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PLASMA miR-103 AND miR-107 LEVELS IN OBESE CHILDREN: THE SIGN OF INSULIN RESISTANCE

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ABSTRACT

Objective: *In this study, it is aimed to research how plasma miR-103 and miR-107 levels are related to insulin resistance changed when comparing obese children to healthy normal-weight children.*

Material and Method: *The study was made on 40 obese children aged 5-17 and with 40 healthy normal-weight children aged 5-17. Plasma miR-103 and miR-107 expressions were analyzed using the Real Time-PCR method.*

Results: *miR-103 and miR-107 values about an obese group were significantly found higher ($p<0.001$) than a control group. It was found a statistically significant level of positive correlation in obese children between miR-103 and body mass index (BMI) ($p<0.001$) and BMI-p ($p<0.01$), insulin ($p<0.01$) and HOMA-IR ($p<0.01$). Also, it was found the statistically significant level of positive correlation in obese children between miR-107 and BMI ($p<0.01$), and insulin ($p<0.05$) ve HOMA-IR ($p<0.05$).*

Conclusion: *In the light of our findings, we can say that obesity increases plasma miR-103 and miR-107 levels in children and these microRNAs showed a positive correlation with parameter HOMA-IR used to evaluate insulin resistance and insulin. miR-103 and miR-107 can shed impressive progress for understanding glucose homeostasis, whether in normal physiology or human disease.*

Keywords: *Obesity, miR-103, miR-107, diabetes, insulin resistance*

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OBEZ ÇOCUKLARDA PLAZMA miR-103 VE miR-107 DÜZEYLERİ: İNSÜLİN DİRENCİNİN İŞARETİ

ÖZET

Amaç: Bu çalışma, sağlıklı normal kilolu çocuklar ile obez çocuklar kıyaslandığında plazma miR-103 ve miR-107 düzeylerinin nasıl değiştiğini ve bu mikroRNA'ların insülin direnciyle ilişkisini araştırmayı amaçlamıştır.

Materyal ve Metot: Çalışma 5-17 yaşları arasında 40 obez çocuk ve 40 sağlıklı normal kilolu çocuklar üzerinde yapıldı. Plazma miR-103 ve miR-107 seviyeleri Real Time-PCR yöntemi kullanılarak analiz edildi.

Bulgular: Obez çocuklara ait miR-103 ve miR-107 değerleri sağlıklı normal kilolu çocuklara göre önemli derecede yüksek bulundu (p<0,001). Obez çocuklarda miR-103 ve BMI (p<0,001) ile BMI-p (p<0,01), insülin (p<0,01) ve HOMA-IR (p<0,01) arasında istatistiksel olarak anlamlı pozitif korelasyon bulundu. Ayrıca obez çocuklarda miR-107 ve BMI (p<0,01) ile insülin (p<0,05) ve HOMA-IR (p<0,05) arasında istatistiksel olarak anlamlı düzeyde pozitif korelasyon bulundu.

Sonuç: Bulgularımız ışığında obezitenin çocuklarda plazma miR-103 ve miR-107 seviyelerinin artırdığını söyleyebiliriz ve bu mikroRNA'lar insülin direncini değerlendirmek için kullanılan HOMA-IR parametresi ile pozitif korelasyon göstermiştir. Bu bağlamda, miR-103 ve miR-107, normal fizyoloji ya da insan sağlığı açısından glukoz homeostazisinin anlaşılması için heyecan verici bir ilerlemenin yolunu açabilir.

Anahtar kelimeler: Obezite, miR-103, miR-107, diyabet, insülin direnci

INTRODUCTION

Overweight and obesity in children has emerged as Overweight and obesity in children has emerged as an important public health problem in the world.[1] According to age and sex, body mass index (BMI) is above the 95th percentile, which is defined by most centers as obesity.[1] There is no determined cause of disease in most cases; such obesity is called primary obesity or exogenous obesity.[2]

The prevalence and seriousness of obesity in children and adolescents increase, and it is described as an epidemic disease.[3] There is a significant increase in the prevalence of morbidity associated with childhood obesity, leading to more severe problems in early adulthood.[1] In parallel with this increase in childhood obesity, more chronic diseases such as type 2 diabetes, metabolic syndrome, hypertension become an essential problem in childhood.[4] Being overweight in childhood is a strong indication of being overweight in later ages.[5] In addition to significantly affecting morbidity and mortality, there is also a very serious social and economic dimension.[6] There is a strong relationship between obesity and diabetes. While type 2 diabetes was not considered a pediatric disease in the past decade, this problem is increasing in the last ten years especially in obese adolescents.

MicroRNAs play a regulatory role in many biological events that related to obesity, including fat metabolism, insulin effect, and adipocyte differentiation.[7] Studies on obese mice have shown that miR-103 and miR-107 play an important role in insulin sensitivity.[8] Decreased miR-103 and miR-107 expression led to an improvement in glucose homeostasis and insulin sensitivity.[8] Since defects in insulin signaling are among the most common and earliest abnormalities to develop type 2 diabetes, these findings suggest that microRNAs represent potential targets for the treatment of type 2 diabetes.[8]

The findings of the association between microRNAs and childhood obesity are still not clear enough. In addition, in this study, we have investigated the correlations between plasma miR-103 and miR-107 levels and homeostasis model evaluation of insulin resistance (HOMA-IR) values in obese children. According to our knowledge, the correlation between plasma miR-103 and miR-107 levels and HOMA-IR values have not been investigated yet. Therefore, in this context, by studying how plasma miR-103 and miR-107 change in obese children.Our research shows that obesity and diseases accompanied by the obesity are intended to present new approaches, especially to the physiopathogenesis of insulin resistance.[9] And it aims to lead new developments in the treatment and diagnosis of these diseases.

MATERIAL AND METHODS

Participants

This study was conducted on 40 obese children aged 5-17 (18 males, 22 females) and 40 healthy children (20 males: 20 females) aged 5-17 years old. All the measurements were made by the same physician at Konya Training and Research Hospital Pediatric

Endocrine Diseases Clinic. All of the children, who participate in this study the presence of blood pressure elevation, cardiovascular disease, obesity, type 2 diabetes mellitus, fat metabolism disorder was recorded in the immediate family and second-degree relatives. In addition, blood pressure measurements and detailed physical examinations were performed using a cube sphygmomanometer according to age and arm length in all participants.

Length Measurement

It was made using a stadiometer. The legs of the children were made naked and joined together to provide the backside of the back of the stadiyometer behind the back, hip, foot heels. And they were provided with steady stance. By lifting the jaw slightly upward from the mandibular collar, paying attention to the parallel of the line passing between the eye and the upper part of the earlid, the length from the head to the base of the foot was also measured.

Scale Measurement

Once a portable precision electronic scale is set to zero on a flat surface; The children stand on it in the morning with an empty stomach and thin underwear.

Calculation of Body Mass Index

Using the height and weight measurements, the BMI is calculated in weight (kg)/height (m^2) formula. For all cases, a BMI between the 85th and 94th (inclusive) percentiles places them in the overweight category, while those ≥ 95th percentile are classified as obese.[10]

Standard Deviation Score (SDS) Calculation

SDs calculation for weighing, height, and BMI values was done by Lambda Mu and Sigma (LMS) method. In this method z=[measured value/M) L - 1]/LS (L: initial value of the curve, M: median value, S: coefficient of variability), (kg), height (cm), BMI (kg/m^2) values of the cases, respectively, instead of using anthropometric measurements, the SDs was calculated for each case.[10,11]

HOMA-IR was calculated as fasting serum glucose (mmol L) x fasting serum insulin (µU ml)/22.5. HOMA-IR scores were accepted to show ≥2.5 insulin resistance.[12]

Control cases were selected from healthy volunteer children, who have no health problems and those with BMI percentage ≤85 percentile was included in the study. The parents of children participating in the study were received written consent before the blood was taken and informed verbally. For the study, approval (and signed informed consent forms) was obtained from Necmettin Erbakan University, Meram Medical Faculty Research and Application Hospital Ethics Committee. The ethic number was 2014/656.

Analytical Methods

Sufficient blood samples were taken from patients with EDTA tubes, flat tubes and PAXgene Blood RNA Tube (Qiagen, Valencia, CA, USA) in the morning after 12-14 hours of hunger. Blood samples from the flat tubes were centrifuged immediately after coagulation and incubated without serum and sera separated. EDTA tubes were centrifuged and the plasmids separated. Samples were taken by serum, plasma, and PAXgene Blood RNA Tube were stored at -80 ° C until the day of analysis. Serum samples were analyzed for fasting glucose, insulin, lipid panels, HbA1c (in plasma) levels and miR-103 and miR-107 levels in PAXgene Blood RNA Tube.

RNA Isolation and Real-Time Quantitative PCR Analysis

RNA isolation and real-time quantitative PCR (RTqPCR) analysis were performed via miRCURY LNA Universal RT microRNA PCR kit (Exiqon, Vedbaek, Denmark) according to manufacturer's protocol. While LightCycler 480 instrument (Roche Diagnostics, Basel, Switzerland) was used to perform RT-PCR, total RNA isolation was performed through Roche high pure miRNA isolation kit following the manufacturer's guidelines.

Quality of RNA was assessed by 260 nm absorbance with a Nanodrop ND1000 spectrophotometer (NanoDrop Technologies Inc, Wilmington, DE, USA) and by capillary electrophoresis with an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). Total RNA was reversely transcribed in 20 µL reactions using miRCURY LNA Universal cDNA synthesis kit (Exiqon) by diluting cDNA at an 80fold rate. Each PCR was carried out in duplicate with LightCycler 480 instrument as a total volume of 20 µL by using 8 µL of diluted cDNA, 2 µL of LNA PCR primary set (HsamiR1435p, HsamiR33a3p, HsamiR7583p, HsamiR370, HsamiR378a5p, HsamiR27a5p, and HsamiR3355p) and 10 mL of miRCURY LNA SYBR Green master mix (Exiqon) according to the instructions offered by the manufacturer. The relative gene expression was calculated with the comparison of cycle times for target PCR using this equation: relative gene expression = 2– (ΔCtsample – ΔCtcontrol).

Table 1. Demographic characteristics of obese and control group

	Control (n=40)	Obese (n=40)	*p*
Gender (Female/Male)	20/20	22/18	0.333
Age (years)	14.29±1.6	14.41±1.3	0.728
Weight (kg)	48.23±7.5	86.59±17.1	p<0.001
Height (cm)	158.64±11.3	161.45±6.5	0.180
BMI (kg/m2)	19.12±2.1	33.92±6.7	p<0.001
BMI-p	25.52±26.9	99.07±1.2	p<0.001
Systolic blood pressure (mmHg)	100.75±8.8	121.38±15.4	p<0.001
Diastolic blood pressure (mmHg)	60.87±6.1	76.00±11.1	p<0.001

Table 2. HOMA-IR values and levels of some biochemical parameters of obese and control group

	Control (n=40)	Obese (n=40)	*p*
Glucose (mg/dL)	82.97±11.6 (59,0-116,0)	89.07±6.8 (64,0-101,0)	0.006
Insulin (µU/mL)	10.09±4.8 (2,3-20,9)	17.65±9.5 (5,3-42,2)	p<0.001
HOMA-IR	2.19±1.1 (0,3-4,9)	3.59±1.8 (0,9-8,3)	p<0.001
HbA1c	4.97±0.9 (3,4-6,8)	5.25±0.6 (3,4-6,8)	0.138
Total Cholesterol (mg/dL)	156.13±42.1 (106,0-369,0)	175.32±32.1 (106,0-269,0)	0.026
Triglyceride (mg/dL)	81.41±43.7 (33,0-260,0)	121.80±73.7 (36,0-398,0)	0.004
HDL-cholesterol (mg/dL)	50.31±8.7 (38,0-75,0)	44.60±9.3 (22,0-66,0)	0.006
LDL-cholesterol (mg/dL)	89.53±38.9 (51,4-289,6)	106.19±27.9 (55,0-188,0)	0.033

The results of the groups were given as (Mean±SD) (Min-Max).

Table 3. Obese and control group miRNA values

	Control* (n=40)	Obese* (n=40)	*p*
miR-103	21.22±30.7 (1,0-170,0)	121.64±120.9 (2,4-545,0)	*p*<0.001
miR-107	39.21±56.3 (0,1-278,0)	190.56±190.4 (6,3-792,4)	*p*<0.001

The results of the groups were given as (Mean±SD) (Min-Max).

Data Analysis

Data analysis targets with Cq values >35 were considered beyond the limit of detection, and all Cq values >35 were excluded out of our criteria.

Measurement of Other Analytes

Serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), blood glucose and HbA1c were measured by commercially available kits based on usual methods by the Abbott Architect C16000 auto-analyzer (Architect C16000 auto-analyzer; Abbott Laboratory, Abbott Park, IL, USA).

Statistical Analysis

Statistical analyses were done using SPSS v. 16.0 (SPSS Inc.,IL, USA). In our study, the results of the groups were given as X±SD. $p<0.05$ was considered significant. One-Sample Kolmogorov-Smirnov Test, which we conducted to compare the differences between the groups, "Independent-Samples t test" was applied for BMI, weight, height, glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol and HbA1c which were found to be suitable for parametric testing.

"2 Independent-Samples" test was performed for BMI-percentile (BMI-***p***), systolic blood pressure, diastolic blood pressure, triglycerides, insulin, HOMA-IR, miR-103 and miR-107, which are suitable for nonparametric testing. Correlation between parameters of our study was made with "Spearman correlation test.

RESULTS

The data including the demographic characteristics of obese and control group are given in Table 1. As can be seen from Table 1, weight, BMI, BMI-*p*, systolic blood pressure and diastolic blood pressure of the obese group were significantly higher than control group ($p<0.001$). There was no significant statistical difference between obesity and control cases about gender, age, and height.

Biochemical parameters of the obese and control group and HOMA-IR values, which are considered to be indicative of insulin resistance, are given in Table 2. As shown in Table 2, glucose ($p<0.01$), insulin ($p<0.001$), total cholesterol ($p<0.05$), triglyceride ($p<0.01$), LDL-cholesterol ($p<0.05$) and HOMA-IR ($p<0.001$), values were significantly higher than the control group. HDL-cholesterol levels were significantly lower than the control group ($p<0.01$). No statistically significant difference was found between HbA1c levels of obesity and control cases.

The miRNA findings of obese and control groups are given in Table 3 and Figure As shown in Table 3, the miR-103 and miR-107 values of the obese group were significantly higher than the control group ($p<0.001$).

Correlations between the miR-103 and miR-107 values of the obese group and the parameters used in assessing obesity and insulin resistance are given in Table 4 and Table 5. BMI (r=0.565; p<0.001), BMI-p (r=0.421; p<0.01), insulin (r=0.447; p<0.01) and HOMA-IR (r=0.426; p<0.01) with miR-103 in obese group as seen in Table 4 had a statistically significant positive correlation. There was no significant correlation between glucose, HbA1c and miR-103. As seen in Table 5, there was a statistically significant positive correlation between miR-107 and BMI (r=0.431; p<0.01), insulin (r=0.391; p<0.05) and HOMA-IR (r=0.376; p<0.05) in obese persons. There was no significant correlation between glucose, HbA1c and miR-107. On the other hand, no significant correlation was found between the miR-103 and miR-107 values of the parameters that used to evaluate obesity and insulin resistance of control group.

DISCUSSION

Obesity is a chronic disease increasingly prevalent in both developed and developing countries, increasingly affecting children as well as adults.[13] The most significant cause of insulin resistance in children is obesity.[9] Lipid metabolism is strictly regulated at the cell level.[7] It has been found that microRNAs regulate genes involved in lipid metabolism, including fatty acid oxidation, lipogenesis, and cholesterol homeostasis.[7,14] By confirming the presence of microRNAs and their interactions with target genes, development in the organism is thought to be an essential point in the discovery of the functions of all microRNAs during disease and other cellular events.[7,14] Studies on obese mice have shown that miR-103 and miR-107 play an essential role in insulin sensitivity. Decreased miR-103 and miR-107 expression led to improving glucose homeostasis and insulin sensitivity.[7,14] Defects in insulin signaling are among the most common and earliest defects of developing type 2 diabetes. These findings indicate that microRNAs represent potential targets for the treatment of type 2 diabetes.[7,14]

In our study, the values of miR-103 and miR-107 that belong to the obese group were significantly higher than the control group. We also found a statistically significant positive correlation in obese subjects with miR-103 and miR-107 between BMI, insulin and HOMA-IR. There is many studies that were done by others are supporting our findings. Some of these studies have also described that miRNAs accelerate adipocyte differentiation.[15-18] miR-103 has been reported to increase its level during differentiation of human preadipocytes.[15] It has been shown that miR-103 is overexpressed in the presence of adipogenic

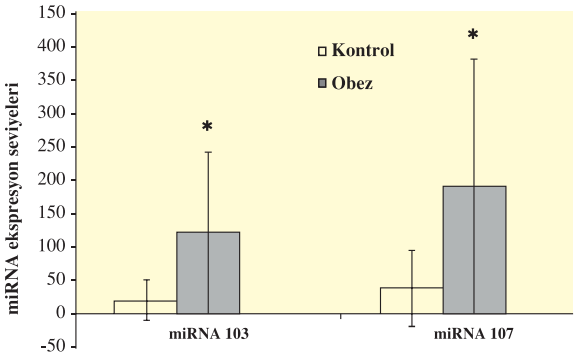

Figure Obese and control group miRNA expression levels (* p<0.001)

stimulation, accompanied by adipogenous, accelerated adipogenic gene expression, and increased triglyceride accumulation. Although in vivo miR-103 was found to be downregulated in mature adipocytes in obese mice.[15]

Some studies have shown that miR-103 is upregulated in the obese human adipose tissue.[19,20] The inconsistency between the studies seems likely to be due to differences in the fat storages between mice and humans. Of course, more experimental work is needed to understand the role of miR-103 in adipogenesis and obesity.

miR-103 and miR-107 are thought to play a role in energy metabolism. These microRNAs are highly conserved, and they have located within the pantothenate kinase (PANK) gene.[21] miR-103 genes

Table 4. Correlation between parameters of obesity and insulin resistance of miR-103 values in obese group

Parameters	miR-103	
BMI	r=0.565	p<0.001
BMI-*p*	r=0.421	p=0.008
Glucose	r=0.184	p=0.270
Insulin	r=0.447	p=0.005
HOMA-IR	r=0.426	p=0.009
HbA1c	r=-0.048	p=0.791

Table 5. Correlation between parameters of obesity and insulin resistance of miR-107 values in obese group

Parameters	miR-107	
BMI	r=0.431	p=0.006
BMI-p	r=0.298	p=0.066
Glucose	r=0.041	p=0.807
Insulin	r=0.391	p=0.015
HOMA-IR	r=0.376	p=0.022
HbA1c	r=-0.063	p=0.727

are constructed of two mature miRNAs (miR-103 (1) and miR-103 (2), whereas miR-107 is composed only of the miR-107 gene.[8] PANK catalyzes the rate-limiting step of pantothenate phosphorylation during the formation of coenzymes (CoA), an important cofactor of a large number of enzymes involved in various metabolic pathways.[21] Trajkovski et al. investigated the relationship between high miR-103, miR-107 expression and obesity in obese mice.[8] In this study, miR-103 and miR-107 were found to be a direct target gene, with caveolin-1 as an important regulator of insulin receptor.[8] Increased caveolin-1 expression leads to stabilization of the insulin receptor, which has resulted in decreasing levels of miR-103 and miR-107 in adipocytes, increasing insulin signaling, decreasing adipocyte size, and increasing insulin-stimulated glucose uptake.[8] These findings also support our results, in fact, it shows that miR-103 and miR-107 is a central feature in insulin resistance.

How can miR-103 and miR-107 control the insulin/glucose balance? miRNAs generally regulate the levels and/or translate hundreds of mRNAs with essentially 3 untranslated regions (3'UTRs). In a study followed by DNA microarray analysis, miR-103 and miR-107 effect on glucose homeostasis, and insulin sensitivity were investigated. The studies revealed caveolin-1, a protein that interacts physically and functionally with the insulin signaling pathway, as a potential target of miR-107.[22-25] Caveolin-1 is a protein that has a central role in the production and repair of cryptic plasma domains, called caveolae.[23,24] This cholesterol/sphingolipid plays an important role as a number-one facilitator of extracellular signal transduction events, including invaginations in rich "small caves" or plasma membranes, endocytosis and insulin signaling. Using many of the cell and animal model systems, researchers have shown an antagonistic effect in the modulation of caveolin-1 expression by the effect of overexpression of miR-103, miR-107, and the phosphorylation of the insulin receptor in their studies. Using caveolin-1-deficient mice to find insulin signaling in adipose tissue and liver. The effects of miR-103 and miR-107 in glucose homeostasis wanted to be shown, but the animals passed away a warning of these studies, the effects of caveolin-1 in animal homeostasis may have pleiotropic effects on cholesterol/lipid metabolism or caveolae-dependent signaling pathways and can independently modulate insulin signal/glucose metabolism.[23] This finding supports that microRNAs targeted at caveolin-1, which have critical inhibition for a cell in insulin insensitivity. The miR-103 and miR-107 disorders contribute potentially to obesity-related metabolic abnormalities.

As reported in many studies, miR-143, miR-103 and miR-107 have been shown to regulate adipocyte differentiation.[15] However, the expression of these microRNAs was found to be downregulated in obese and genetically insulin-resistant mouse models (ob/ob). It is likely that the model is stimulated as part of the pathology via an inflammatory pathway.[15] Insulin resistance has been associated with increased hepatic lipogenesis and steatosis associated with obesity.[26,27] Besides, there may be fat/metabolite traffic and signal complexity between the adipose tissue and the liver, which plays a vital role in meeting the energy needs of glucose homeostasis and metabolic control.

The small number of patients in our study has limited our potentials, so increasing the number of the patients will contribute more to the researches in this regard.

As a result, it has been shown that miRNAs coordinate several components of pathways that guide a majority in animal and human development or physiology.[28-32] It is noteworthy that miR-103 and miR-107 controls the expression of additional genes, including insulin response and modulation of glucose/energy homeostasis from these miRNAs. Furthermore, pantothenate kinase (PANK) is important for the production of CoA, which is the key cofactor of miR-103 and miR-107 in various metabolic processes, is functionally linked to host genes.[7,33] Thus, miR-103 and miR-107 may try to integrate several internal metabolic circuits that govern physiological homeostasis.

We can say that the above research data and our findings indicate that plasma miR-103 and miR-107 levels are elevated in obese children, and we can say that these microRNAs have a positive correlation with the parameter HOMA-IR used in the evaluation of insulin and insulin resistance. miR-103 and miR-107 system can shed impressive progress for understanding glucose homeostasis, whether in normal physiology or human disease.

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*The authors declare that there are no conflicts of interest.

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