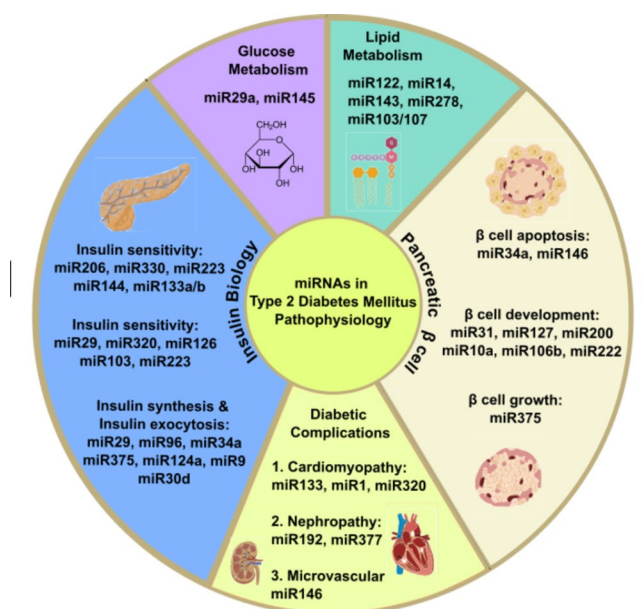
**Fig.1** Schematic representation depicting the various miRNAs involved in Type 2 diabetes mellitus pathophysiology and its complications

## Micro RNAs dysregulated in T2DM

Over the past decades, colossal efforts have been given to appreciate the role of non-coding miRNA in T2DM pathophysiology. In recent years, more and more specific types of miRNAs have been illustrated not only intracellularly but also in diverse extracellular body fluids. Current investigations in clinical and animal models about specific profiling of miRNAs are highlighted in this section. It has been suggested by a meta-analysis study that miR-29a, miR-34a, miR-103, miR-107, Mir-132, miR-144, miR-375 may be treated as a signature biomarker for T2DM (Figure I) [23].

**miR-375** It is considered as the first micro RNA to be well defined in the pancreas [24]. Research analysis reported a significant reduction in beta-cell mass by deletion of miR-375, which subsequently leads to a diabetic state [25]. This could be due to an increase in glucose-stimulated insulin secretion (GSIS) in primary beta-cell due to the omission of miR-375. On the contrary, another study on ob/ob mice reported increased pancreatic islet cells which were accordant with prediabetic hyperplasia [26]. Taken together, all these findings could suggest the key role played by miR-375 in glucose metabolism and beta-cell proliferation. Interestingly, another finding has highlighted the pivotal role of miR-375 in predicting T2DM even before onset, thus making it valuable as a prognostic marker [27]. Consistent with this finding, a recent study to assess miR-375 in diabetes patients and their first-degree relatives by quantitative real-time PCR noted that it may serve as a stable biomarker for an early finding of T2DM among high-risk

individuals [28]. It is already mentioned that miR-375 is predominantly expressed in β cells of the pancreas, overexpression of the aforementioned micro RNA leads to reduced β cell mass via PI3-Akt pathway (phosphatidylinositol 3-kinase, protein kinase B) and subsequently, insulin secretion is curtailed [29]. Until now, various animal and human studies have highlighted the significant role of miR-375 for miR-375 for β cell phenotype, which could decipher futuristic therapeutics in T2DM [30–32]. It is noteworthy that, in total pancreatectomy and islet auto-transplantation patients, miR-375 expression was significantly correlated with exogenous insulin requirement [33]. All these findings could reveal an intriguing function of miR-375 as a beta cell marker. Besides this, there is also limited evidence to encourage the therapeutic role of the above micro RNA in the prevention of complications [34]. Until now, the potential utility of miR-375 as a new biomarker in T2DM is not well established or confirmed in human studies. However, future long-term human research studies are indispensable to clarify and interpret this robust postulation.

**miR-103** It is well known that timely intervention is highly essential to limit the increasing prevalence of T2DM. As previously stated, miRNA plays a pivotal role in controlling glucose homeostasis. Importantly, various studies have revealed the importance of miR-103 in the experimental model of diabetes. Rome et al. have revealed the role of extracellular miR-103 in the regulation of adipose tissue and control of glucose metabolism leading to T2DM in humans [35]. The expression of platelet-derived miR-103 is downregulated in individuals with prediabetes confirming its adverse regulation by Wang et al. [36]. In this study, the author could observe the altered expression of several miRNAs in patients with microvascular complications. Yet another recent study also highlighted the potential role of the above said noncoding micro RNA as a novel biomarker for the diagnosis of type 2 diabetes [37]. This report is consistent with other reports suggesting the predictive role of miR-103 in pre-diabetes subjects.

**miR-7a** MiR-7a has been considerably explored in type 2 DM and it seems to play an important role in regulating several biological functions. Evidence has demonstrated that miR-7 is indispensable for the maintenance of endocrine beta-cell mass [38]. Based on the above analysis, miR-7a was noted to be reduced in obese/diabetic mouse models and human islets from obese and moderately diabetic persons with compromised beta-cell function. This further corroborates the regulatory role of micro RNA that sustains the contention. Yet another recent study also highlighted the potential role of islet-specific miR-7a in serum to predict its contribution to the microvascular complication of T2DM

[39]. It is noteworthy to mention that miR-7a has been found to regulate pancreatic biology. In this sense, a current study by Zhenyu et al. illustrates the role of miR-7a in diabetic retinopathy, a diabetic complication that leads to vision loss [40]. The author tried to substantiate the regulatory role of miR-7a via VEGF (vascular endothelial growth factor) expression and matrix metalloproteinase, which eventually bring about retinal complications of diabetes. These reports confirmed the interaction of miR-7a with IRS-2 which in turn regulates PI3K/Akt/VEGF cascade [41]. Furthermore, it has been illustrated that miR-7 negatively controls beta-cell proliferation through the mTOR (mammalian target of Rapamycin) signaling pathway [34]. This experimental evidence encourages the beneficial role of miR-7a in the treatment of diabetes. In the above study, the author could find decreased beta-cell miR-7a expression in an obese diabetic mouse model and obese diabetic patients.

### miR-34a

Although microRNAs are established to be vital regulators of pancreatic β-cells proliferation, differentiation, and apoptosis, the intrinsic method of implementation remains obscure. There are smattering investigations of their relationship with blood glucose metabolism. In recent times, miR-34a is considered a major micro RNA found to mediate the lipotoxic effect of pancreatic β-cells in hyperlipidemia mice [42]. Based on findings, it is speculated that miR-34a can impede Wnt (Wingless-related integration site) signaling cascade, which affects beta-cell proliferation and thus inhibits transcription factors in beta cells [43]. In an attempt to investigate the expression profile of miR-34a in T2DM, Shen et al. demonstrated elevated micro RNA levels in peripheral blood mononuclear cells [44]. As an increasing number of research articles have underlined the prospective role of micro RNA in the pathophysiology of metabolic diseases like T2DM, it could be suggested as a biomarker for diagnosis or prognosis. Correspondingly, this opens up the possibility of one miRNA candidate having the capability to regulate entire biological pathways that are pathogenically disrupted in a patient.

### miR-133, 29a &200:

In recent years, several studies have identified the changes in miRNA associated with several diseases. Micro RNAs can reflect changes in diabetes-related tissues like the pancreas, skeletal muscle, and adipose tissues. They also can regulate the insulin signaling pathway and glucose absorption in target tissues. But there is always a presenting demand for a novel treatment option for diabetes in course of the early stages of the disease so as to manage the occurrence of complications. It was demonstrated recently that skeletal muscle miR-133 levels are upregulated in pre-diabetes as well as diabetes patients and this has also been shown to be implicated in IR [45]. Thus, it may be evaluated in the diagnosis of early stages of T2DM. Additionally, it is also hypothesized from a meta-analysis that overexpression and upregulation of miR-29a are associated with glucose homeostasis across several insulin-sensitive tissues with pertinence to type 2DM [46]. Conflicting reports are shown regarding the role of miR-200 in diabetes kindred studies. It is documented to play a deleterious role in diabetes advancement by inducing inflammation and endothelial dysfunction. Whereas, some findings have been linked to the anti-inflammatory protective effect of miR-200 [47] .

### Let-7:

Even though enlighted technique and multifaceted impact of miRNA on physiological pursuit have not been elucidated, current advancement is made in unraveling the individual role of Let-7 in well-defined metabolic disorder. It is comprised of 9 mature Let-7 members, encoded by 12 distinct loci in human beings. It will be interesting to address that of late genetically engineered mouse models of Let-7 are reported to be comprehended in assessment and modulation of metabolic disease like T2DM [48]. Although the function of Let-7 family members as a tumor suppressor is well reported, there has been collected discussion on their potential role in perturbation of glucose metabolism and insulin signaling pathway [5] .Instinctually, anti-Let-7 ameliorates insulin sensitivity by refurbishing the execution of IRS-2 [49]. Thus, the knockdown of Let-7 could impart consequential cognizance in the molecular pathogenesis of diabetes and it could also yield a perspective in therapeutics of T2DM. The ability to intimately enumerate human research studies and animal models demonstrate that Le-7 reveals female-specific acclivity in patients with metabolic syndrome [50]. This may promote generating diabetes and complications. In addition, emerging evidence validates the significant role of Let-7 in the autocrine role of interleukin-13 (IL-13) on skeletal muscle glucose metabolism in TDM [51]. Molecular characteristics of the connection between non-coding RNA and metabolic disease necessitate additional explication.

### Others [miR-107, miR-132, miR-144, Mir-320]

To deep understanding the biological functions, micro RNA function has improved impressively and there has been an equanimous exchange of views regarding its prospective beneficial use as therapeutics in T2DM. Apart from the

above-discussed miRNAs, enormous miRNAs were comprehended to be distinctively demonstrated to play a crucial role in T2DM by regulating glucose metabolism. Consistent reports of miR-107 in multiple tissues (liver, adipose tissues, pancreas) as well as in circulation demonstrate its potential role as a biomarker of T2DM [52]. This meta-analysis of type 2 diabetes miRNA expression profiling also connotes the interrelation of miRNA not only with diabetes but also with its long-term intricacies. Yuqing et al. endeavored to investigate the clinical consequence of dysfunctional miRNAs in diabetes by conducting target prediction and pathway enrichment analysis, which furnishes molecular perception on the outcome of miRNA in various tissues during the progress of diabetes [53]. As per this study, miR-132-3p has been implemented in the regulation of insulin signaling pathways via targeting AMP-activated protein kinase. In addition, the above study also provides information on the effect of said micro RNA on mitogen-activated protein kinase, which can subsequently affect glucose transport at high glucose levels. Furthermore, emerging evidence supports the remarkable upregulation of miR-144 in T2DM [54]. It is already known that T2DM, hypertension, and cardiovascular diseases are firmly connected to obesity. T2DM is inevitably associated with adipogenesis. But it is not completely understandable and comprehensible if miR-144 modulates adipogenesis. Recent research has indicated that miR-144 focuses on FOX01 to attenuate the inhibitory effect of adiponectin on adipogenesis (54). Hence further studies with sizable and intelligible populations are obviously desired to conclude this miRNA-mediated nexus. It is worth mentioning here that DM is a metabolic disease characterized by IR which impedes functions of other organs through hyperglycemia and dyslipidemia. Accumulating evidence demonstrates altered miR-320 expression in blood/tissues of patients and animal models with diabetes and related complications [55]. This elucidates the potential contribution of miR-320 as a biomarker for glucose and lipid-associated diseases.

## Conclusions

DM has developed a global epidemic. The prevalence of T2DM is increasing across the world significantly. It is anticipated to go beyond 450 million by 2030. Owing to the rising burden, this metabolic disease has become a global challenge. Undeniably, long-term chronic care should be provided to control this non-communicable disease. In such an instance, an expeditious diagnosis might bring about delayed occurrences of chronic complications. Although inceptive consideration on miRNAs was long ago, contemporary chores on this field widely imbued the role of this non-coding RNA in diagnostic research. Presently, a set of miRNAs have been acknowledged as biomarkers with high sustained inflections. Mounting line of corroborations stands up for the association of miRNA with dysregulation of metabolic processes. In recent years, specific extracellular miRNAs have been demonstrated and correlated with diabetes mellitus. Research findings suggest that these evolutionary non-coding miRNAs could probably impart to the pathogenesis of T2DM due to their contribution to pancreatic beta-cell function. As explained in this review, numerous animal and human studies endorse the identification of a steady level of miRNA in body fluid. More so it is easy to access miRNA via sensitive tests like a quantitative polymerase chain reaction. However, it is difficult to consider all the miRNAs due to the growing number of miRNAs involved in T2DM. On that account, these findings are burdensome to determine which miRNAs are the best circulatory biomarkers. Nevertheless, diligent research and more randomized controlled studies are required to explore the repeatability of these research observations. Centered on the comprehension of this review, it can be concluded that miRNA could be contemplated as a non-invasive test for diagnosis and clinical monitoring of disease progression. Future clinical trials will likely pursue to take advantage of the significant paradigm shift from the decade-old investigations to an alluring perspective of non-coding miRNA for clinical implementation in T2DM.

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