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RESEARCH ARTICLE

MiRNA and its role in prognosis of obesity and diabetes biomarkers

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Abstract: Diabetes mellitus is a metabolic syndrome that may affect most people at different age, Dysregulation in pancreatic β-cells to secrete insulin may be early detected among children. From different risk factors that may cause T2DM is obesity, the adipose tissue distribution in human body which causes several degrees of elevation body mass index (BMI). MicroRNA (miRNA) is a genetic sequence that is attributed with many metabolic and nonmetabolic functions in human body. In diabetes mellitus, miRNA may be attributed with prognosis this disease, such as miR-375 suppresses glucose-induced insulin secretion by targeting myotrophin mRNA. Moreover, miR-200b/c family and miR-203 are the most significantly dysregulated in obesity. This review aims to summarize the main miRNA sequences that may predict diabetes mellitus and its prognosis in addition to obesity and miRNA role in its control. In conclusion, miRNA regulation has a great contribution in the management of obesity and adipose tissue distribution in the human body, as well the different miRNA expressions may enhance diabetes downregulation and then control the hyperglycemia crises among pre-diabetic and diabetic patients. Different miRNA controlling approaches must be carried out to contribute diabetes prognosis and control prediabetic patients who are risky for diabetes.

Keywords: Metabolic syndrome, diabetes mellitus, miRNA regulation, hyperglycemia crises.

INTRODUCTION

Diabetes mellitus is defined as a metabolic disorder which appeared with current and chronic stage of increasing blood glucose level. Diabetes mellitus encompasses various categories, primarily type 1 and type 2 [1], in addition to secondary causes associated with endocrinopathies and steroid administration, among others. The primary subtypes of diabetes mellitus are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) [2], generally arising from impaired insulin secretion T1DM and/or action T2DM. T1DM typically manifests in children or adolescents, but T2DM is thought to affect middle-aged and older individuals experiencing chronic hyperglycemia due to inadequate lifestyle and dietary decisions [3]. There is no extreme difference between the two main types of diabetes mellitus, resulting in differing etiologies, symptoms, and therapeutic approaches for each type [1].

Obesity is a condition characterized by the excessive buildup of body fat, adversely affecting an individual's health. This differs from being overweight, where the weight may derive from muscle, bone, adipose tissue, or bodily fluids. The lifetime risk of diabetes in males be from adults who are aging more than 18 years old who have raised level of body mass index (BMI) to give an estimate from 7% to 70% [4].

The recent identification class of endogenous short RNAs known as microRNAs (miRNAs) which has elucidated their functions in the regulation of glucose homeostasis [5]. MiRNAs are a unique category of non-coding RNAs, present in both flora and fauna, that modulate gene expression post-transcriptionally by cleaving or obstructing the translation of particular target mRNAs. MiRNA expression is frequently specific to tissue type or developmental stage, hence playing a remarkable role in the gene expression reduction and suppression during various periods of different biological processes [6,7].

Recent discoveries indicate that miRNAs directly influence insulin production, pancreatic islet formation, and beta cell differentiation [8], while also indirectly regulating glucose and lipid metabolism and contributing to secondary problems related to diabetes. The conditional ablation of Dicer 1, the exclusive Dicer enzyme responsible for miRNA synthesis in humans and mice, resulted in significant abnormalities across all pancreatic lineages in mice [8,9]. In conclusion, miRNA regulation significantly contributes to management of obesity and adipose tissue distribution in the human body. While varying miRNA expression may facilitate the downregulation of diabetes and subsequently regulate hyperglycemic crises in pre-diabetic and diabetic patients. Diverse miRNA regulatory strategies should be implemented to enhance diabetes prediction and manage prediabetic individuals at high risk, such as those with obesity. Therefore, this review aims to investigate the role of miRNA in controlling diabetes prognosis and its contributions for diabetes treatment.

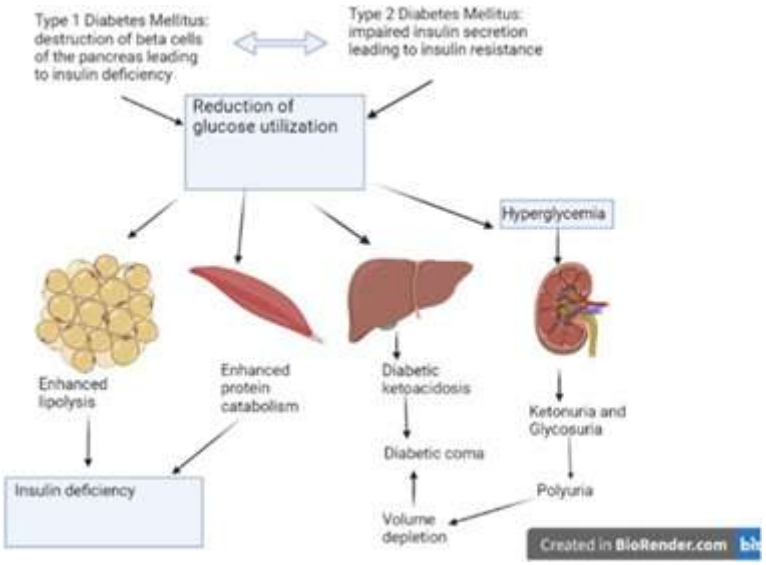

Figure 1. A summary of the pathology of diabetes mellitus

MATERIAL AND METHODS

2.1 Obesity as a risk for diabetes prognosis

Obesity is one of the main risk factors associated with diabetes mellitus, specifically, the insulin independent type. Adipose tissue functions as the principal energy reservoir in the body, providing a crucial transportable energy source necessary for survival during times of food deprivation. The excessive accumulation of adipose tissue results in various metabolic disorders and diseases, such as atherogenic dyslipidemia [10], nonalcoholic fatty liver disease, prediabetes, β-cell dysfunction, and type 2 diabetes. Increasing the body mass index (BMI), a measure of obesity, is associated with a heightened risk of acquiring type 2 diabetes. The distribution of triglycerides and fats leads to the risk of metabolic diseases associated with obesity. Obesity causes insulin resistance, which requiring an elevated insulin level in individuals with obesity to maintain normal glucose level.

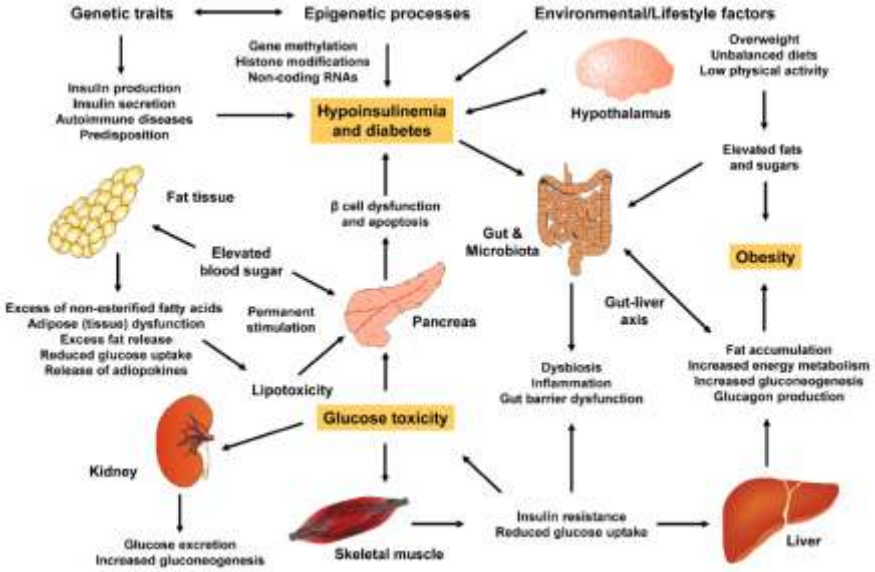

Figure 2. Obesity and its link to diabetes mellitus

2.2 MiRNA related to diabetes

Over the past decade, researchers have increasingly focused on miRNAs due to their involvement in the development and progression of T2DM. These molecules influence various biological functions such as insulin release, glucose regulation, and fat metabolism, which are the key factors in diabetes. Due to their connection to these pathways, miRNAs have gained attention as potential biomarkers for predicting disease outcomes. For example, miR-375 is primarily found in pancreatic islets and is closely linked to insulin secretion; disruptions in its expression have been associated with beta-

cell dysfunction in T2DM. Likewise, miR-146a and miR-21 have been connected to inflammation and show irregular patterns in diabetic patients, suggesting they may contribute to complications that arise from the disease [10].

It has been noted that using miRNAs as prognostic tool with their stability which was remarked in various bodily fluids, which makes them excellent candidates for non-invasive testing. This opens the door to using miRNAs in early diagnosis and disease monitoring. In addition, changes in miRNA levels have been observed in diabetes-related complications, such as damage to the kidneys, eyes, and blood vessels. For instance, different exchanged expressions of both miR-29 as well as the miR-192 have been attributed with diabetes. While miR-126 has been associated with vascular issues and impaired endothelial function. Monitoring such miRNAs might allow for earlier detection of complications and providing opportunities for timely and tailored treatment approaches [11-14].

Beyond their diagnostic capabilities, miRNAs also offer deeper insights into disrupted molecular mechanisms in T2DM. Studies using high-throughput technologies and computational tools have helped map miRNA–mRNA interactions that impact key signaling routes, such as the PI3K/Akt pathway—vital for insulin action. Gaining a clearer picture of these networks can lead to the discovery of new treatment targets and a better grasp of disease processes. However, several obstacles need to be overcome before miRNA-based diagnostics and treatments can be fully applied in healthcare settings. Challenges include developing standardized detection methods, ensuring reliability across larger populations, and improving the accuracy of these tools. Despite these hurdles, continuous progress in genomics and molecular research strengthens the case for miRNAs as important tools in diabetes care. Ultimately, miRNAs offer real potential not only for predicting how diabetes progresses but also for shaping future treatment strategies that are more personalized and effective [15].

2.3 MiRNA pathways unveiled to diabetes

MicroRNAs (miRNAs) are characterized as small, non-coding single-stranded, RNAs to enhance many biological activities. More than 60% of protein-coding genes in cells are targets miRNAs, which partially hybridize with 3' UTR sequence to mRNA targets through their 5'-proximal region. This targeting complex mechanism is rigorously governed by several biological factors, leading to reduce gene expression [13].

Studies conducted by different researchers have shown that miR-21 overexpression can inhibit the mesangial cells proliferation in the elevated glucose environments, while increased Akt activation fosters mesangial cell hypertrophy and raises fibronectin expression. Homologs were subsequently recognized in humans and mice [11]. The maturation of miR-155 follows the conventional miRNA biogenesis pathway, beginning with the transcription of pri-miRNA, which is then processed by the nuclear microprocessor complex (consisting of Drosha and DGCR8 proteins), yielding a 65-nucleotide stem-loop precursor miRNA (pre-miR-155) [9]. To yield from the dicer RNA duplexes of roughly 22 nucleotides in length (Bielska et al., 2021). The Argonaute protein interacts with short RNA duplexes, forming a crucial component of the multi-subunit assembly termed the RNA-induced silencing complex (RISC), which generates single-stranded RNA molecules that can bind to mRNA.

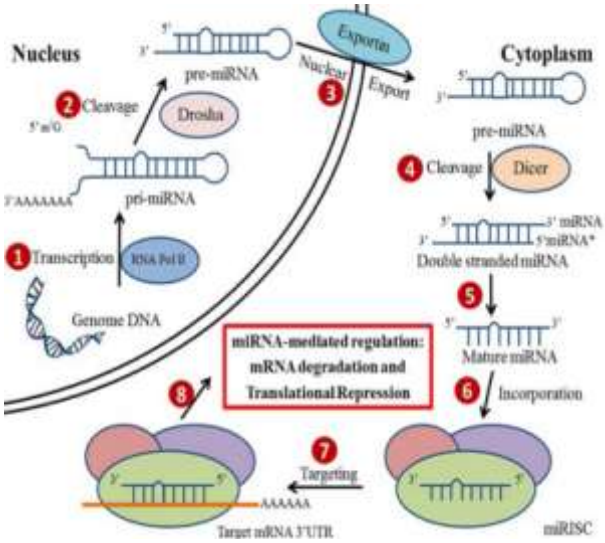

Figure 3. MiRNAs mediated regulation

2.4 Obesity control by miRNA

The obesity and its related to miRNA overexpression in different loci has been reported previously.

This approach allows adipose tissue to influence gene expression in several metabolic organs. Exosomal miRNAs originating from adipose tissue have been definitively demonstrated to influence the hepatic production of fibroblast growth factor 21 (FGF-21), which is involved in homeostasis of glucose [2,14]. This comprehensive study suggests that miRNAs may serve as biomarkers for metabolic disorders and could be utilized in therapeutic approaches.

A multitude of miRNAs have been recognized as regulators of the differentiation and functionality of beige and brown adipose tissues. Understanding the role of miRNAs in the thermogenic activation of brown adipose tissue and the browning of white adipose tissue could provide new therapeutic targets for obesity and associated metabolic diseases.

MicroRNA (miR)-21 is frequently increased in numerous chronic diseases, including obesity. MiR-21 is elevated in the epididymal white adipose tissue of obese mice relative to the normal weight counterparts, and in type 2 diabetic obese individuals compared to non-diabetic obese individuals. The miR-21 facilitates adipogenic differentiation by altering transforming growth factor β signaling which is essential for angiogenesis through the modulation of vascular endothelial growth factor A (VEGF-A), acknowledged as a thermogenesis regulator. However, the precise mechanisms regulating its correlation with obesity, type 2 diabetes, or insulin resistance remain ambiguous [14].

A study by Keller et al., who reported that expression of 10 miRN as regulated by adipogenesis was analyzed using real-time qPCR. Among the miRNAs evaluated, miR-21 exhibited strong expression in human adipose tissue and showed a positive correlation with BMI ($p < 0.001$).

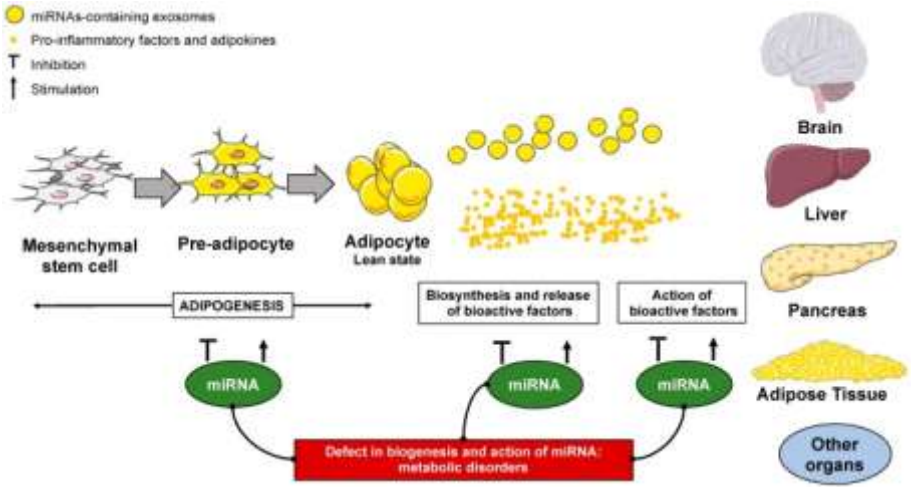

Figure 4. Adipose tissue involvement among obese patients and miRNA functions

It has been reported in previous literature the ability of in silico and in vivo studies to control diabetes and obesity with miRNA techniques that silences the disease progression and other risk factors.

2.5 MicroRNA as a treatment approach

The reduction in β-cell viability and functionality was indirectly associated with disrupted glucose homeostasis. Comprehensive research indicates that miRNA expression profiles in pancreatic β-cells differ between individuals with T2DM and those without the disorder.

MicroRNAs engage in multiple biological processes, encompassing cell growth, proliferation, differentiation, apoptosis, and metabolism. Approximately 2000 miRNAs have been found in Homo sapiens, with the majority of protein-coding genes thought to be directly regulated by these entities. Moreover, each miRNA can bind to and modulate several targets, so affecting various levels simultaneously. Although numerous circulating miRNAs exhibit moderate expression levels, significant redundancy among the targets that is seen [8].

Depletion and malfunctioning of β-cells are hallmark features of both type 1 and type 2 diabetes mellitus. The manufacture and release of insulin in β-cells are meticulously controlled by a network of transcriptional activators and repressors that dictate β-cell fate and activate genes in response to fluctuations in plasma glucose levels. The findings of miRNAs have introduced a new regulatory dimension in the management of essential parameters related to β-cell differentiation and proliferation, insulin production and release, as well as β-cell viability and regeneration.
Multiple miRNAs can modulate insulin production and glucose-stimulated insulin secretion (GSIS). Research has shown that miR-15a, miR-30d and miR-375 are essential for insulin gene expression, insulin synthesis, and glucose-mediated insulin secretion [1,13].

Certain frequently prescribed hypoglycemic medications are associated with adverse effects, including an elevation in cardiovascular risk factors. A notable constraint of existing therapy approaches for T2DM is their failure to completely halt disease development.

A study by Kong et al., who aims to investigate the clinical relevance of seven diabetes-associated serum microRNAs (miR-29a, miR-9, miR-30d, miR-124a, miR-34a, miR-146a, and miR-375) in the pathogenesis of T2D. A total of 56 participants were enrolled, comprising 18 newly diagnosed T2D patients, and 19 individuals with pre-diabetes. Canonical discriminant analysis identified 70.6% of n-T2D participants (12/17) using the canonical discriminant function, although s-NGT and pre-diabetes subjects were indistinguishable from one another.

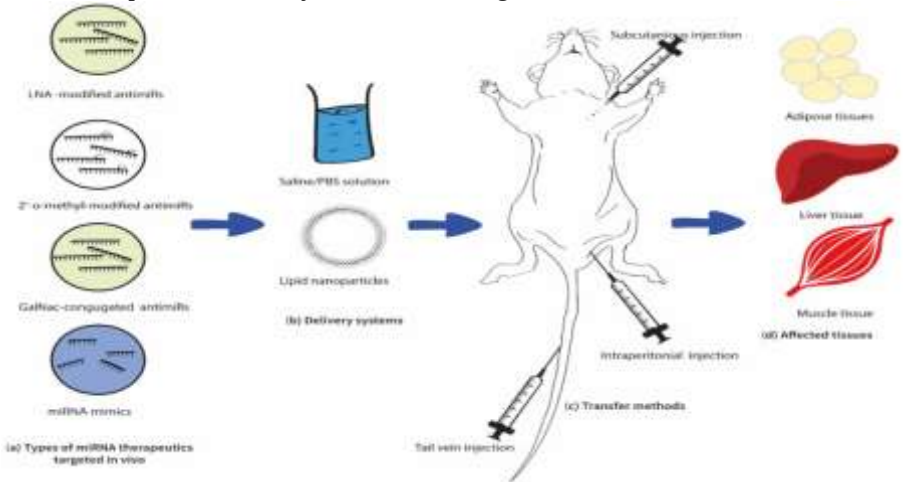

Figure 5. Overview of contemporary in vivo methodologies in miRNA therapies for Type 2 DM.

CONCLUSION

In conclusion, miRNA regulation has a great contribution in the management of obesity and adipose tissue distribution in the human body, as well the different miRNA expressions may enhance diabetes downregulation and then control the hyperglycemia crises among pre-diabetic and diabetic patients. Different miRNA controlling approaches must be carried out to contribute to the diabetes prognosis and control prediabetic patients who are risky for diabetes such as obese.

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