Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
NAAS Rating: 3.53
JMPS 2019; 7(4): 34-38

Received: 19-05-2019
Accepted: 21-06-2019

Firnus Haile
Institute of Biotechnology, University of Gondar, and Gondar, Ethiopia

Mequanente Dagnaw
Institute of Biotechnology, University of Gondar, and Gondar, Ethiopia

Nega Berhane
Institute of Biotechnology, University of Gondar, and Gondar, Ethiopia

Correspondence
Firnus Haile
Institute of Biotechnology, University of Gondar, and Gondar, Ethiopia

A review on regulatory roles of micro RNA and micro RNA based therapeutics for diabetics mellitus

Firnus Haile, Mequanente Dagnaw and Nega Berhane

Abstract
Diabetes mellitus (DM) is a group of chronic metabolic disorders characterized by impaired glucose homeostasis that results in hyperglycemia due to increased insulin resistance in insulin sensitive tissues (liver, skeletal muscle, adipose tissue, etc.) and/or disturbance in insulin secretion in pancreatic β cells. The causes of diabetes mellitus are various, including both genetic and environmental factors and it is a major cause of complication such as renal failure and stroke. About 50% of diabetic patients have end-stage renal disease (ESRD), requiring painful and costly dialysis. Current treatments for diabetes cannot efficiently control glycaemic levels, resulting in episodes of hyper- and hypoglycaemia, which increase the possibility of developing secondary complications such as retinopathy, nephropathy and neuropathy. In the search for more-targeted molecular therapies, microRNAs implicated in insulin secretion and diabetic complications have recently attracted attention. MiRNAs are non-coding RNA molecules which are about 22 nucleotides in size inhibit the expression of a target messenger RNA (mRNA) molecule by binding to its 3'-UTR through complimentary base pairing. The process of miRNA biogenesis occurs in both nucleus and cytoplasm.
There is heightened interest in evaluating miRNAs as a potential biomarker for various diseases especially because of improvement in the technologies for miRNA detection in vitro and in vivo. These include quantitative PCR, microarrays, and high throughput deep sequencing. MiRNAs are readily detectable in plasma and urine and their stability in these biofluids make them ideal candidate biomarker for noninvasive much needed early detection of diabetic complication.
Because of the role of miRNAs in regulating several path ways, miRNA should the promise of being able to yield a new class of therapeutics.

Keywords: Diabetes mellitus, MicroRNA, biomarker

1. Introduction
Diabetes mellitus is a progressive metabolic disease that is characterized by high blood sugar and is a great threat to human health. According to the World Health Organization (WHO), there are currently >400 million people suffering from diabetes worldwide, and that number will reach 552 million by 2030 (Feng *et al.* 2016) [5]. Diabetes has become a major health problem in the USA. Recent studies report that 9.5% of the US population has diabetes and 23.8% of people with diabetes are undiagnosed according to the National Diabetes Statistics Reports, 2017. It is predicted that there will be a 54% increase in diabetes prevalence in USA by 2030 (H. Zhang & Pollin, 2018) [25]. The increasing incidence of both type 1 (T1D) and type 2 diabetes (T2D) is a worldwide concern that augments the rates of various micro- and macrovascular complications. About 40% of diabetic patients develop diabetic kidney disease (DKD), which leads to chronic kidney diseases (CKD) and end-stage renal disease (ESRD). Several biochemical and signal transduction mechanisms leading to DKD have been studied over the years, but the increasing rates of the disease indicate that we need a better understanding of the underlying molecular mechanisms. Since the number of protein-coding genes is limited, noncoding RNAs (ncRNAs) including microRNAs (miRNAs) and long noncoding RNA (lncRNA) have become attractive molecules for identifying drug targets for human diseases. (Kato, 2018) [8].
MiRNAs are a family of short noncoding RNAs they are endogenous gene regulators at posttranscriptional level, targeting complementary mRNA sequence and so promoting their degradation and/or interfering with their translation (Petrillo *et al.* 2017) [18]. MiRNAs molecules which are about 22 nucleotides in size inhibit the expression of a target mRNA

molecule by Binding to its 3'-UTR through complimentary base pairing (Nalluri & Barh, 2016) [15]. MiRNAs play important roles in cellular proliferation, apoptosis, and differentiation (Liu *et al.* 2014) [13]. Moreover, miRNAs have emerged as prognostic and predictive biomarkers for human diseases owing to their high stability and presence in blood, urine, and other body fluids (Kato & Natarajan, 2015) [2]. Many studies have confirmed the involvement of miRNA changes in the diabetes pathogenesis, both from T1D and T2D. Altered miRNAs level could serve as marker for diagnosis or prognosis; miRNAs and their targets could be further developed for therapeutic targets. (H. Zhang & Pollin, 2018) [25]. MiRNAs act at several points in the distinct pathways inducing insulin secretion or resistance, so they could be potential therapeutic targets for diabetes (Mafi *et al.* 2018) [14]. Recent successful clinical trial utilizing a miRNA therapeutic for suppression of hepatitis C virus replication have raised the possibility for developing miRNA-based therapeutics for other diseases as well (Bhatt *et al.* 2015) [2].

2. Diabetes and its Complication

Diabetes mellitus (DM) is a group of chronic metabolic disorders characterized by impaired glucose homeostasis that results in hyperglycemia due to increased insulin resistance in insulin sensitive tissues (liver, skeletal muscle, adipose tissue, etc.) and/or disturbance in insulin secretion in pancreatic β cells (Park *et al.* 2013) [17]. About 50% of diabetic patients have end-stage renal disease (ESRD), requiring painful and costly dialysis. Unfortunately, these diabetic patients also have a higher risk of macrovascular complications. It is now widely accepted that improved glycemic control reduces the development and delays the progression of microvascular complications in both TD-1 and TD-2 diabetes (Kato & Natarajan, 2015) [2]. It is a significant public health concern as its rising incidence has greatly increased the cost of treating both diabetes and its numerous debilitating complications (Liu *et al.* 2014) [13]. According to report of committee on the classification and diagnosis criteria of diabetes mellitus (Report, 2010) [19] diabetes complications constitute the major causes of morbidity and mortality in diabetic patients. Tissues adversely affected by diabetes may include cardiac and skeletal muscle, liver, kidney, and endothelium. Hyperglycemia and hyperlipedemia damage these tissues causing conditions such as fatty liver, stroke, kidney failure, neuropathy, and blindness (Fernandez-Valverde, Taft, & Mattick, 2011) [6]. The causes of diabetes mellitus are various, including both genetic and environmental factors. Insufficient insulin secretion can occur in association with destruction of pancreatic islet β cells or due to dysfunction within the pancreatic β cell themselves. Besides the decrease in insulin supply, decreased insulin sensitivity can contribute to relative insufficient insulin action. In either case, the principal mechanism for development of diabetes is decreased functional pancreatic β cell mass that results in failure to provide adequate insulin action on the organs (Report, 2010) [19]. nucleotides in size inhibit the expression of

3. Biogenesis of Micro RNA

The process of miRNA biogenesis occurs in both nucleus and cytoplasm (Mafi *et al.* 2018) [14]. miRNA is encoded by a specific DNA region called a "mitron," and stem-loop pri-miRNAs with hundreds of base pairs are synthesized under the action of RNA polymerase II (Zou & Zhang, 2018) [27]. Initially, miRNA genes are transcripted by RNA polymerase II; then, primary transcripts (pri-miRNAs) are capped and polyadenylated. The pri-miRNAs with several hairpin-like structures form the stem-loop precursor of miRNAs (~70 nucleotides long), which is modified by the ribonuclease III (Drosha) in a microprocessor complex or by DiGeorge syndrome critical region gene 8 (DGCR8) (Mafi *et al.* 2018) [14]. The resulting pre-miRNA hairpin is then exported from the nucleus to cytoplasm by a complex formed by Exportin 5 and Ran-GTP. In the cytoplasm, the RNase III enzyme Dicer in complex with TAR RNA binding protein (TRBP) cleaves the premiRNA hairpin to its mature length (~22-nt long), giving rise to a miRNA:miRNA* duplex (Akhtar *et al.* 2016) [1].

Finally, the duplex miRNAs with approximately 22 base pair double-strand RNAs are generated. The next step will be loading the miRNA strand (guide strand) into the RNA-induced silencing complex (RISC), while the other strand is rapidly degraded. The RISC complex is a multiprotein complex including the Argonaute (Ago) family and the mature miRNA, which is necessary for miRNA-mediated gene silencing. The miRNA-RISC can be the specified binding sites within the 3′-UTR of the target mRNA, depending on the degree of complementarily between the miRNA and the target mRNA transcript (Mafi *et al.* 2018) [14]. The main constituents of the RISC are members of the Argonaute (AGO) family that have robust endonuclease activity to degrade the target mRNAs or to block protein translation (Schena *et al.* 2014) [20]. Usually, one strand ("passenger" strand, also known as the star strand or "-5-p") of this short-lived duplex disappears, whereas the other strand ("guide" strand or "-3p") becomes the mature miRNA (Y. Zhang *et al.* 2017) [26]; so miRNAs can help with translational repression, protein synthesis inhibition, and accelerated transcript degradation through uncapping and deadenylation or mRNA cleavage (Mafi *et al.* 2018) [14].

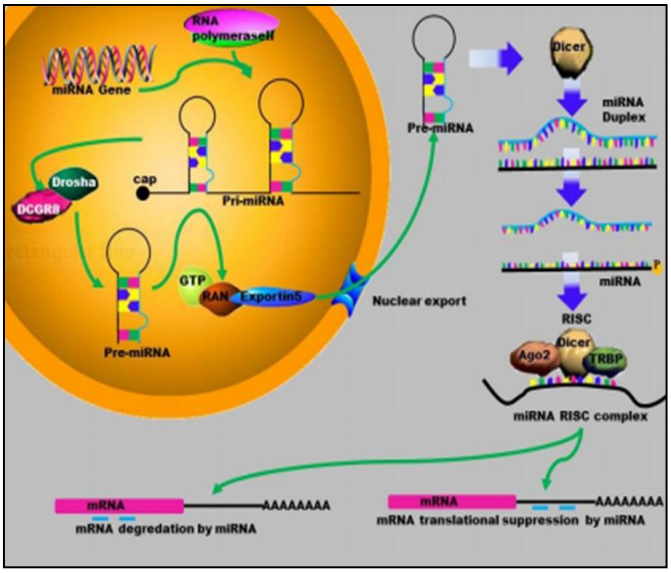

Fig 1: Biogenesis and maturation of miRNA both in the nucleus and cytoplasm.

4. Regulatory roles of Micro RNA in diabetes

4.1 Micro RNA and Diabetes

Current treatments for diabetes cannot efficiently control glycaemic levels, resulting in episodes of hyper- and hypoglycaemia, which increases the possibility of developing secondary complications such as retinopathy, nephropathy and neuropathy. The family of miRNAs has been found to have a major contribution in alteration of gene expression and is involved in β-cells dysfunction and insulin resistance.

Recent evidence show that miRNAs can play a role in regulating glucose homeostasis, through modifying the β-cell insulin producing function, insulin secretion and signaling pathways of insulin functions in peripheral tissues such as liver, muscle, and adipose tissue. Initially, the beneficial impacts of miRNAs were identified for different cancers. However, recently there has been a huge interest toward their application in other diseases, including diabetes (Mafi *et al.* 2018) [14].

4.1.1. MicroRNA and pancreatic β cells

Pancreatic α- and β-cells are the main cell types regulating glucose metabolism through the secretion of glucagon and insulin, respectively (Latreille *et al.* 2015) [11]. Pancreatic *B*-cells play a fundamental role in glucose homeostasis, releasing insulin in response to glucose levels in the bloodstream. Insulin then triggers glucose uptake in its target tissues, such as the liver, kidney, skeletal muscle, and cardiac muscle. Absence or malfunction of β -cells leads to diabetes due to lack of insulin producing cells (T1D), or to the inability to increase insulin levels to sufficiently stimulate glucose uptake in the face of insulin resistance (T2D) (Fernandez-Valverde *et al.* 2011) [6]. Generally, miRNA affect β-cells through the regulation of cell survival and apoptosis, proliferation, differentiation, or function, especially insulin secretion. To regulate β-cell survival and apoptosis, miRNAs usually function by targeting cell apoptosis-related genes, such as the pro-apoptotic gene Bax and the anti-apoptotic gene Bcl-2. In β-cell proliferation, some miRNAs play positive roles, while other miRNAs exhibit negative effects. One of the most important miRNA regulators is miR-375, which was originally reported as a pancreatic islet-specific miRNA (Hashimoto & Tanaka, 2017) [7]. And which is highly expressed in both human and mouse pancreatic β-cells and is indispensable in maintaining normal pancreatic β-cell mass. (Feng *et al.* 2016) [5].

4.1.2. MicroRNA and insulin resistance (IR)

IR refers to the impaired cellular response to insulin and the inability of normal amounts of insulin to achieve normal glucose homeostasis, which is a hallmark of T2DM. In this process, the insulin signaling pathway plays a central role. It is a highly complicated network that is initiated by insulin binding to the insulin receptor (INSR) on the cell surface, followed by the insulin receptor substrate launching downstream signaling cascades including phosphoinositide 3-kinase (PI3K), AKT serine/threonine kinase (AKT), and glucose transporter 4 (GLUT4). A growing body of evidence indicates that IR is associated with defects in insulin signaling. Notably, miRNAs may link insulin signaling and IR (Feng *et al.* 2016) [5].

5. MicroRNA as a potential biomarker for diabetes

5.1 Circulating microRNA as a novel biomarker for diabetes

There is heightened interest in evaluating miRNAs as a potential biomarker for various diseases especially because of improvement in the technologies for miRNA detection in vitro and in vivo. These include quantitative PCR, microarrays, and high throughput deep sequencing. MiRNAs are readily detectable in plasma and urine and their stability in these biofluids make them ideal candidate biomarker for noninvasive much needed early detection of diabetic complication. This is critical because such early detection can enhance clinical management, improve long term outcomes, and greatly increase quality of life (Kato, Castro, & Natarajan, 2013) [9]. The presence of miRNAs in the blood at first may seems surprising because serum contains ribonucleases (RNase). However, plasma miRNAs are resistant to RNase digestion and to several harsh laboratory conditions. As evidenced by many reports, miRNAs are not present in blood in native form but are released in microvesicular structures, such as exosomes or apoptotic bodies, and circulate in side membrane delimited vesicles that protect them from degradation. Circulating microvesicles are thought to favor cell to cell communication as well as to exchange genetic information between healthy and injured cells and tissues. Therefore, miRNA profiling from microvesicles circulating in the blood could reflect the physiopathological state of an individual. Results suggests that plasma miRNAs could vary according to healthy and disease state, making them attractive new biomarkers. In the context of diabetes, biomarkers could be particularly useful in preventing the development of the disease because diabetic patients generally are detected too late (Soo, Yu, & Chiu, 2006) [23].

5.1.1 Circulating miRNA biomarker for type-1 diabetes

The diagnostic approaches for T1D have been developed, there is a need to identify novel predictive molecules to identify and monitor disease progression with greater accuracy (Latreille *et al.* 2015) [11]. In recent study (Trionfini & Benigni, 2017) [24] showed that evidence that miR-375 can serve as a biomarker for detecting β cell death and predicting diabetes in mice. They show that circulating miR-375 levels increase rapidly in vivo upon injecting mice with the β cell toxin STZ, suggesting that there is a pool of miR-375 that is immediately released during β cell death. This increase precedes diabetes, demonstrating the utility of their method to detect β cell death before overt diabetes occurs. Moreover, this increase lasts about 1 week in the circulation, suggesting that miR-375 levels reflect recent β cell loss. These observations highlight the sensitivity of their detection system and indicate that assay of circulating miR-375 by qPCR may serve as a useful tool in clinical settings to detect ongoing β cell death. Thus, development of other predictive, noninvasive blood markers of β cell damage and diabetes, such as circulating miR-375 levels, is warranted. The quantification of miR-375 and/or other such miRNAs might have clinical utility to detect ongoing β cell death in patients with type 1 or type 2 diabetes (Erener *et al.* 2013) [4]. Recently reported by (Hashimoto & Tanaka, 2017) [7] the first comparison of miRNA levels in serum samples from children with or without type 1 diabetes. Those investigators identified 12 miRNAs (miR-152, miR-30a-5p, miR-181a, miR-24, miR-148a, miR-210, miR-27a, miR-29a, miR-26a, miR-27b, miR-25 and miR-200a) that were differentially expressed in patients with type- 1 diabetes. Interestingly, some of the miRNAs are associated with apoptosis (miR-24, miR-25, miR-26a, miR-181a and miR-210) and regulation of pancreatic β cells (miR-24, miR-29a, miR-148a and miR 200a).

5.1.2 Circulating miRNA for type-2 diabetes

In 2014 Liu *et al.* investigated that circulating miR-126 could be used to distinguish T2DM patients, as well as pre-diabetic subjects from healthy subjects. Further studies with a large cohort of patients are required to validate and develop miR-126 as a serum biomarker for T2DM and pre-diabetes, and possibly for monitoring disease progression and treatment response. These results encourage the use of serum miR-126

as a biomarker for pre-diabetes and diabetes mellitus, as well as therapeutic response. As reported by (Soo *et al.* 2006) [23] the comparison of pooled plasma miRNAs from diabetic subjects with age and sex-matched controls led to the identification of 13 miRNAs differently expressed in diabetic patients. Among them the expression of 5 miRNAs (miR-15a, miR-28-3p, miR-126, miR-223 and miR-320) already was altered before the manifestation of the diabetes. The determination of the levels of this cluster of 5 miRNAs was sufficient to identify 70% of the type 2 diabetic patients. The diabetic subjects escaping detection had lower fasting glucose levels or were patients with well controlled diabetes. The validity of this miRNA signatures as a tool to diagnose type 2diabetes remains to be confirmed by other large independent studies. And also, Cross-sectional studies disclosed a marked increase of miR-140-5p, miR-142-3p, and miR-222 and decreased miR-423-5p, miR-125b, miR-192, miR-195, miR-130b, miR-532-5p, and miR-126 in T2D patients (Ortega *et al.* 2014). Another study analyzed blood samples of 265 individuals that included patients with metabolic syndrome, type 2 diabetes, hypercholesterolemia and hypertension, and observed upregulation of miR-150, miR-192, miR-27a, miR-320a and miR-375 in type 2 diabetes patients. Of these, levels of miR-27a and miR-320a correlated strongly with fasting glucose level (Hashimoto & Tanaka, 2017) [7].

In addition, microarray profiling studies identified the miRNAs miR-144, miR-146a, miR-150, and miR-182 as four diabetes-related miRNAs in rat peripheral blood. Among these miRNAs, circulating miR-144 levels were correlated with a reduction in the expression of its target, IRS1, at both the mRNA and protein levels, implying a new potential diagnostic and therapeutic target of type 2 diabetes (Y. Zhang *et al.* 2017) [26]. Many studies have shown that circulating miRNAs are remarkably stable in body fluids. However, a recent study demonstrated that circulating levels of some miRNAs are reduced in plasma samples of patients with severe chronic renal failure when compared with subjects with mild renal impairment or minimal renal function. These findings have important implications for the use of circulating miRNAs as biomarkers in individuals with severe renal damage (Schena *et al.* 2014) [20].

6. Micro RNA based therapeutics

Because of the role of miRNAs in regulating several path ways, miRNA should the promise of being able to yield a new class of therapeutics. Basically, miRNA-based therapies comprise two approaches: miRNA inhibition or replacement (Trionfini & Benigni, 2017) [24]. The role of miRNAs in the pathophysiology of several renal diseases may open new avenues for a miRNA-based therapy. Recently, a great interest of the scientific community has been focused on the use of chemically engineered antisense oligonucleotides targeting specific miRNAs termed mimics or antagomirs when able to reproduce or inhibit specific miRNA function, respectively (Petrillo *et al.*, 2017) [18]. Currently, there are three main strategies available for inactivating miRNAs whose expression is increased in a particular disease: individual miRNA knockout, sponge miRNA, and antisense oligonucleotide (Distefano *et al.* 2013) [3].

6.1 Individual miRNA Knockout

This is the only approach that guarantees a complete loss of miRNA activity and, therefore, this is the best method to functionally characterize a particular miRNA and determine if its total inactivation causes secondary effects. The drawback is that the generation of engineered animals is costly and time consuming (Distefano *et al.* 2013) [3].

6.2 Sponge miRNA

These are small RNA transcripts containing multiple copies of the target-binding site for a miRNA of interest, which are produced from transgenes within cells. Sponges provide alternative binding sites for miRNAs, and thereby sequester them from interaction with downstream targets. Although this method has the advantage of being able to simultaneously down regulate miRNAs with functional redundancy, it cannot distinguish between miRNAs with the same seeding. Thus, sponge miRNA is a good method to study the combined effect of a whole family of related miRNAs, but not to functionally characterize an individual miRNA (Distefano *et al.* 2013) [3].

6.3 Antisense Oligonucleotide (ASO)

This is the most commonly used method to inhibit miRNA activity, and the one with the highest potential for the development of miR-based therapeutics for different diseases, including diabetic nephropathy. ASO is a single-stranded reverse complement oligonucleotide, which sequesters the mature miRNA and precludes its binding to the target sequence (Distefano *et al.* 2013) [3]. The tendency to control the expression of miRNAs levels using chemically modified, stable, nuclease-resistant oligonucleotides (miRNA inhibitors and mimics) could be developed for the treatment of patients in the future (Mafi *et al.* 2018) [14].

7. Conclusion

Generally, diabetes is a significant public health concern as its rising incidence has greatly increased the cost of treating both diabetes and its numerous debilitating complications these complications constitute the major causes of morbidity and mortality in diabetic patients. In the context of diabetes, biomarkers could be particularly useful in preventing the development of the disease because diabetic patients generally are detected too late so, miRNA with the help of the current advanced technology including microarrays and quantitative PCRs followed by high throughput generation sequencing in detecting diabetes is promising. Therefore, miRNAs have helped researchers in developing miRNAs as a therapeutic target and a reliable potential biomarker. Because of they are readily detectable in plasma and urine and their stability in these biofluids make them ideal candidate biomarker for noninvasive much needed early detection of diabetic complication.

Therefore, the role of miRNAs in the pathophysiology of several renal diseases may open new avenues for a miRNA-based therapy mainly because of its relevance in the development of diagnostic, prognostic and therapeutic strategies.

8. Reference

1. Akhtar MM, Micolucci L, Islam MS, Olivieri F, Rocopio AD *et al.* Bioinformatic tools for microRNA dissection. Nucleic Acids Research. 2016; 44(1):24-44.
2. Bhatt K, Kato M, Natarajan R. Emerging Roles of microRNAs in the Pathophysiology of Renal Diseases. American Journal of Physiology-Renal Physiology, 2015 (98), ajprenal.00387.2015.
3. Distefano JK, Taila M, Alvarez ML. Emerging roles for miRNAs in the development, diagnosis, and treatment of diabetic nephropathy. Current Diabetes Reports. 2013; 13(4):582–591.

4. Erener S, Mojibian M, Fox JK, Denroche HC, Kieffer TJ. Circulating miR-375 as a biomarker of ??-cell death and diabetes in mice. Endocrinology. 2013; 154(2):603-608.
5. Feng J, Xing W, Xie L. Regulatory roles of microRNAs in diabetes. International Journal of Molecular Sciences. 2016; 17(10):1-12. https://doi.org/10.3390/ijms17101729
6. Fernandez-Valverde SL, Taft RJ, Mattick JS. MicroRNAs in ??-cell biology, insulin resistance, diabetes and its complications. Diabetes. 2011; 60(7):1825-1831.
7. Hashimoto N, Tanaka T. Role of miRNAs in the pathogenesis and susceptibility of diabetes mellitus. Journal of Human Genetics. 2017; 62(2):141-150.
8. Kato M. Noncoding RNAs as therapeutic targets in early stage diabetic kidney disease. 2018; 2018(3):197–209.
9. Kato M, Castro NE, Natarajan R. MicroRNAs: Potential mediators and biomarkers of diabetic complications. Free Radical Biology and Medicine. 2013; 64:85-94.
10. Kato M, Natarajan R. MicroRNAs in diabetic nephropathy: Functions, biomarkers, and therapeutic targets. Annals of the New York Academy of Sciences. 2015; 1353(1):72-88.
11. Latreille M, Herrmanns K, Renwick N, Tuschl T, Malecki MT, McCarthy MI *et al.* miR-375 gene dosage in pancreatic β-cells: implications for regulation of β-cell mass and biomarker development. Journal of Molecular Medicine. 2015; 93(10):1159–1169. https://doi.org/10.1007/s00109-015-1296-9
12. Li R, Chung AC, K Yu X, Lan HY. microRNAs in Diabetic Kidney Disease. - PubMed - NCBI, 2014.
13. Liu Y, Gao G, Yang C, Zhou K, Shen B, Liang H, *et al.*.. The role of circulating microRNA-126 (miR-126): A novel biomarker for screening prediabetes and newly diagnosed type 2 diabetes mellitus. International Journal of Molecular Sciences. 2014; 15(6):10567–10577. https://doi.org/10.3390/ijms150610567
14. Mafi A, Aghadavod E, Mirhosseini N, Mobini M, Asemi Z. The effects of expression of different microRNAs on insulin secretion and diabetic nephropathy progression. Journal of Cellular Physiology, 2018, 1-9. https://doi.org/10.1002/jcp.26895
15. Nalluri JJ, Barh D. Towards a Comprehensive Understanding of miRNA Regulome and miRNA Interaction Networks. Journal of Pharmacogenomics & Pharmacoproteomics, 2016, 7(3). https://doi.org/10.4172/2153-0645.1000160
16. Ortega FJ, Mercader JM, Moreno-Navarrete JM, Rovira O, Guerra E, Esteve E *et al.* Profiling of circulating microRNAs reveals common microRNAs linked to type 2 diabetes that change with insulin sensitization. Diabetes Care, 2014); 37(5): 1375–1383. https://doi.org/10.2337/dc13-1847
17. Park SY, Jeong HJ, Yang WM, Lee W. Implications of microRNAs in the pathogenesis of diabetes. Archives of Pharmacal Research. 2013; 36(2):154-166.
18. Petrillo F, Iervolino A, Zacchia M, Simeoni A, Masella C, Capolongo G *et al.* MicroRNAs in Renal Diseases: A Potential Novel Therapeutic Target. Kidney Diseases. 2017; 3(3):111–119. https://doi.org/10.1159/000481730
19. Report S. Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus, 2010, 1(5). https://doi.org/10.1111/j.2040-1124.2010.00074.x
20. Schena FP, Serino G, Sallustio F. MicroRNAs in kidney diseases: New promising biomarkers for diagnosis and monitoring. Nephrology Dialysis Transplantation. 2014; 29(4):755-763.
21. Sethupathy P. The Promise and Challenge of Therapeutic MicroRNA Silencing in Diabetes and Metabolic Diseases. Current Diabetes Reports. 2016; 16(6):2-7.
22. Simpson K, Wonnacott A, Fraser DJ, Bowen T. MicroRNAs in Diabetic Nephropathy: From Biomarkers to Therapy. Current Diabetes Reports. 2016; 16(3):1-7.
23. Soo SC, Yu KM, Chiu WK. Modeling and fabrication of artistic products based on IFS fractal representation. CAD Computer Aided Design, 2006; 38(7):755-769.
24. Trionfini P, Benigni A. MicroRNAs as Master Regulators of Glomerular Function in Health and Disease. Journal of the American Society of Nephrology, 2017; 28(6):1686-1696.
25. Zhang H, Pollin TI. Epigenetics Variation and Pathogenesis in Diabetes. Current Diabetes Reports. 2018; 18(11):1-7. https://doi.org/10.1007/s11892-018-1091-4.
26. Zhang Y, Sun X, Icli B, Feinberg MW. Emerging roles for microRNAs in diabetic microvascular disease: Novel targets for therapy. Endocrine Reviews. 2017; 38(2):145-168.
27. Zou YF, Zhang W. Role of microRNA in the detection, progression, and intervention of acute kidney injury. Experimental Biology and Medicine, 2018; 243(2):129-136.