Turkish Online Journal of Qualitative Inquiry (TOJQI)
Volume 11, Issue 4, June 2020: 2529-2538
DOI: 10.53555/tojqi.v11i4.10203

Research Article

Recent On Diabetes And Related Complications In Relation To Mirnas

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Abstract:
Multiple consequences are linked to diabetes, a multifactorial polygenic disease. Growing data suggests that numerous miRNAs play a role in the issues linked to diabetes. Additionally, some ncRNA have been linked to the regulation of both learned and innate immunity. MiRNAs and their involvement in diabetic complications are still up for debate, though. We will talk about new developments in miRNA, potential processes, and their biological function in complications related to diabetes in this review.

Keywords:- miRNA, Insulin, DNA.

1. Introduction

A complex metabolic illness known as diabetes mellitus (DM) affects people all over the world [1, 2]. In Type 1 diabetes mellitus (T1DM), autoimmune -cell destruction causes an insulin shortage. Insulin resistance, hyperglycemia, and decreased insulin production are the hallmarks of type 2 diabetes mellitus (T2DM). Both kinds of diabetes can lead to coronary heart disease (CHD), peripheral artery disease, stroke, nephropathy, retinopathy, neuropathy, and cardiomyopathy, albeit T2DM is much more common [3]. In fact, whether they are macrovascular or microvascular, many diabetes problems have vascular origins. The risk of ischemic heart disease, renal failure, stroke, lower limb amputations, and blindness is often higher among diabetics.
Therefore, diabetes is acknowledged as a significant risk factor for cardiovascular disorders [4]. Diabetes is characterized by hyperglycemia, hyperinsulinemia, obesity, and dyslipidemia [5, 6]. Growing evidence from epidemiological and experimental studies have also suggested that T2DM associated with an increased risk of several types of cancer, including prostate, liver, kidney and breast cancers [7-10]. Further, *In vivo* and *in vitro* models demonstrated that insulin, IGFI, and IGFII signaling is positively correlated to tumorigenesis [11-13]. Insulin, IGFI, and IGFII signaling through cognate or hybrid receptors can induce tumorigenesis, which may partly explain the link between diabetes and cancer [14-16]. As insulin resistance and hyperinsulinemia are hallmarks of diabetes, it is conceivable that the metabolic syndrome is also linked to increased cancer risk [1719].
The central dogma theory state that DNA transfer their information into RNA by transcription and finally RNA code the information into protein. Growing evidence of RNA regulatory world challenge the central dogma theory, RNA could store the genetic information and catalyzed the reaction [20]. In recent years, non-coding RNAs (ncRNAs) are emerging as therapeutic tool for treatment of numerous diseases including diabetes and its associated complications [21]. Based on function, endogenous ncRNAs classified as structural ncRNAs and regulatory ncRNAs. Structural ncRNAs includes transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), spliceosomalu RNAs (snRNAs), and snoRNAs, while regulatory ncRNAs small interfering RNA (siRNA), micro-RNAs (miRNAs), piwi-RNAs (piRNAs), long ncRNAs, and long intergenic ncRNAs [20, 22].
Among non-coding RNAs (ncRNAs), microRNAs (miRNAs; miRs) are emerging

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therapeutic targets in a broad range of diseases including diabetes. miRNAs are evolutionarily conserved with an approximately length of 22 nucleotide (nt) that play crucial role in posttranscriptional regulation. It is estimated that miRNAs account for 1–5% of all expressed human genes and that they can regulate the expression of more than 30% of the protein-coding genes [23]. Once miRNAs transcribed from DNA sequences into primary miRNAs, subsequently processed by two RNAs III proteins such as Drosha (nucleus) and Dicer (cytoplasm). Further, miRNA modify by RNA editing, RNA methylation, uridylation and adenylation; Argonaute loading; and RNA decay [24]. To date, 940 distinct miRNAs molecules have been identified within the human genome (http://microrna.sanger.ac.uk) [25].

International initiatives investigating clinical miRNA therapeutics may result in a novel armada of more efficacious and mechanism-oriented therapeutics for complex diseases. Initial reports about the role of miRNAs in cardiovascular pathologies have stimulated tremendous interest, resulting in a substantial increase in literature about its functions in the cardiovascular system. As diabetes is one of the most important risk factors for the development of cardiovascular diseases, miRNAs involved in diabetes-related cardiovascular disorders have also received a great deal of attention. Studies indicate that miRNAs can be used as biomarkers [26], and newer developments further describe the molecular mechanisms of how miRNAs are involved in cardiovascular diseases and diabetes[27]. Serum miRNA-based signatures would make it possible to comprehensively analyze diabetic complications instead of using more invasive procedures [28]. This review hopes to highlight and summarize exciting miRNA-based mechanisms, diagnostics, and therapeutic developments related to diseases linked with diabetes.

2.Epidemiology

Diabetes is a multifactorial chronic disease whose incidence is considered epidemic. In 1985, the World Health Organization (WHO) estimated that there were 30 million people worldwide suffering from diabetes. This number increased to 135 million in 1995 and 217 million in 2005. Currently, more than 346 million people have diabetes. WHO predicts that more than 366 million people will have diabetes by the year 2030. This increase in prevalence, driven principally by an increase in T2DM, is occurring in both developing and developed countries. The Indian subcontinent has emerged as the capital of this diabetes epidemic. The reported prevalence of diabetes in adults living in this area and between the ages of 20 and 79 is as follows: **Bangladesh 9.85%, India 8.31%, Nepal 3.03%, and Pakistan 6.72%,** and **Sri Lanka 7.77%** [29-31].

Presently, approximately 62 million Indians are diabetic, and that number is expected to rise to more than one hundred million by 2030 [32]. T2DM causes serious physical harm and can be an economic burden for the afflicted. Similarly, the incidence of T1DM is increasing worldwide, at a rate of approximately 3% per year [32, 33]. T1DM or insulin-dependent diabetes mellitus (IDDM) is a lifelong metabolic disorder caused by insulin deficiency with secondary autoimmune destruction of the insulin-producing pancreatic β-cells [34]. This organ-specific destruction is mediated by T helper-1 (Th1) lymphocytes and develops due to interactions between susceptibility genes, environmental factors, and other risk factors. Usually diagnosed in children, adolescents, and young adults, it can be bound up with psychological, familial, and social disorders [35, 36]. Epidemiological investigations show the geographical differences of T1DM incidence; the age adjusted incidence of T1DM varied from 0.1/100,000 per year in **China** to 40.9/100,000 per year in **Finland** [37].

In the second half of the 20th century, it became clear that the relentless increase in prevalence of T2DM was not limited to economically affluent countries. Presently, T2DM prevalence is highest in **Saudi Arabia. T2DM afflicts over 10% of adults in the USA, Switzerland, and Austria. Prevalence is low in Norway, China and Iceland.** Epidemiologists predict that T2DM prevalence will increase 2.5-fold in the Middle East, Latin America, Sub Saharan Africa, India, and rest of

Asia in first third of the 21st century. In China, the number of patients with T2DM will be doubled by 2030. In economically advanced countries, the estimated increase by 2030 is 50% [38].
Cardiovascular disease (CVD) is the leading cause of death in the world. In 2008, the estimated number of deaths from CVD was 17.3 million, comprising about 30% of all deaths [39].
Global CVD deaths are projected to increase to 23.4 million by 2030, comprising 35% of all deaths. CVD is the most prevalent cause of mortality and morbidity among people with T1DM and T2DM [8–10]. In 2004, in the USA, the presence of CVD and stroke was found in 68% and 16% of deaths related to diabetes, respectively, among people older than 65 years. Mortality due to heart disease and stroke in adult diabetics is two to four times higher than those without diabetes. Patients with T2DM but without a previous history of myocardial infarction have the same risk of coronary artery disease (CAD) as non-diabetic subjects that have a history of myocardial infarction [40]. However, it is uncertain as to whether the cardiovascular risk conferred by diabetes is truly equivalent to that of a previous myocardial infarction. In general, patients with diabetes aggregate other co-morbidities such as obesity, hypertension, and dyslipidemia which all contribute to increased CVD risk [41-43].

3.Biochemistry & Cell Biology

Insulin and Insulin-like Growth Factor (IGF) have important physiological roles in the body and in the development of diabetes and associated complications. Insulin and IGF are peptides that regulate cellular growth, proliferation, metabolism, differentiation, apoptosis, and glucose homeostasis [44]. The peptides have 40-80% amino acid homology, making it difficult to discern differences between their ligand-receptor interactions. The Insulin/IGF signaling system is comprised of three ligands: IGF-I, IGF-II, and insulin itself. The ligands interact with at least seven receptors: type I IGF receptor (IGF-IR); type II IGF receptor (IGFIIR); insulin receptor A (IR-A); insulin receptor B (IR-B); hybrid receptors of IGF and IR-A; hybrid receptors of IGF and IR-B; and hybrid receptors of IR-A and IR-B. The actions of insulin are mediated through the tyrosine kinase IR. This receptor is a heterotetrameric protein consisting of two extracellular αsubunits and two transmembrane β-subunits [45]. Ligand binding to α-subunits of IRs stimulates the intrinsic tyrosine kinase activity of the β-subunits. In turn, the receptor autophosphorylates and transphosphorylates intracellular substrates that lead to complex downstream signaling cascades. The activated IR complex can activate several substrates, including IR substrate proteins (IRS14), Gab-1, Cbl, Shc, Phosphatidyl Inositol 3-Kinase (PIK3), Akt, mTOR, MAPK and regulatory protein families, all of which can ultimately contribute to diabetic cancer in pathologic conditions [46].

IRs and IGF-IRs are expressed over in a variety of cancers, including prostate, breast, osteosarcoma and thyroid carcinomas [47-50]. It is therefore conceivable that an upregulation of hybrid receptors could be partly responsible for the development of these cancers. IGF-IR are highly homologous to IRs, sharing 84% amino acid identity in the kinase domain, and 100% conservation of the ATP binding pocket domain [51, 52]. Proreceptors of IRs and IGFRs can heterodimerize to form insulin-IGF hybrids, which are comprised of two α-subunits and two βsubunits, with one subunit from each proreceptor. Similarly, all IRs and IGFRs have two extracellular α-subunits and two transmembrane β-subunits jointed by disulfide bonds [16, 53]. Insulin binds with high affinity to IR-A, IR-B and IGF-1R. IGF-1 binds to IGF-IR, the hybrid IGF-
IR/IR-A, and the hybrid IGF-IR/IR-B. IGF-2 binds to IR-A, IGF-IR, and to the hybrid IGF-IR/IRA [54, 55]. Hybrid heterodimeric receptors could play a role in receptor signaling in normal and abnormal tissues. Research with cancer cell lines suggests that autophosphorylation of IR/IGF-IR hybrid receptors - in response to insulin and IGFI binding – increases cell proliferation, indicating that hybrid receptors were the major mediators of IGF signaling in these cells [56-59]. Aberrant IR-A expression may contribute to the deregulated response of cancer cells in at least two ways: (a) IR overexpression increases the sensitivity of insulin and increases the pleiotropic effects of circulating

insulin, especially during hyperinsulinemia and insulin resistance and (b) IR-A overexpression increases hybrid receptor formation with IGF-IR and IR-B [60]. These studies, together with the finding that IR-A is often aberrantly expressed in cancer cells, have strengthened the hypothesis that insulin resistance and compensatory hyperinsulinemia are a major link between diabetes and cancer-associated cardiovascular complications [61].

4. Physiology & Relevance/Importance

miRNAs control insulin signaling in target tissues, including liver, skeletal muscle, and adipose tissues. Insulin resistance describes the failure of target tissues to respond adequately forinsulin circulation. Insulin resistance in adipose tissue and skeletal muscle decreases glucose uptake and the local storage of triglycerides and glycogen. Insulin resistance in liver tissue leads to reduced synthesis and storage of glycogen, with a concomitant failure to suppress glucose production. Collectively, resistance results in elevated insulin, blood glucose, and free fatty acid levels; that is, hallmarks of diabetes and associated cancer and cardiovascular complications. If a compensatory increase in pancreatic β-cell function is insufficient, T2DM comes to action. The aim of the present review is to describe the role of miRNAs in diabetes and diabetes-associated cardiovascular complications. Changes in normal miRNA expression in diabetes-associated CVD are presented below. The role of miRNAs as biomarkers in diabetes and its potential as a therapeutic target for correcting aberrant pathways is also discussed.

5. miRNAs as biomarkers

Recent evidence suggested that one third of diabetes patients develop various complications such as cancer, cardiovascular and nephropathy [62] Growing evidence from gene profiling has been suggested that miRNAs could be a promising target for diabetes and its associated complications. For instance, increased expression of the miR29 family in muscle, adipose, and liver tissue is strongly associated with insulin resistance in the diabetic GK rat model [63]. Another study using the same model observed several fold change in miR-24 in skeletal muscle [64]. Moreover, urinary exosome miRNA-451-5p several fold increased in diabetic nephropathy model [62]. Plasma profiling of miRNA from T2DM patients established diabetic signature [65]. Furthermore, miR30a inhibit myocardial fibrosis by inhibiting the CTGF via binding with 3'-UTR site of CTGF and improve the cardiac function in rats [66] and MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signaling in fibroblast [67].

5.1 miRNA in Insulin synthesis, release, and resistance miRNAs hold promise in novel therapies because they are naturally occurring and often deregulated in diabetes cancer and cardiovascular disease. Deep understanding of miRNA function in differential gene regulations leading us to develop more efficacious molecules that modulate the miRNA function in diabetes and its associated complications [68]. Insulin resistance is not only a critical hallmark for chronic inflammation and compromised microvascular function, but also major risk factor for type-2 diabetes as well as cardiovascular disease. However, growing accumulating evidence demonstrate that restoration of insulin resistance may ameliorate the diabetes associated complications. Targeting the miRNA expression or function can be used as therapeutic tool to improve diabetes-associated microvascular dysfunction and its clinical ramification [69].

T2DM and hyperinsulinemia are associated with proliferation, migration, and dedifferentiation of VSMCs during the pathogenesis of atherosclerosis. IGF-1R and mammalian target of rapamycin (mTOR) have been demonstrated to be the underlying signaling pathways of these processes. Recently, it was suggested that miR-99a regulates the phenotypic changes of VSMCs in cancer cells. Fascinatingly, the inducing effect of high-dose insulin on proliferation, migration, and dedifferentiation of VSMCs was partially inhibited by an analog of miR-99a [70].

Diabetes mellitus and miRNA

miRNA Biomarkers Ref. miR-375 alone or in combination with miR-9 Pre-diabetes and T2D[71, 72]miR-34a and miR-125b Type 2 diabetes mellitus [73]
miR-503 upregulated Type 2 diabetes mellitus [74]miR-1225-5p and miR-320c Type 1 diabetes [75]miR-146a, miR-199a-3p, and miR-30e) were deregulated
Type 2diabetes mellitus [76] Over-expression of miR-494 improved pancreatic β-cell dysfunction Type 2 diabetes mellitus [77]miR-494 knockdown exhibited decreased insulin secretion Type 2 diabetes mellitus [77]
miR-203-3p inhibits osteogenesis in jaw bones of diabetic ratsType 2 diabetes mellitus[78]miR-106b,
miR-363, miR-486, miR-532, miR-92a and miR-93 Type 2 diabetes mellitus [79]miRNA (miR)-203a-3p expression level was significantly decreased Type 2 diabetes mellitus [79, 80]
Down-regulated miRNA was miR-184 Type 2 diabetes mellitus [81]
Over-expression of microRNA-26a Type 2 diabetes mellitus[82]

Insulin-resistance, Diabetes, and miRNA		
miRNA13	Biomarkers	Ref.
miR-214 downregulation	Insulin-resistance	[83]
miR-181a-5p and miR-23a-3p was reduced	Insulin-resistance	[84]
miR-125b inhibits insulin sensitivity	Insulin-resistance	[85]
miR-96 decreased the expression of IRS-1 in myocytes	Insulin-resistance	[86]
miR-335	regulating insulin secretion	[87]
reduced level of miR-21 might associate with obesity and its related metabolic traits such as hyperinsulinaemia	Insulin-resistance	[88]
circulating microRNA-375 (miR-375)	biomarker for beta cytoprotective effect	[89, 90]
Upregulation of miRNA miR-330-3p	target genes involved in proliferation, differentiation, and insulin secretion	[85]
miR-122 up	Insulin-resistance	[91]
up-regulation of miR-222	Insulin-resistance	[92]
miR-16 and miR-107 were positively associated with insulin sensitivity	Insulin-resistance	[93]
miR-146a levels in peripheral blood leukocytes are negatively associated with a state of insulin resistance	Insulin-resistance	[94]
Insulin increased and glucose reduced **miRNA**-340 expression		[95]

Nephropathy

Diabetic nephropathy (DN) occurs in an estimated 40% of diabetic patients [96]. As the incidence of diabetes and DN increases, so too does the incidence of end-stage renal disease (ESRD). Indeed, diabetes is the most common cause of ESRD in Europe and the USA. Treatment for ESRD involves dialysis- a time-consuming, stressful, and potentially costly therapy for patients. Currently, kidney transplant is the only alternative therapy to treatment with dialysis. DN is thought to manifest due to various haemodynamic and structural changes. For example, on a molecular level, hyperglycemia-induced metabolic changes can increase concentrations of reactive oxygen species and alter levels of advanced glycation end-products, both of which have been shown to be key players in the pathogenesis of ESRD [97, 98]. Insulin resistance is associated with deficiencies in vascular regulation and podocyte function, both of which are important for proper renal function [99]. For the nephron, diabetic nephropathy most often involves thickening of the glomerular basement membrane, a widening of podocyte slits, and an excessive increase in mesangial cells and mesangial matrix [100]. Ultimately, reduced or failed renal function can be lethal.

Clinically, diagnosis and monitoring of DN conventionally relies upon the detection of urinary microalbuminuria. This practice has several issues, including: (a) not all patients with microalbuminuria progress to a deleterious state of nephropathy, (b) patients may have already

experienced tissue damage before microalbuminuria is detectable, and (c) the diagnostic tool is specific for podocyte dysfunction but not DN [99]. It is therefore possible that miRNA diagnostic tools replace current clinical practice in the monitoring of DN in diabetic patients. Determining levels of certain circulating miRNAs could be a more clinically efficacious procedure. However, appropriate miRNAs must be identified as reliable DN biomarkers.

As reviewed by Simpson and colleagues, in vitro and in vivo animal model studies were important in identifying miRNAs implicated in the pathogenesis of DN [99]. Clinical investigations have demonstrated associations and correlations between levels of these identified miRNAs and human DN. Bijkerk et al. identified increased concentrations of 10 miRNAs and decreased concentrations of 2 miRNAs in the plasma of T1DM patients with DN relative to those without DN, and additionally showed that these miRNA levels generally normalize following organ transplantation [101]. Building from the knowledge of the levels of has-miR-152-3p in T1DM patients with DN from this study, a combination of next-generation sequencing and quantitative reverse transcription-polymerase chain techniques were used to identify its up regulation in T2DM patients with DN [102]. Additionally, miRNAs 21, 29, and 93 were identified by Wang et al. as biomarkers of renal fibrosis, a hallmark of DN [103]. miRNAs 21 and 29, in combination with miR-192, were later used to predict the progression and pathogenesis of DN in patients [104]. Recently, Dr. Swasti group, reported that miRNA 451-5p and miRNA16 upregulated in urinary exosome of streptozotocin induced diabetic rats [62]. Taken together, these studies indicate that miRNAs could be used in the future as powerful diagnostic tools and potential therapeutic targets.

Biomarkers			
miRNA			Ref.
miR-146a down	**D**iabetic nephropathy and type 2 diabetes		[105]
Increased plasma levels of hsa152-3p -miR-	Diabetic nephropathy	and type 2 diabetes	[102]
Diabetic Nephropathy in Urinary exosomal miRNA451-5p and miR-16		Rats	[62]
Over- expression of miR302a-3p	**D**iabetic nephropathy and	type 2 diabetes	[106]
miR-377 and miR-216a	Nephropathy in pediatric	type 1 diabetes	[107]
Dozens of miRNA	Diabetic nephropathy and	type 1 diabetes	[101]

Diabetic Retinopathy

Diabetic retinopathy is a microvascular complication of diabetes [108]. Diabetes or poor control of blood sugar damages the blood vessels of the light-sensitive tissue of the eye's retina, which leads to retinopathy. Diabetic retinopathy (DR) can cause vision disabilities and blindness. The prevalence of diabetes is the main leading cause of blindness in patients aged 20 to 64 in the USA. Early management of proliferative DR is especially important for preventing complications. [109]. Understanding the roles of miRNA in the pathogenesis of DR could be central to developing therapeutics that reduce the incidence of diabetes-associated visual complications [110]. *Kovacs and colleagues*first showed that the expression of about 200 miRNAs was altered in retinas and retinal endothelial cells in diabetic rodent model. They reported that 96 miRNAs were upregulated and 110 were down regulated [111]. Similarly, Wu et al. substantiate the *Kovacs* finding, and found that expression of 11 and 6 miRNAs were increased and decreased, respectively, ten weeks after diabetes onset [112]. Further, Mortuza*et al.* in human retinal endothelial cells, found that miR-195

regulates the SIRT1-mediated changes of diabetic retinopathy. SIRT1 is a deacetylase, and imparts crucial role in cell survival, metabolism, and cycle regulation [113]. Further, Mastropasqua et al., elucidated the biochemical significance of some of miRNAs in DR [110].

Nonetheless, Qing et al. finding suggest that serum profiling of miRNA levels can be used as biomarkers or as diagnostic tools for proliferative DR [114]. Similarly, Gao and colleagues created a profile of three different miRNAs which correctly identified in T2DM-DR with an accuracy of 93.7% [115]. Although it is possible to create more detailed profiles by using a combination of more sophisticated miRNA algorithms and other serum biomarkers, here we highlight the potential efficacy of miRNA diagnostics in DR.

miRNA	Biomarkers	Ref.
MiR-1273g-3p is involved in the progression of Diabetic Retinopathy	Diabetic Retinopathy	[116]
miR-34a, miR-15a-5p, miR-15a-3p, miR-16-1-5p Up regulated	Cataract	[90]
miR-125b and miRNA-16-1-3p Down-regulated	Cataract	[90]

Cardiomyopathy

Diabetes is a major risk factor for cardiomyopathy, impairs the cardiac muscle function. Diabetic cardiomyopathy (DCM) occurs independently of cardiovascular diseases and hypertension in both types of diabetic patients [117]. There are numerous possible mechanisms such as changes in substrate metabolism, oxidative stress, endoplasmic reticulum stress, formation of extracellular matrix proteins, advanced glycation end products and insulin resistance contributes to early development of DCM. Subsequently, several events, such as steatosis, fibrosis, apoptosis, and remodeling of cardiomyocytes happen and this leads to decrease in cardiac function body [118, 119]. Recently numerous miRNAs identified in the diabetic heart and they might can acts as cardioprotective or contribute to cardiomyopathy [120]. Cardiac function energetically coupled to mitochondria, and diabetic associated mitochondrial function one of the major cause of cardiomyopathy [121]. miRNA not only control the metabolic transition but also control the substrate metabolism, apoptosis, and reactive oxygen species. miRNA expression regulated by epigenetics, exosomal transport, processing, and posttranscriptional modifications. Although the exact mechanism of DCM remains elusive; however, emerging miRNA-based therapies open the new avenue for DCM treatment [122]. In table (XX) we have summarized the miRNA-based therapies.

Biomarkers
miRNA Ref
miR-29 was dysregulated in resistance arterioles[71]
Increased miR-221 and -222 [123]
Antago-miR155 reduced cell apoptosis and restored the cardiac functionhearts of diabetic mice[124]
MiR-193-5p is an active angiogenic factor in diabetic cardiomyopathyIGFR1 Pathways [125]miR-18a-5p regulated high glucose-induced endothelial-mesenchymal Cardiac fibrosis through the [125]transitionNotch2 pathway
Diabetes, increased inflammatory cytokine and extracellular matrix [126]protein productions and associated cardiac functional alterations are regulated by endothelial miR-146a

Fracture Healing

Diabetes is a multifactorial polygenic disease, and growing evidence suggest that it impairs the bone healing [127]. About 25 % of DM patients at least once in their life have recalcitrant to

wounds healing problems [128]. In the last few years numerous miRNAs identified which has therapeutic targets.

miRNA	Biomarkers	Ref.
miR-140-3p, miR-140-5p and miR-181a-1-3p Down-regulated	Diabetic and Healing	[129]
miR-210-3p and miR-222-3p Up-regulated	Diabetic and Healing	[129]
Therapeutic potential of miR-132 in chronic wounds	Diabeticand Healing	[130]
Down regulation of microRNA-126 (miR-126)	Diabetic and Healing	[131]

Adipogenesis

Obesity is a major metabolic health problem in world, and their number steeply increasing. Numerous comorbid effects associated with obesity such as type 2 diabetes, hypertension, cardiovascular disease, and certain kind or cancer. Growing evidence shows alteration in miRNAs associated with adipogenesis and obesity [132]. Several studies have shown that miRNAs play most important regulatory roles in adipocyte differentiation and lipid metabolism, and its dysregulation leads to pathogenesis of obesity associated complications. Targeting the adipocytes associated miRNA not only open the new therapeutic avenue but also used as early biomarker for detection and treatment of obesity associated complications [133]. Here, is the list of potentially identified miRNA in obesity could be used as therapeutics target in future research.

miRNA	Biomarkers	Ref.
Mmu-mir-23a-3p down	Adiposeness	[134]
MicroRNA 23a-3p and 1a-3p up	Adiposeness	[134, 135]
miR-27a attenuated hepatic de novo lipogenesis and alleviated obesity		[89]
miR-146a-5p suppressed adiposeness		[136]
miR-100 reduced expression of mammalian target of rapamycin (mTOR) and Insulin Growth Factor Receptor (IGFR) directly	Obesity and Type 2 diabetes	[135, 137, 138]
hsa-miR-144-3p was lower in epicardial adipose tissue in response to hyperglycemia		[139]
MicroRNA-192	Controller of adipocyte	[140]
Suppression of miRNA-205	Formation of adipocytes	[141]
Obesity and insulin resistance, focusing on the miR-17/92, miR-143-145, miR-130, let-7, miR-221/222, miR-200, miR-223, miR-29 and miR-375 families, as well as miRNA changes by relevant tissue (adipose, liver and skeletal muscle		[142]
miR-455 regulates brown adipocyte differentiation and thermogenesis		[143]
Inhibition of miR-375 also mediated a decreased adipogenic differentiation and increased ADIPOR2 expression levels		[144]
miR-342-3p is a powerful enhancer of the adiposeness of human adipose derived human mesenchymal stem cells		[145]
miR-106b and miR-93 as negative regulators of brown adipocyte differentiation		[146]
miR-15a/b over-expression had a positive effect on adiposeness		[138]

Conclusion and Future direction:

Growing evidence from recent studies on miRNAs:

Emergence of miRNAs as a new class of gene regulators and their proven role in different diseases' progression has opened new avenues for therapeutic discovery. Interest in miRNAs is now more than ever, and the literature is getting enriched rapidly with reports on novel miRNAs, their

validated gene targets, and the development of miRNA-based therapeutics. The realization of a miRNA-based therapeutic approach in clinics; however, may still be far from sightand several hindrances pertaining to the stability, specificity, and delivery of short oligonucleotides need to be overcome. Nonetheless, phase I clinical trial with antimiR-122 for treatment of hypolipidemia has already been initiated based on exciting preliminary data in non-human primates. With increasing interest, further research in miRNA functions and technological advancements, miRNA-based therapeutics may create a paradigm-shift in medicine and pharmaceutical industry.

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