



MicroRNAs as biomarkers in induced metabolic syndrome in rats

M.A. Al-Hayali , A.A. Hussein  and N.G. Mustafa 

Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

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Correspondence:

M.A. Al-Hayali

muttaa_vet@uomosul.edu.iq

Abstract

Metabolic syndrome (Mets), consists of many clinical changes, such as dyslipidemia, obesity, resistance to insulin, and oxidative stress. It is become a global epidemic health problem. In recent years, microRNAs used as biomarkers have been critical in regulating this pathophysiological prominence, and their diagnosis and therapy. This study analyzes the purpose of miRNAs function in metabolic syndrome via focusing on the miR- 122 and miR- 126, which act as an essential key element in regulating the homeostasis of lipids by controlling the lipoprotein generation and cholesterol synthesis in the liver. Twenty-one rats, 2.5 months old, were randomly split into 3 groups: the control group was given standard diet and tap water, the second group: was treated with 40% fructose for 15 days, and the third group: was treated with 40% fructose daily for 30 days. miR-122 level was most significantly elevated (with a 40.12-fold change) in the third group. Meanwhile, miR-126 was unregulated in the second group with an 18.20-fold change. This indicates that miR-122 irregularities are affected in the progression of diabetes mellitus type 2 by inducing hyperglycemia, dyslipidemia, and insulin resistance. It can be concluded that circulating microRNAs were principally associated with glucose, lipid metabolism, metabolic syndrome, immunological function, inflammatory diseases, and malignancy disorders.

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Introduction

Metabolic syndrome (MetS) is a disorder of metabolism which results in weight gain, insulin resistance, dyslipidemia and hypertension. It is effectively related to an elevated developing risk of atherosclerosis and heart disease (1). MetS, likewise acknowledged as hypertriglyceridemic waist, syndrome X, insulin resistance syndrome, and the lethal quartet, is now recognized as a severe cardiovascular risk factor (2). MetS is a complex metabolic modification and was closely investigated worldwide for its reverse effects on health of individuals and its potent cooperation next to heart problems and type 2 diabetes (3,4). It includes the collection of arterial hypertension, dyslipidemia, central obesity, and decreased glucose metabolism (5). Generally, investigations determine the spread of MetS coming from the unanimity indicated through the Panel treatment for adults (6). The phenotype of MetS can be identified persons at risk for

noncommunicable diseases (NCDs) (7,8). The hypothesis is that a high fructose diet elevates the danger of metabolic syndrome (9,10). Consequently, the MetS raises the hazard for evolving diabetes and cardiovascular disorders (11,12). It is highly accepted that fructose is absorbed by glucose transporters (GLUT) in the small intestine mostly GLUT-2 and GLUT-5 (13). In hepatocytes, fructose is quickly transformed into fructose-1-phosphate, mainly converted into glucose, glycogen, and lactate (14). Because fructose has an acceptable flavor analogous to sucrose, a small production of fructose postprandial is elevated in plasma glucose compared to another typical carbohydrate, so it appeared to be a great option for a sweetening factor in a diabetic diet (15). Studies on animals and human clinical research have examined some of the mechanisms connected with increment consumption of fructose with the Mets and recommended that extremely consuming fructose may elevate lipid synthesis, stimulate insulin resistance, and

increase the chance of increased blood pressure (16-20). On the other hand, microRNAs (miRNAs) are tiny (about 18-25 nucleotides), evolutionary protected, non-coding RNA molecules and have a remarkable action in controlling the expression of genes at the plane of post-translational, resulting in modifications in the way protein translation (21). These molecules have gained significant consideration in recent decades because of their involvement in gene expression regulation (22). They were described in *Caenorhabditis elegans* for the first time in the early nineties, and are believed to be necessary for regulating the expression of genes in both plant and animal cells (23). Changes in miRNA expression manners are assumed to concern some physiological and biological activities and have been linked to most human disorders (24,25). miRNAs are made available for extracellular release as membrane-enveloped microvesicles, like exosomes, which can be held by nearby cells (26,27). In the last ten years, a number of miR-controlled pathways have been hypothesized to clarify the augmented risk of cancer in the state of metabolic syndrome (28). MiRNAs usually regulate the target gene's expression by completely pairing to the mRNA's 3'-untranslated region, stimulating the repressive of the target mRNA (29,30). This inhibitory influence can happen via transcript suppression, transcript destabilization, or both. MiRNAs typically regulate many genes participating in a particular signaling cascade or cellular process, developing them strong biological controllers. MicroRNAs have been found to communicate information on all physiological activities studied, including metabolic homeostasis (30,31). There are several steps in the miRNA mechanism of action, including several proteins (32); they make initial contact with their intended targets at the 3'UTR, 5'UTR, or even a promoter area of the aim mRNA. The relationship between miRNA and a gene's promoter area may have a reverse effect, promoting gene expression (33). According to current research, most miRNAs in mammal cells are only partly complemented by target mRNAs, which appears sufficient to reduce the consistent translation of target mRNA (24,34). MiR-122 is nearly an enrichment miRNA in the hepatocytes, representing about 75% of total miRNA expression in hepatocytes with up to 135,000 copies/cell (35-38). It has an essential role in a massive range of liver activities, including cholesterol metabolism, responding to stress, hepatic cancer, infection with viruses, and regulation of liver genes (36-39). Two featured studies have found that antisense targeting miR-122 reduces plasma cholesterol levels and affects cholesterol production (35,40). Decreasing levels of MiR-126 are even noticed in topics with prediabetic persons compared to the healthy, and there is a relationship between its serum level and the risk for subsequent Type 2 diabetic mellitus (41). IRS-1's influence on DNA repair and replication and cell development, may explain the effect of mir-126 on cancer growth and metastasis. Down-regulation of MiR-126 promotes progressing tumor, angiogenesis,

migration, and survival via it is impact on many genes and molecular channels, including oncogenes like SLC7A5, EGFL7, KRAS, CRK, HOXA9, ADAM9, IRS-1, CADM1, SOX2, PAX-4, PI3K and VEGF (42,43).

Our study aims to analyze the perform of miRNAs in the metabolic syndrome through focusing on miR-122 and miR-126, which act as essential critical elements in regulating the homeostasis of lipids by controlling lipoprotein generation and cholesterol synthesis in the liver.

Materials and methods

Ethical approve

The approval of ethics for the current study was obtained from the animal care and use Committee approved in the College of Veterinary Medicine of Mosul University with reference number UM.VET.2023.079 on 15/8/2023.

Experimental animals

Male Sprague-Dawley rats were employed in this study, and all procedures followed the National Institutes of Health's guidelines for using also attention in animal used in laboratories. Trials were performed using adult 2-3-month-old rats weighing 210 ± 25 g, obtained from the College of Veterinary Medicine, University of Mosul, Iraq. The animals used were kept in the cages with plastic floor and exposed to a 12-hour light /dark cycle (44,45). Animals were given time to acclimatize to the laboratory environment for a period of five days before the experiments began. They were maintained on a standard rodent diet, and water was available as *ad libitum*. Twenty-one rats were assembled at random into three groups, each group of 7 animals, as follows; the control group was fed on a standard diet and tap water. The second group was treated with 40% fructose with drinking water daily for 15 consecutive days. The third group was treated with 40% fructose with drinking water daily for 30 consecutive days.

Collection of the blood

Blood samples 2-4 ml were obtained from the orbital sinus at weekly intervals. The samples were centrifuged, and the serum was separated. The samples were rapidly kept at -80°C for molecular assay, and biochemical analysis of serum insulin level, glucose, total cholesterol, triglycerides, HDL, VLDL, and LDL was done using the automatic enzyme method (Genri-GS200-China). The atherogenic index (AI) is calculated as $\text{AI} = \frac{\text{total cholesterol}-\text{HDL}}{\text{HDL}}$ (46,47).

miRNA isolation

Serum mir-122 and mir-126 were isolated using a GeneAll RiboEx kit (RiboEx total RNA, No:301-002), and then miRNA-cDNA synthesis using a Gene All Hybrid-R miRNA (cat No: 315-150) Primers used in miRNA-cDNA are designed as shown in table 1.

Table 1: miRNA-cDNA primers

MiRNA	Primers
miR-122-SL	GAAAGAAGGCGAGGAGCAGATC
	GAGGAAGAGACGGAAGAATGTG
	CGTCTCGCTTCTTTCCAAACACC
miR-126-SL	GAAAGAAGGCGAGGAGCAGATC
	GAGGAAGAAGACGGAAGAATGT
	GCGTCTCGCCTTCTTTTCGCGTACC
snRNA-RNU6	CGCTTCACGAATTTGCGTGTACB

After the master mix was prepared for miRNA-cDNA synthesis, the reverse transcription process was started. The reverse transcription reaction conditions applied to miRNA to obtain cDNA as follows: (cycle 1; 25°C for 10 minutes, cycle 2: 37°C for 120 minutes, cycle 3; 85°C for 5 minutes, cycle 4: 4°C). The received miRNA-cDNA samples were kept at -80°C until the qPCR step.

Real-Time PCR

qPCR reaction was initiated using primers (miR-122-F: TGGAGTGTGACAATGGTGTTTG, miR-126-F: CATTATTACTTTTGGTACGCG, Universal reverse: CGAGGAAGAAGACGGAAGAAT, snRNA-RNU6-F: GCTTCGGCAGCACATATACTAAAAT, snRNA-RNU6-R: CGCTTCACGAATTTGCGTGTACAT), and the master mix was prepared. The conditions needed for the qPCR reaction as follows: Initial denaturation one cycle for 300 seconds at 95°C. Denaturation for 10-30 seconds at 95°C and annealing for 10-60 seconds at 60°C (both denaturation and annealing extend for 40 cycles). Finally, extension, one cycle at 72°C for 5 seconds. Melting curve consistent with the qPCR instrument manual, and reactions were done on (Applied Biosystems™ 7500 Fast Real-Time PCR apparatus. The significant threshold cycle (CT) for hybridization of a specific primer with a particular target (miR-122 cDNA) as that appears with a denaturation temperature between 75-85°C. The significant plot for the fluorescent signal is due to hybridization of specific primer with specific cDNA, which begins to elevate at 14 threshold cycles with overexpression for some samples and non-significant amplification for other samples.

Statistical analysis

Result data was entered into an Excel sheet and then uploaded onto GraphPad Prism version 8are, and biochemical parameters were set as means ± SE using SPSS (ver. 22). The significance of differences between groups was assessed via one-way analysis of variance (ANOVA) with Duncan's test. A significant difference was considered at P≤0.05 (48).

Results

This study showed different glucose, cholesterol, triglyceride, HDL, VLDL, and LDL serum levels, as shown below in table 2. The levels of serum glucose significantly increased in groups treated with 40% fructose for 15 and 30 days comparison to the control group. Serum triglyceride levels increased significantly in groups treated with 40% fructose for 30 days and 15 days, respectively, compared with the control. The administration of fructose causes a significant rise in serum cholesterol levels in both treated groups. It can be noticed that there was an increase in HDL and VLDL serum levels in the group treated with 40% fructose for 30 days compared with the control group. The serum level of LDL increased in the third group, but no significant increase when the second group was compared to the control group (Figure 1). Molecular results of mir-126 and mir-122 using qPCR melting curve plot show the products' amplification and confirm that it represents a single melting temperature. Also, there was no primer dimer formation (Figures 2 and 3). The levels of serum miR-122 were significantly increased in rat groups treated with fructose at 40 % for 15 and 30 days with 26.63, 40.12, then the control group, with 4.99-fold changes (each grouping P < 0.001). Gene expression of miR-126 was significantly highly upregulated to the second group an 18.20-fold change, then the third group with a 12.95-fold change compared to an 8.01-fold change for the control group. In contrast, miR- 126 level was down-regulation in the second and third groups with 19.99 and 9.66 folds change, respectively (Figure 4), and a significant positive correlation between miR-122 and VLDL, LDL and TGTC.

Table 2: Biochemical parameters of the control group, 15 days (40%) and 30 days (40%)

Groups	Glucose	Cholesterol	Triglyceride	HDL	VLDL	LDL	AI
Control	88.80±3.36 ^a	74.30±1.60 ^a	81.50±1.936 ^a	19.55±1.46 ^a	16.85±1.11 ^a	26.02±1.52 ^a	2
15 day (40%)	127.25±3.40 ^b	80.57±0.92 ^b	103.62±2.65 ^b	21.35±1.09 ^{ab}	20.77±0.536 ^b	28.27±1.12 ^a	2.74
30day (40%)	131.30±1.69 ^b	98.12±1.799 ^c	166±2.483 ^c	24±1.075 ^b	33.95±1.596 ^c	36.92±1.030 ^b	3.18

Each value represents mean ± SE. Different letters in each row characterize a significant (p ≤ 0.05) difference compared to the control group.

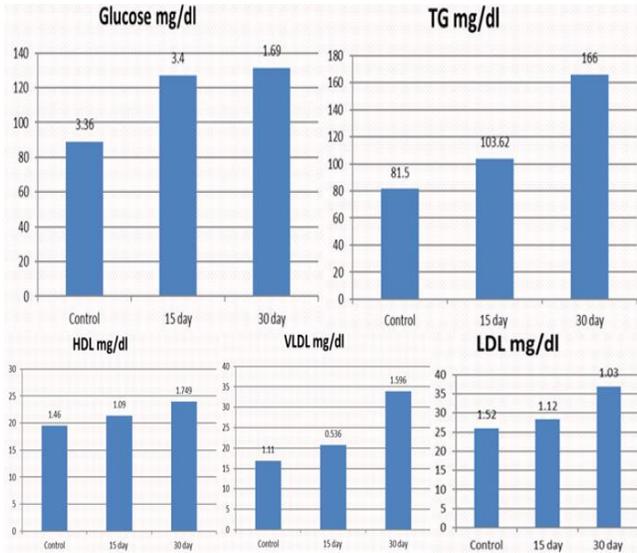


Figure 1: Effect of 40% fructose in drinking 15 and 30 days on the serum glucose, triglyceride, HDL, VLDL, and LDL.

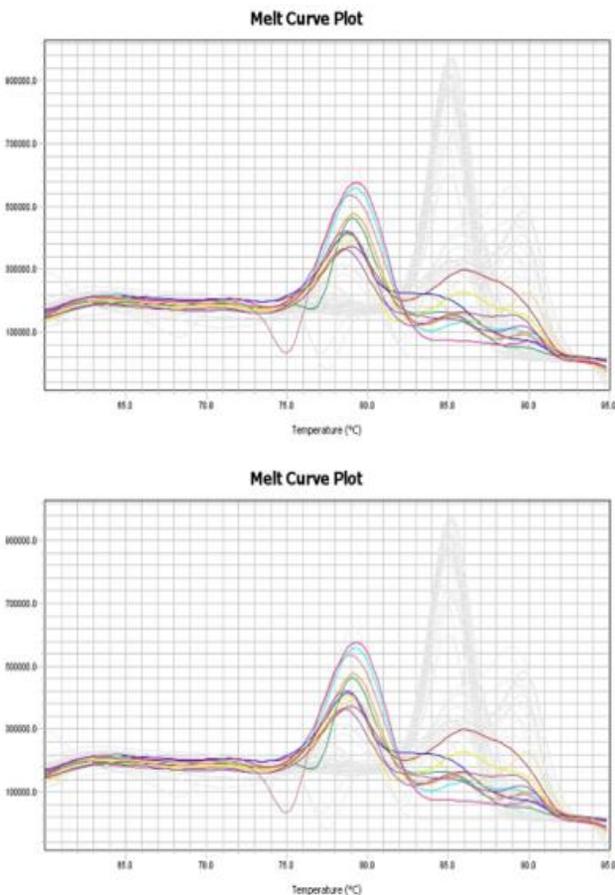


Figure 2: Melt curve showing the melting temperature of amplicon for each microRNA: (A) miR-126 and (B) miR-122.

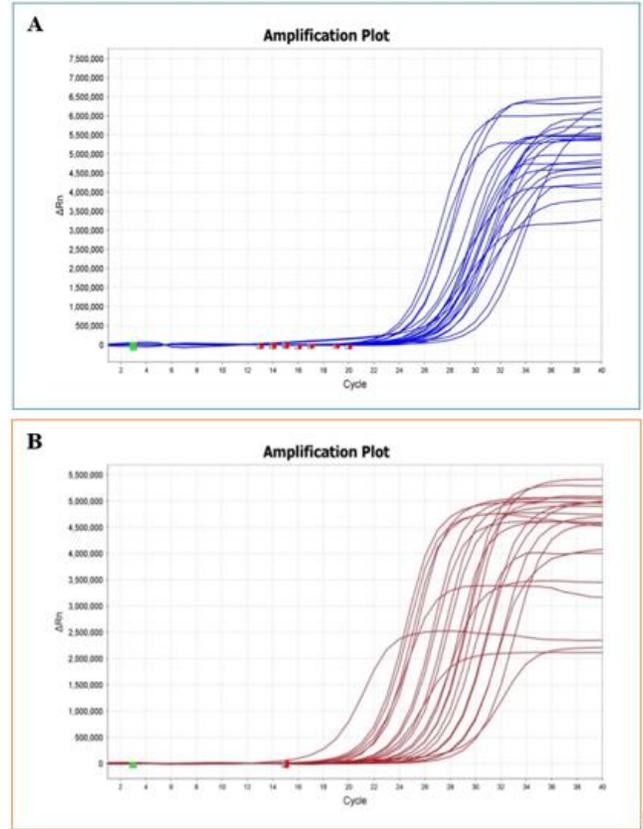


Figure 3: Represent amplification plot for (a) mir-126 and (b) mir-122.

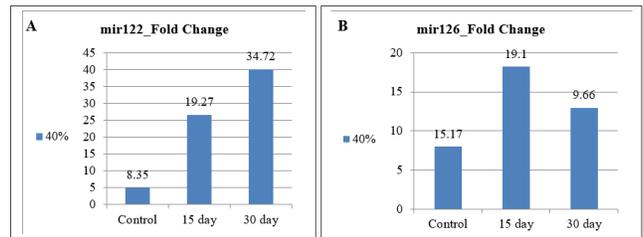


Figure 4: Relative expression levels of a) miR-122 and b) miR-126.

Discussion

Collected data indicated that several sources (such as IRIR, hyperglycemia, obesity, and hyperlipidemia) show an essential function in altering the expression of many Mir-RNAs in organs regulating lipid and glucose metabolism (49). These, in turn, affect complicated and multifactorial processes, such as proliferation, inflammation, differentiation, carcinogenesis, and aging (50). MiR-122 circulating level increases in diabetes type 2 or common metabolic syndrome, strongly correlate with

monounsaturated and saturated fatty acids. In a predictable case, miR-122 levels are increased before T2D and metabolic syndrome are manifested. Levels of miR-122 are positively related to prime lipids (TG, HDL, and LDL) due to their impact on enzymes implicated in hepatic lipid metabolism (51). A significant positive correlation exists between miR-122 and insulin resistance (52). MiR-122 is key in energy homeostasis by involving metabolic pathways, including tricarboxylic acid cycle (TCA), glycolysis, pyruvate metabolism, and gluconeogenesis pathways (53).

In addition, MiR-126 can modify expression in fatness and CCL2 by genes encoding STAT6, MAX, NFkB1, RELB, and ETS1 proteins (54-57). MiR-126 has been continuously related to T2D and controlling angiogenesis and vascular integrity through Notch1 inhibitor delta-like one homolog (Dlk1) and Ago2/Mex3a complex (58-60). Furthermore, in carbohydrate metabolism, MiR-122 is considered a hepato-specific miRNA influence in the regulation of homeostasis of cholesterol of hepatic origin and fatty acid metabolism. As a result, MiR-122 dysregulation is possibly a concern for T2DM-linked dyslipidemia. We observed that MiR-122 positively correlates with TC, TG, VLDL, and LDL. In concurrence with our finding, Rashed *et al.* and Gao *et al.* described a statistically significant relation amongst miR-122 with the TG, LDL and TC in type diabetic persons either with or heart problems, especially diseases associated with coronary arteries (61,62).

So, a significant and positive correlation between miR-122 and LDL-C and Small-Density LDL (sdLDL) may be attributed to its regulated impacts on the cholesterol biosynthesis pathway. In agreement with our findings, Jones *et al.* (63) discovered a substantial beneficial relationship between insulin resistance and MiR-122 gene expression suggested that miR-122 is likely a contender as a screening indicator for metabolic consequences and obesity. Targeting Antisense MiR-122 results in the down-regulation of a diverse set of genes that participate in lipoprotein and lipids biosynthesis, including 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme in the cholesterol production pathway microsomal triglyceride transfer protein and 3-hydroxy-3-methylglutaryl-CoA synthase 1 (64). These proteins have no direct objectives of miR-122, and the mechanisms by which miR-122 controls their expression are still unclear (51).

Conclusion

Circulating microRNAs were principally associated with lipid metabolism, adiposity, and glycemic metabolism. We emphasized the relationship between miR-122 and miR-126 expressions and hazard aspects for metabolic syndrome. Circulating miR-122 represents the most attractive and exciting goals for metabolic-related abnormalities. It can be used as a marker of the liver's lipid metabolism and promote inflammatory reactions in the context of liver steatosis.

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Conflicts of interest

The authors declare that they have no competing interests.

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ميكرو رنا كمؤشر حيوي في متلازمة الأيض المستحدث في الجرذان

مطاع عبد المطلب عبد، احمد علي حسين و نشأت غالب مصطفى

فرع الفسلجة والكيمياء الحياتية والأدوية، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

تظهر متلازمة التمثيل الغذائي العديد من التغيرات السريرية مثل اضطراب شحوم الدم والسمنة ومقاومة الأنسولين والإجهاد التأكسدي. في السنوات الأخيرة استخدم ميكرو رنا كمؤشرات حيوية ولها دورًا حاسمًا في تنظيم هذه الفعاليات الفسيولوجية وأيضًا في التشخيص والعلاج. تقوم هذه الدراسة على تحليل تأثير ميكرو رنا في متلازمة التمثيل الغذائي من خلال التركيز على ميكرو رنا ١٢٢ وميكرو رنا ١٢٦ والتي تعمل كعناصر أساسية في تنظيم توازن الدهون عن طريق التحكم في توليد البروتين الدهني وتخليق الكوليسترول في الكبد. تم توزيع ١٥-٢١ جرد، بعمر ٢-٣ أشهر، عشوائياً إلى ثلاث مجموعات، مجموعة السيطرة تغذت على نظام غذائي قياسي وماء، المجموعة الثانية (أ): تم إعطاء سكر الفركتوز ٤٠٪ يومياً ولمدة ١٥ يوم، المجموعة الثالثة (ب): تم إعطاء سكر الفركتوز ٤٠٪ يومياً ولمدة ٣٠ يوماً. لوحظ أن مستوى ميكرو رنا ١٢٢ مرتفع بشكل ملحوظ (مع التغيير الكمي ١٢،٤٠) في المجموعة الثانية بينما كان المستوى ميكرو رنا ١٢٦ منظم في المجموعة الثالثة مع تغيير الكمي قدره ٢٠،١٨. يمكن أن يشير ذلك إلى أن عدم انتظام ميكرو رنا ١٢٢ المسؤول في تطور داء السكري من النوع ٢ عن طريق إحداث ارتفاع السكر في الدم وخلل شحوم الدم على طول مقاومة الأنسولين. يمكن أن نستنتج أن ميكرو رنا المنتشرة كانت مرتبطة بشكل أساسي باضطرابات استقلاب الجلوكوز والدهون ومتلازمة التمثيل الغذائي.