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Original Article

Association of MicroRNA-103 expression with type 2 diabetes mellitus

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Abstract

Background: Type 2 diabetes mellitus (T2DM), the most prevalent metabolic disorder worldwide, has genetic, epigenetic, and environmental contributors. Among them, circulating microRNAs (miRNAs/miRs) have attracted considerable attention. This study aimed to investigate the regulatory role of miR-103 in T2DM development.

Methods: The miR-103 expression was evaluated in 33 participants with T2DM compared with 38 healthy controls using quantitative real-time polymerase chain reaction (q-RT PCR). Fasting blood glucose (FBS), fasting insulin (Fin), hemoglobin A1c (HbA1c), triglycerides (TG), and cholesterol (Chol) were also determined in serum. Basal insulin resistance and sensitivity were determined using the homeostasis model assessment insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), respectively.

Results: There was a significant decrease in miR-103 levels in patients with T2DM ($p<0.002$). Serum miR-103 expression levels showed a strong correlation with age, FBS, HbA1c, TG, Chol levels, and HOMA-IR and QUICKI indices.

Conclusion: The downregulation of miR-103 in T2DM patients suggests the diagnostic potential of miR-103 evaluation in conjunction with other diagnostic approaches.

Keywords: MicroRNAs, miR-103, Type 2 diabetes mellitus, Insulin resistance.

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The most prevalent metabolic disease worldwide is type 2 diabetes mellitus (T2DM), accounting for over 90% of all diabetes cases (1). The incidence of T2DM has doubled in the last 30 years and is estimated to double in the next 20 years, making it a significant global burden (2, 3). T2DM is characterized by glucose homeostasis impairment and occurs due to a defect in either insulin secretion (progressive beta-cell dysfunction) or function, followed by impaired glucose tolerance (IGT), hyperglycemia, and insulin resistance (IR) (4, 5).

IR refers to resistance to insulin-mediated glucose uptake, whether endogenous or exogenous insulin caused by dysregulated insulin signaling in target tissues. The temporal priority of the onset of IR and beta cell dysfunction is still inconsistent in the literature. The majority of patients with T2DM are expected to be obese, which can lead to some degree of insulin resistance (1). However, this progressive condition is associated with organ damage, malfunction, and failure, which may ultimately lead to some long-term complications including retinopathy, nephropathy, and neuropathy with the risk of foot ulceration, hypertension, Charcot arthropathies, sexual dysfunction, dyslipidemia, and cardiovascular disease (1, 6-10). Despite all these significant complications, T2DM is usually diagnosed late because hyperglycemia is not severe enough in the early stages (1).

Given the growth of the world's elderly population, changing lifestyle and dietary patterns, and increasing obesity, this growing global burden must be prevented by understanding the exact underlying mechanism followed by early diagnosis (5, 11-13).

The development and progression of T2DM may be affected by several genetic, epigenetic and environmental factors. Among them, some dysregulated microRNAs (miRs or miRNAs) dysregulations have been associated with glucose homeostasis, insulin sensitivity, and T2DM onset. These miRs are considered potential biomarkers and are referred to as "riboregulators of glucose homeostasis" (5, 11-13). MiRs are small (approximately 22 nucleotides), conserved, endogenous, single-strand non-coding RNAs that regulate the expression of multiple target genes, primarily through post-transcriptional gene regulation (5). They regulate the expression of messenger RNAs (mRNAs) either through transcriptional degradation or translational inhibition due to complementary binding, mainly to the 3′ untranslated region (3′UTR) of target, depending on complete or partial matching, respectively (11). Zhu et al. perform a meta-analysis reporting 151 differentially expressed miRNAs in cultured cells, blood, or tissue samples (e.g., liver, adipose tissue, pancreas, and muscle) of T2DM in humans and animal models, of which only 51 are significantly differentially expressed. They introduced 8 miRs (miR-29a, miR-34a, miR-103, miR-107, miR-132, miR-142-3p, miR-144, and, miR-375) as possible T2DM markers (14).

Reports suggest that circulating miRs, which exist outside the cells in various body fluids, including plasma, serum, and urine, may be more promising biomarkers for T2DM diagnosis because of their circulating stability and unique expression patterns. In addition, they can be more easily detected by less invasive techniques (12). Among all miRs, miR-103 has an interesting history; shreds of evidence revealed that overexpression of miR-103/107 (which, surprisingly, differs by only one nucleotide) results in the downregulation of the insulin signaling pathway in diet-induced obese mice (15).

Therefore, miR-103 may serve as an insulin sensitivity modulator and a new target for T2DM diagnosis and/or treatment. As the literature shows, a wide range of conflicting findings on whether mir-103 is up-or down-regulated in T2DM, there was no consistent evidence to support the trend of mir-103 expression in this condition (14, 16-19). Therefore, this work was designed to investigate the mir-103 expression level along with some other biochemical markers in T2DM patients compared with healthy controls.

Methods

Participants: Serum samples were collected from 33 patients suffering from T2DM and 38 healthy participants who were supposed as controls. The participants with T2DM were all newly diagnosed outpatients who were not taking any medications for their condition at the time. T2DM was confirmed based on WHO guidelines with fasting glucose levels greater than 126 mg/dl (19). Exclusion criteria included diabetic foot, active nephropathy, retinopathy, cardiovascular disease, high blood pressure, acute infection, chronic inflammation, and malignant tumors. Weight (kg)/height $(m)^2$ was the formula used to determine body mass index (BMI) (20). The Ethics Committee of Babol University of Medical Sciences approved the study methodology, and all participants signed written informed consent forms prior to the study.

Measurements: Ten milliliters of peripheral blood were collected from all participants after a 10-12 hour fast, which were immediately centrifuged at 3000g for 10 minutes, serum was separated, and stored at -80°C until further study. Glucose, insulin, hemoglobin A1c (HbA1c), cholesterol (Chol), triglyceride (TG), and miR-103 levels were determined in serum. Fasting insulin (Fins) was measured using the Monobind Insulin ELISA kit with a 0.114 µIU/mL sensitivity. The ion exchange chromatography column (Biosystems kit, Spain) was used to measure HbA1c. The HOMA model was utilized to determine the insulin resistance index, or homeostasis model assessment insulin resistance (HOMA-IR): (fasting insulin × fasting glucose)/22.5 (21). The following model was used to calculate the quantitative insulin sensitivity check index (QUICKI): 1 / (log(fasting insulin µU/mL) + log(fasting glucose mg/dL)) (22).

RNA extraction and cDNA synthesis: Using Trizol reagent and the company's instructions, total RNA was extracted from serum samples (Invitrogen, Carlsbad, CA, USA) and a NanoDrop spectrophotometer (Thermo Scientific, Wilmington, USA) was used to assess its concentration and quality. For cDNA synthesis, specific primers were designed for miR-103a-3p and miR-16 (as endogenous control) (table 1). Briefly, a 10 µL reaction mixture comprising 4.5 µL RT Master Mix and 4.5 µL water treated with diethyl pyrocarbonate (DEPC) was filled with 160 ng total RNA, which is equivalent to one µL RNA. The mixture was then incubated in a peqSTAR thermocycler (PEQLAB Biotechnology GMBH, Erlangen, Germany) at 16, 42, and 72 ^{0}C for 30, 30, and 10 minutes, respectively.

Quantitative Real-time polymerase chain reaction: Using SYBR-Green/ROX qPCR Master mix 2X protocol (Qiagen Rotor-Gene Q, Germany), one µL of the generated cDNA was subjected to qRT-PCR to assess the differential expression levels of miR-103 and miR-16 as a target gene

and an endogenous gene, respectively. Every qPCR reaction was carried out in a 20 µL total volume that included one µL of each primer, one µL cDNA, seven µL DEPC water, and 10 µL of Master Mix. The qPCR temperature profile used for the qPCR consisted of 40 cycles of 95 and 60 ^{0}C for 12 and 30 seconds, respectively, after 10 minutes of denaturation at 95˚C. The fold change ratio of miR-103 expression was determined by $2^{-\Delta\Delta CT}$±SEM. Polyacrylamide gel electrophoresis (PAGE) and melting curve analysis were performed as a measure of amplification specificity.

Statistical analysis: SPSS Version 24.00 was used for all statistical analyses (SPSS Inc., Chicago, IL). For continuous variables, descriptive characteristics of the participants based on their diabetic status were reported as mean ± SD. For the purpose of assessing clinical and demographic differences across groups, the Mann-Whitney U test was employed. Next, a receiver operating characteristic (ROC) curve was plotted for the cut-off values of mir-103-fold change, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The impact of clinical factors (miR-103-fold change, age, triglycerides, cholesterol, and Fins) on diabetic status was modeled using binary logistic regression modeling. Next, in a multivariate two-way general linear model, the participant groups and the miRNA-103 expression were incorporated as independent and dependent variables, respectively. Multiple linear regression models with backward entry of independent variables were employed. Multivariable-adjusted odds ratios (ORs) with 95% confidence intervals were used to present the results, and statistical significance was defined as p-values less than 0.05.

Table 1. The primer sequences for cDNA synthesis and q-RT PCR

miRbase accession number	Primer Name	Sequence (5'-3')
MIMAT0000101	**hsa-miR-103a-3p-RT**	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACTCATAGC
	hsa-miR-103a-3p-forward	AGCAGCATTGTACAGGGCTATG
MIMAT0000069	**hsa-miR-16-5p-RT**	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACCGCCAAT
	hsa-miR-16-5p-forward	GGTAGCAGCACGTAAATATTGGCG
	Universal-reverse	GTGCAGGGTCCGAGGT

Results

Demographic and clinical characteristics: Seventy-one persons participated in this study, including 33 type 2 diabetes mellitus (14 males and 19 females) and 38 healthy controls (20 males and 18 females). To assess the BMI potential impact on FBS levels, all participants were split into three groups (<25, 25-29.9, and ≥30 kg/m^2). The result of chi-squared tests revealed no significant difference among BMI subgroups. Groups were significantly different for fasting blood glucose, HbA1c, HOMA-IR, QUICKI, triglyceride, cholesterol, and mir-103-fold change, except for Fins level. FBS, HbA1c, HOMA-IR, triglyceride, and cholesterol in T2DM patients were significantly higher, and QUICKI and mir-103-fold change were lower than in healthy controls (table 2).

The serum expression of miR-103: Firstly, the Shapiro-Wilk test was performed to determine if the variables deviated from the standard curve, and the finding indicated that they did. To evaluate the demographic and clinical differences, the Mann-Whitney U test was employed. The findings demonstrated that T2DM patients' expression of miR-103 was considerably lower than that of healthy individuals (1.52 ±0.81-fold change vs. 0.99±1.06, p<0.002) (figure 1).

The diagnostic potential of miR-103 to discriminate T2DM: The accuracy, sensitivity, and specificity of serum miRNA expression levels were evaluated in a receiver operating characteristic (ROC) analysis to examine its potential as a predictive biomarker for T2DM. The ROC curves area and under the ROC curve (AUC) were utilized to discriminate between individuals with and without T2DM. The cut-off value of 1.05 miR-103-fold change demonstrated the optimum diagnostic accuracy to discriminate two groups according to the ROC analysis: AUC= 0.715 (95% CI= 0.591-0.839); sensitivity= 60.6%; specificity= 34.2%; positive predictive value (PPV)= 49.21% and negative predictive value (NPV)= 51.35% (figure 2).

Table 2. The demographic and clinical features of the participants based on diabetic status

Demographic Characteristics				
		Control (n=38)	T2DM (n=33)	P value
Number	Male	20	14	0.39
	Female	18	19	
Age (yrs)		41.29±6.80	48.06±9.52	0.002
BMI (kg/m^2)	<25	10 (26.3%)	5 (15.2%)	0.373
	25-29.9	17 (44.7%)	14 (42.4%)	
	≥30	11 (28.9%)	14(42.4%)	
Clinical Characteristics				
FBS (mg/dL)		86.76±11.17	209.97±70.67	< 0.001
Fins (µIU/mL)		8.21±4.42	8.052±5.66	0.433
HbA1c (%)		5.35±.60	8.62±2.38	< 0.001
Chol (mg/dL)		192.89±31.84	237.00±69.07	0.001
TG (mg/dL)		159.13±68.86	219.45±229.29	0.012
HOMA-IR		1.8031±1.10045	3.8155±2.61	< 0.001
QUICKI		0.3607±0.03424	0.3270±0.0385	< 0.001
mir-103 Fold change		1.52 ±0.81	0.99±1.06	0.002

BMI: Body Mass Index, FBS: Fasting Blood Sugar, Fins: Fasting Insulin, HbA1c: Hemoglobin A1c, Chol: cholesterol, TG: Triglyceride, HOMA-IR: homeostasis model assessment insulin resistance, and QUICKI: quantitative insulin sensitivity check index.

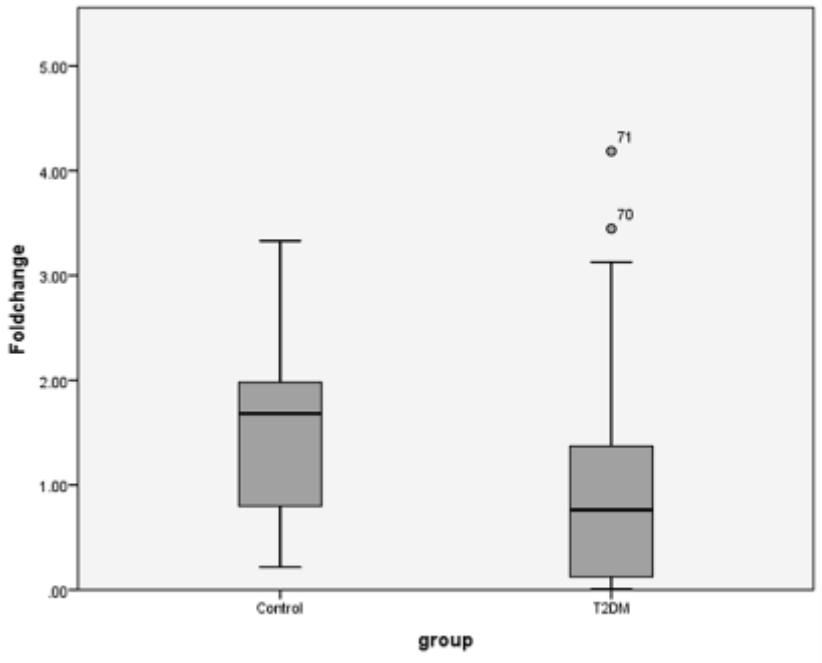

Figure 1. Differential serum expression of miR-103 in T2DM patients compared with healthy controls

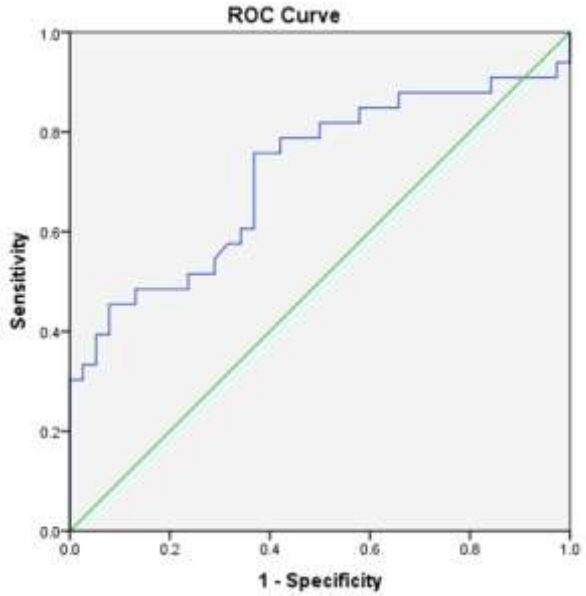

Figure 2. Diagnostic accuracy of serum miR-103 expression to discriminate T2DM patients from healthy controls (AUC=0 .715, %95 CI: 0.591- 0.839)

Association of miRNA levels with clinical manifestations: Backward multiple linear regression models were utilized to further analyze the impact of miR-103-fold change, age, TG, Chol, and Fins, which were suspected to have a confounding effect in predicting the risk of T2DM. We included T2DM and control groups as dependent variables and miR-103-fold change, age, TG, Chol, and Fins as independent variables. The regression model indicated that although fold change alone could be a discriminating factor for T2DM, age, and cholesterol were more reliable predictors of T2DM compared to miR-103-fold change (table 3).

Table 3. Binary logistic regression analysis of factors affecting T2DM

	P value	OR	95% CI
miR-103 Fold change	0.161	0.622	0.319-1.209
Age	0.039	1.080	1.004-1.162
TG	0.859	1.001	0.991-1.011
CHOL	0.041	1.018	1.001-1.037
Fins	0.475	0.960	0.857-1.074

TG: Triglyceride, CHOL: Cholesterol; Fins: Fasting Insulin

Discussion

This study investigated the levels of miR-103 expression in patients with T2DM. According to our findings, miR-103 expression was slightly lower in patients with T2DM than in healthy individuals. This finding is consistent with Q Xu et al.'s study which demonstrated higher miR-103/107 serum expression in patients with T2DM compared to controls (23). They also discovered a noticeable association between miR-103/107 expression and HOMA-IR, a leading indicator of insulin resistance that is crucial for the onset of T2DM. They also have discovered a positive correlation between increased serum miR-103 expression and HOMA-IR in non-alcoholic fatty liver disease patients (24). Similarly, we found that miR-103 serum expression levels were correlated with age, FBS, HbA1c, TG, Chol levels, and HOMA-IR and QUICKI indices, suggesting the miR-103 involvement in glucose and lipid metabolism. In contrast to our findings and those of Q Xu et al., some studies have reported controversial findings regarding miR-103 expression in obesity, which is closely associated with

T2DM. For instance, miR-103 expression was reduced in whole blood in both sexes of obese individuals. Additionally, the plasma level of miR-103 showed a significant association with lower pregnancy weight gain in gestational obese women. These reports suggest that miR-103 may have differential roles in obesity and T2DM (25, 26). Herrera et al. previously presented the expression pattern of some miRs in the insulin target tissues of three rat strains with different glycemic statuses. The miR-103 liver expression profile showed an apparent upregulation with increasing strain-specific glycemic phenotype (27). In addition, Vatandoost et al. found elevated levels of miR-103 in peripheral blood mononuclear cells (PBMC) of T2DM as well as pre-diabetic rats compared to normal healthy controls (28). These reports suggest that miR-103 may function differently in various tissues and animal species.

The miR-103/107 gene sequence is situated inside the pantothenate kinase (PANK) gene's introns, which is involved in the coenzyme A (CoA) synthesis pathway that regulates levels acetyl-CoA in cells. Mir-103/107 targets insulin receptor substrate-1 (IRS-1), which promotes glucose uptake and insulin signaling via the caveolae protein Cav-1 (15, 29). In rodents, mir-103/107 knockdown and subsequent upregulation of Cav-1 resulted in increased insulin signaling and insulin-stimulated glucose uptake. Mir-103/107, in contrast, indirectly reduces the IRS-1 expression by decreasing its stability and interaction with Cav-1, thereby reducing the efficiency of insulin signaling. In other words, mir-103/107 indirectly decreases IRS-1 expression, the main mediator in insulin signaling pathway, by reducing its stability and interaction with Cav-1 (12, 15).

Furthermore, there are two isoforms in the mir-103 family: miR-103a and miR-103b. While miR-103a influences insulin sensitivity and glucose homeostasis in obesity and T2DM, it has been reported that that platelet-derived miR-103b may be utilized as a diagnostic marker for T2DM (5). It was reported that pre-DM and T2DM subjects had significantly higher and lower levels of circulating miR-103a and miR-103b, respectively. The negative association between reduced levels of CAV-1 and increased expression of miR-103a suggests that miR-103a may have a complementary regulatory binding site in the 3′UTRs of CAV-1. Additionally, a negative correlation was found between decreased plasma miR-103b and increased levels of its target frizzled-related protein 4 (SFRP4) (29).

The three paralogs of mir-103, including miR-103-1, miR-103-2, and miR-107, are all encoded by a sequence within the PANK gene, which its enzyme product phosphorylates the pantothenate (Vitamin B5) in the coenzyme A (CoA) synthesis pathway. This rate-limiting step regulates the cellular Acetyl-CoA levels that account for over a hundred reactions, including carbohydrate and lipid metabolism (30).

According to H. Xie *et al.*, the ectopic expression of some miRNAs in obese mice were upregulated during the differentiation of 3T3-L1 adipocyte cells while in the obese state, they tend to be downregulated. For example, mir-103 expression showed a 9-fold increase during adipogenesis as measured by triglyceride accumulation. They also suggested that TNF-α treatment provides a chronic local inflammatory environment and reduces adipogenesis accompanied by decreased miR-103 and miR-143 expression (31). Expression of miR-103, together with that of miR-143, was found to be associated with the upregulation of some pro-adipogenic factors in early stages, such as peroxisome proliferator-activated receptor (PPAR2), G0/G1 switch 2 (G0s2), fatty acid binding protein 4 (FABP4), glucose transporter 4 (GLUT4) and adiponectin. Moreover, they introduce a long list of downstream effectors for these miRs that are associated with metabolism of acetyl-CoA and lipids, among which Cav-1 is remarkable (30, 31).

Our study concludes that miR-103 expression is downregulated in patients with T2DM. However, considering our modest cross-sectional design of the assay, its predictive value is not sufficiently strong. Therefore, more extensive research is required to substantiate this assertion. Nevertheless, evaluating the expression of miR-103 alongside other diagnostic methods could enhance our comprehension of the pathogenesis of T2DM and present innovative therapeutic possibilities. The findings of current study, when combined with those of earlier research, suggest that miR-103 may have varying roles in different tissues, species, and metabolic conditions.

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Ethics approval: The study protocol was approved by the Ethics Committee of our University and informed written consent was obtained from all participants before the beginning of the study.
Conflict of interests: The authors declare no conflicts of interest.

Authors' contribution: Mahnoosh Rafiee conceived and Hadi Parsian designed the project. Mahnoosh Rafiee, Farzin Sadeghi, Ali Mirzapour and Bahare Korani acquired the data. Atiyeh Al-e-Ahmad, Soraya Khafri Hadi Parsian analyzed and interpreted the data. Atiyeh Al-e-Ahmad and Hadi Parsian wrote the paper.

References

1. Association AD. Diagnosis and classification of diabetes mellitus. Diabetes care 2010; 33: S62-9.
2. Lau E, Carvalho D, Pina-Vaz C, Barbosa JA, Freitas P. Beyond gut microbiota: understanding obesity and type 2 diabetes. Hormones (Athens) 2015; 14: 358-69.
3. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87: 4-14.
4. Barker A, Langenberg C, Wareham NJ. Genetic determinants of glucose homeostasis. Best Pract Res Clin Endocrinol Metab 2012; 26: 159-70.
5. Chakraborty C, Doss CGP, Bandyopadhyay S, Agoramoorthy G. Influence of miRNA in insulin signaling pathway and insulin resistance: micro-molecules with a major role in type-2 diabetes. Wiley Interdiscip Rev RNA 2014; 5: 697-712.
6. Schlienger J-L. Type 2 diabetes complications. Presse Med 2013; 42: 839-48. [in French]
7. Avogaro A, Giorda C, Maggini M, et al. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. Diabetes Care 2007; 30: 1241-7.
8. Happich M, Breitscheidel L, Meisinger C, et al. Cross-sectional analysis of adult diabetes type 1 and type 2 patients with diabetic microvascular complications from a German retrospective observational study. Curr Med Res Opin 2007; 23: 1367-74.
9. De Mattia G, Bravi MC, Laurenti O, et al. Endothelial dysfunction and oxidative stress in type 1 and type 2 diabetic patients without clinical macrovascular complications. Diabetes Res Clin Pract 2008; 79: 337-42.
10. Connelly K, Kelly D, Gilbert R. Clinically relevant models of diabetic cardiac complications. Circ Res 2007; 101: e78.
11. Vienberg S, Geiger J, Madsen S, Dalgaard LT. Micro RNA s in metabolism. Acta Physiol (Oxf) 2017; 219: 346-61.
12. Feng J, Xing W, Xie L. Regulatory roles of microRNAs in diabetes. Int J Mol Sci 2016; 17: 1729.
13. Pandey AK, Agarwal P, Kaur K, Datta M. MicroRNAs in diabetes: tiny players in big disease. Cell Physiol Biochem 2009; 23: 221-32.
14. Zhu H, Leung SW. Identification of microRNA biomarkers in type 2 diabetes: a meta-analysis of controlled profiling studies. Diabetologia 2015; 58: 900-11.
15. Trajkovski M, Hausser J, Soutschek J, et al. MicroRNAs 103 and 107 regulate insulin sensitivity. Nature 2011; 474: 649-53.
16. Guay C, Roggli E, Nesca V, Jacovetti C, Regazzi R. Diabetes mellitus, a microRNA-related disease? Transl Res 2011; 157: 253-64.
17. Hamar P. Role of regulatory micro RNAs in type 2 diabetes mellitus–related inflammation. Nucleic Acid Ther 2012; 22: 289-94.
18. McClelland AD, Kantharidis P. microRNA in the development of diabetic complications. Clin Sci (Lond) 2014; 126: 95-110.
19. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. 2006. Available from: (It's not found, pleas add URL). Accessed Jul, 0?, 202?.
20. Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. Nutr Today 2015; 50: 117-28.
21. Song Y, Manson JE, Tinker L, et al. Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women: the Women's Health Initiative Observational Study. Diabetes Care 2007; 30: 1747-52.
22. Hřebíček Ji, Janout Vr, Malinčíková J, Horáková D, Cížek Lk. Detection of insulin resistance by simple quantitative insulin sensitivity check index QUICKI for epidemiological assessment and prevention. J Clin Endocrinol Metab 2002; 87: 144-7.
23. Xu Q, Shang Y, Li Y, et al. MicroRNAs 103 and 107 link type 2 diabetes and post-menopausal breast cancer. Int J Diabetes Dev Ctries 2016; 36: 40-4.
24. Xu Q, Li Y, Shang YF, Wang HL, Yao MX. miRNA-103: molecular link between insulin resistance and nonalcoholic fatty liver disease. World J Gastroenterol 2015; 21: 511-6.
25. Murri M, Insenser M, Fernández-Durán E, San-Millán JL, Escobar-Morreale HF. Effects of polycystic ovary syndrome (PCOS), sex hormones, and obesity on circulating miRNA-21, miRNA-27b, miRNA-103, and miRNA-155 expression. J Clin Endocrinol Metab 2013; 98: E1835-44.

26. Carreras-Badosa G, Bonmatí A, Ortega FJ, et al. Altered circulating miRNA expression profile in pregestational and gestational obesity. J Clin Endocrinol Metab 2015; 100: E1446-56.
27. Herrera BM, Lockstone HE, Taylor JM, et al. Global microRNA expression profiles in insulin target tissues in a spontaneous rat model of type 2 diabetes. Diabetologia 2010; 53: 1099-109.
28. Vatandoost N, Amini M, Iraj B, Momenzadeh S, Salehi R. Dysregulated miR-103 and miR-143 expression in peripheral blood mononuclear cells from induced prediabetes and type 2 diabetes rats. Gene 2015; 572: 95-100.
29. Luo M, Xu C, Luo Y, et al. Circulating miR-103 family as potential biomarkers for type 2 diabetes through targeting CAV-1 and SFRP4. Acta Diabetol 2020; 57: 309-22.
30. Wilfred BR, Wang WX, Nelson PT. Energizing miRNA research: a review of the role of miRNAs in lipid metabolism, with a prediction that miR-103/107 regulates human metabolic pathways. Mol Genet Metab 2007; 91: 209-17.
31. Xie H, Lim B, Lodish HF. MicroRNAs induced during adipogenesis that accelerate fat cell development are downregulated in obesity. Diabetes 2009; 58: 1050-7.