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Study the association of circulating level of Irisin with the anthropometric and metabolic parameters in normal weight, overweight and obese children

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Abstract:

The goal of this study is to study the association of circulating level of Irisin with the anthropometric and metabolic parameters in normal weight, overweight and obese children. It's a cross sectional study conducted on 69 children, grouped into 3 groups ; normal weight (BMI<85th), overweight (BMI≥85th), and obese group (BMI≥ 95th percentile for age and sex) (39 males and 30 females), (20 normal weight, 13 overweight, 36 obese children). aged 6-18 years. All are recruited from Endocrinology Pediatric clinic in Beni Suef University. All participants were subjected to history taking and clinical examination, anthropometric assessment (weight, height, pubertal assessment, waist circumference and hip circumference) and laboratory tests (Serum Irisin, serum cholesterol, serum high density lipoprotein, serum triglycerides, serum fasting insulin, serum fasting glucose, oral glucose tolerance test). Insulin resistance and sensitivity were assessed by calculating HOMA-IR. The obese group of 36 children (52.2%) had a higher level of Irisin than the normal weight and the overweight groups (P-value<0.001). The obese group had a significant higher prevalence of metabolic syndrome regarding the MSC Cook's and the MSC deFerranti criteria. The obese group had a significant linear positive correlation between the Irisin level and BP, BMI, cholesterol level, fasting insulin, fasting glucose, the number of criteria of Metabolic Syndrome as regards International Diabetic Federation and the HOMA IR score. Results revealed that Irisin as well as HOMA-IR can predict presence of metabolic syndrome with high sensitivity and specificity at different levels.

Keywords: obese children ; Irisin ; metabolic syndrome.

1. Introduction:

Childhood obesity, a great worldwide health problem facing not only high and middle income, but also low income countries affecting physical, psychological, and psychosocial health. [1]

Excess weight of the enlarged adipose tissue mass, together with metabolic changes associated to obesity, both increase the risk of developing certain diseases and conditions [2]. The severity of these co-morbidities typically increases with the severity of obesity [3].

Children with obesity are more likely to become victims of bullying and discrimination, poor self-esteem, anxiety, depression, and decreased health-related quality of life [4].

Hypertension [5], dyslipidemia, low levels of high density lipoprotein cholesterol, and elevated levels of triglycerides [6], Echocardiographic findings including left ventricular hypertrophy, increased left ventricular and left atrial diameters, and systolic and diastolic dysfunction [7]. Beside the previously mentioned cardiovascular problems, Obese children are at risk of suffering hyperinsulinemia, insulin resistance, prediabetes, and subsequently T2DM [8]. Early presentation of type II D.M. is associated with more rapid deterioration of glycemic control and progression of diabetes-related complications such as microalbuminuria, dyslipidemia, and hypertension [9]. Obstructive sleep apnea (OSA) [10], alveolar hypoventilation and oxygen desaturation [11], and asthma [12], All are possible complications associated to childhood obesity.

Liver affection ranging from simple fatty liver up to progressive steatohepatitis and cirrhosis [13]. Musculoskeletal affection in the form of more frequent fractures, joint pain, and lower extremity malalignment [14]. Skin abnormalities, including Acanthosis nigricans, intertrigo, hidradenitis suppurativa, furunculosis, and stretch marks usually associate obesity [15].

Obese girls may experience Menstrual irregularities, acne, and hirsutism (polycystic ovary syndrome) [16].

Metabolic syndrome - a major health problem strongly correlated to obesity - is known as a group of cardiovascular risk factors often clustered together with a condition of insulin resistance [17].

According to IDEFICS (Identification and prevention of Dietary - and lifestyle - induced health Effects in Children and infants); metabolic syndrome is identified as presence of central obesity represented by waist circumference more than 90th Percentile [18], Elevated blood pressure with SBP above 90th percentile or DBP above 90th percentile [19], Dyslipidaemia in the form of Triglycerides above 90th percentile or HDL cholesterol below 10th Percentile [20], and hyperglycemia

with fasting glucose above 90th percentile or HOMA-insulin resistance above 90th percentile [21].

Irisin, a new molecule found circulating in plasma of obese children. Studies were established to identify whether Irisin role is to protect against harmful outcome of obesity or if it is one of the harmful consequences by itself. Then come Boström, et al., 2012 to identify Irisin as a protective hormone that have the ability to induce browning of white adipose tissue increasing energy expenditure and protecting against insulin resistance and obesity [22]. Irisin is produced by human muscles and adipose tissue [23].

Furthermore, Irisin was found to be secreted from different tissues and organs other than muscles and adipose tissue. It's secreted by liver, spleen, stomach, pancreas, adipose tissue, cardiovascular system (CVS), brain, bone, kidneys, ovaries, testis, immune system, peripheral myelin sheath, intestinal L cells and pancreatic islets, and fetal skeletal muscle cells as evidenced by Irisin staining [24]. Irisin plays a role in preserving integrity of brain and protection against neurodegenerative diseases, such as Alzheimer's disease [25].

Irisin may exert a potential anti-ageing effects [26].

Irisin mediates the protective effects of physical activity on lipid and glucose metabolism and on inflammation as well [27].

Irisin plays a role in preserving Liver cell integrity protecting against oxidative stress, inflammation and apoptosis [28].

Studies have been going forward to discover availability of using Irisin as a synthetic molecule applied by therapeutic doses to human cells [29].

Although Irisin may not replace the valuable outcome of exercise, it could still be used as an attractive molecule in treatment of metabolic diseases and muscle disorders regarding its effects on human adipocytes and myocytes as well [30]. The aim of the study is to evaluate the association of plasma level of Irisin with the anthropometric and metabolic parameters in normal weight, overweight and obese children.

2. Patients and Methods:

This was a cross sectional study performed in Endocrinology Pediatric clinic in Beni Suef University hospital over one year (from June 2018 to June 2019) involving 69 children, verbal consents were obtained.

2.1 Inclusion criteria:

1. Age group from 6 years up to 18 years.
2. Exogenous obesity BMI > 95% percentile and overweight BMI > 85% percentile, based on the Egyptian Growth Chart [31].
3. Normal weight children.

Exclusion criteria:

1. Patients less than 6 years old, more than 18 years old.
2. Obesity with impaired mentality.

3. Obesity associated with syndromes.

4. Obesity associated with genetic disorders.

5. Endocrinal causes of obesity (Cushing, hypothyroidism,….etc).

6. Underweight children.

2.2 All subjects were subjected to:

1. History taking:

Personal History: Name, age (date of birth), sex, address and phone number.

Perinatal History:

A- Prenatal: Diabetes, hypertension, others

B- Natal: Preterm / full term, NVD / CS, and birth weight.

C- Post natal history: Convulsions, jaundice, NICU admission.

Developmental History: Delayed / normal.

Nutritional History: Exclusive breast feeding till 6 months or not.

Medical History:

A- History of any present or past illness.

B- History of drug intake.

C- Chronic disease, chronic therapy, chronic endocrine disorders.

Family History of obesity, diabetes mellitus or hypertension.

2. Clinical examination:

General examination: (blood pressure, pubertal assessment, complete physical examination: Chest, Cardiac, Abdominal, Neurological and skin examination for presence of Acanthosis Nigricans a marker for Insulin Resistance.

Anthropometric assessment: (weight, height, waist circumference and hip circumference).

3. Laboratory tests: (Serum Irisin, cholesterol, high density lipoprotein, triglycerides, fasting insulin, serum fasting glucose, and oral glucose tolerance test).

4. Insulin resistance and sensitivity were assessed by calculating HOMA-IR (Homeostasis model assessment method-Insulin Resistance) from fasting insulin and fasting glucose.

5. Metabolic syndrome criteria were applied according to:

Mc-cooks criteria [32], MSC ATPIII criteria, MSC deFerranti criteria [33], MSC IDF criteria [34].

6. BMI was calculated by applying the following formula:

$$\text{BMI} = \frac{\text{weight in kg}}{(\text{length or height in m2})}$$

Then plotted on Egyptian Growth Percentile Charts to be categorized into :

Normal weight.

Obese (BMI equal or above the 95th percentile).

Overweight (BMI equal or above the 85th percentile but less than the 95th percentile).

7. Waist /hip ratio is then calculated after measuring waist and hip circumferences.

Statistical methodology:

Data were analyzed using the software, Statistical Package for Social Science, (SPSS) version 19. Frequency distribution with its percentage and descriptive statistics with mean and standard deviation were calculated. Chi-square, t-test, correlations were done whenever

needed. P values of less than 0.05 were considered significant.

3. Results:

The current study is cross sectional study conducted on 69 normal weight (BMI<85th), overweight (BMI≥85th), and obese subjects (BMI≥ 95th percentile for age and sex) (39 males and 30 females), (20 normal weight, 13 overweight, 36 obese children), aged 6-18 years. All are recruited from Endocrinology Pediatric clinic in Beni Suef university hospital over one year from June 2018 to June 2019.

Table (1): Baseline characteristics of all studied groups:

Characteristics	Normal N=20 no.(28.98%)	Overweight N=13 no.(18.84%)	Obese N=36 no.(52.17%)	P-value
Age Mean±SD	10.9±3.37	11.1±1.5	10.3±2.3	0.569
Sex Females Males	10(50) 10(50)	8(61.5) 5(38.5)	21(58.3) 15(41.7)	.768

Scale data was presented as mean ± SD& categorical data was presented as number (%)

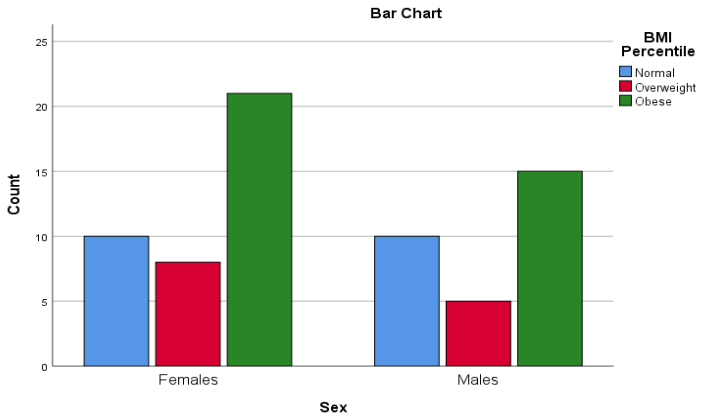


Figure (1) Sex distribution in the studied groups.

Table (1) & figure (1) showed that there were no statistically significant differences between groups regarding their age and sex distribution (P-value>0.05).

Table (2) Family history and past history of overweight and obese groups:

History	Overweight N=13 no.(%)	Obese N=36 no.(%)	P-value
Similar condition			
No	10(76.9)	18(50)	0.167
Yes	3(23.1)	18(50)	
FH of HTN			
No	5(38.5)	16(44.4)	0.644
Yes	8(61.5)	20(55.6)	
FH of DM			
No	6(46.2)	16(44.4)	0.666
Yes	7(43.8)	20(55.6)	

Scale data was presented as mean ± SD & categorical data was presented as number (%)

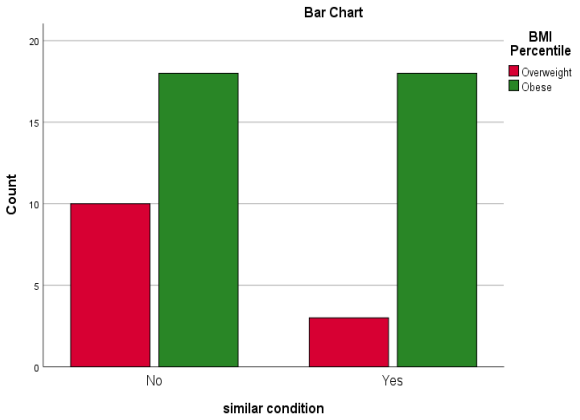


Figure (2)

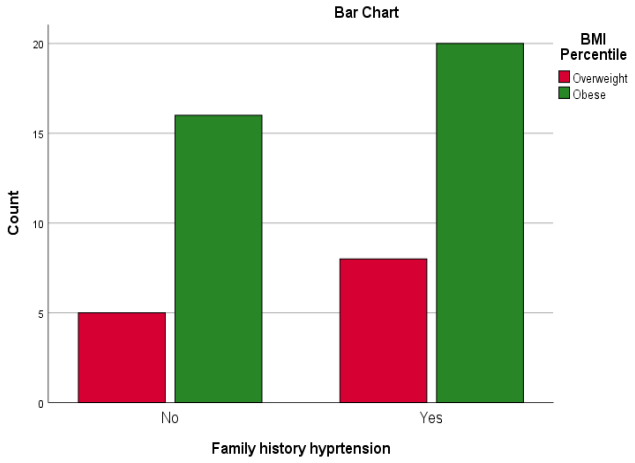


Figure (3)

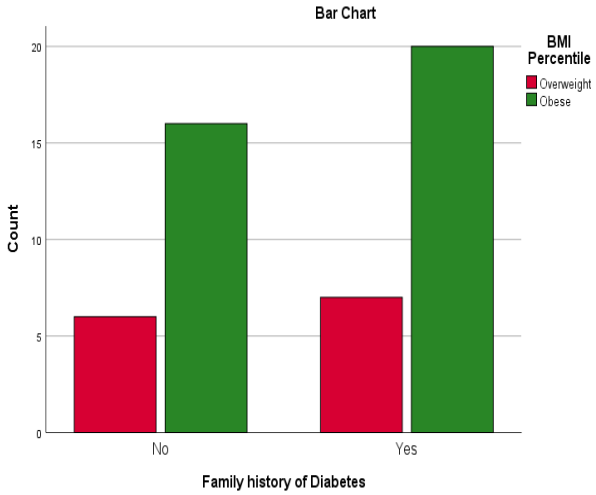


Figure (4)

Figures (2, 3, 4) History distribution among the overweight and the obese groups

Table (2) & figure (2, 3, 4) showed that there were no statistically significant differences between the overweight and the obese groups regarding presence of similar conditions, and family history of hypertension or diabetes (P-value>0.05).

Table (3) General examination of all studied groups:

Examination	Normal N=20 no.(%)	Overweight N=13 no.(%)	Obese N=36 no.(%)	P-value
Skin				
Normal	20(100)	12(92.3)	24(66.7)	0.005*
Acanthosisnegricans	0 (0)	1(7.7)	12(33.3)	
Skeletal				
Normal	20(100)	13(100)	36(100)	-----
Chest				
Normal	20(100)	13(100)	36(100)	-----
CNS				
Normal	20(100)	13(100)	36(100)	-----

Categorical data was presented as number (%) *P-value is significant

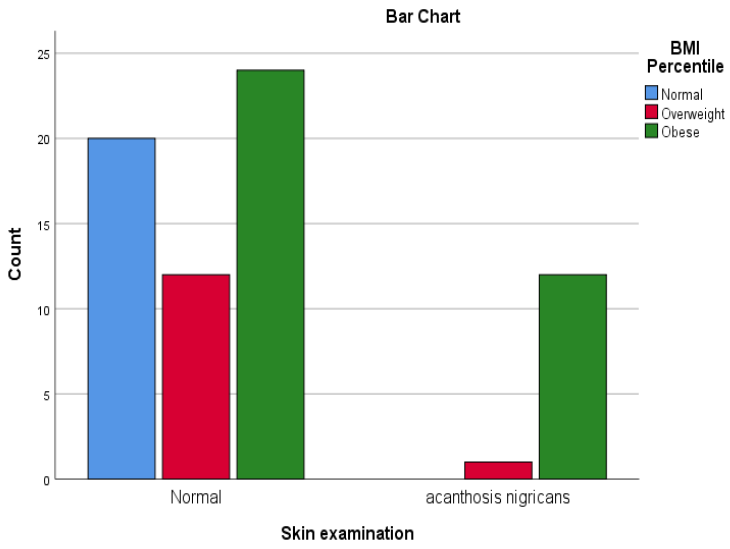


Figure (5) Skin examination

Table (3) & figure (5) showed that there was a statistically significant differences between groups regarding the presence of acanthosis negricans (P-value<0.05) as the obese children had the highest prevalence of it (33.3%).

Table (4) Distribution of blood pressure among all the studied groups:

Blood pressure		Normal N=20 no.(%)	Overweight N=13 no.(%)	Obese N=36 no.(%)	P-value
Normal	Systolic				
	50th	7(35)	2(15.4)	2(5.6)	
	90th	13(65)	7(53.8)	9(25)	<0.001**
High	95th				
	99th	0(0)	3(23.1)	19(52.8)	
		0(0)	1(7.7)	6(16.7)	
Normal	Diastolic				
	50th	2(10)	0(0)	0(0)	
	90th	18(90)	3(23.1)	10(27.8)	<0.001**
High	95th				
	99th	0(0)	10(76.9)	19(52.8)	
		0(0)	0(0)	7(19.4)	

Categorical data was presented as number (%) *P-value is highly significant

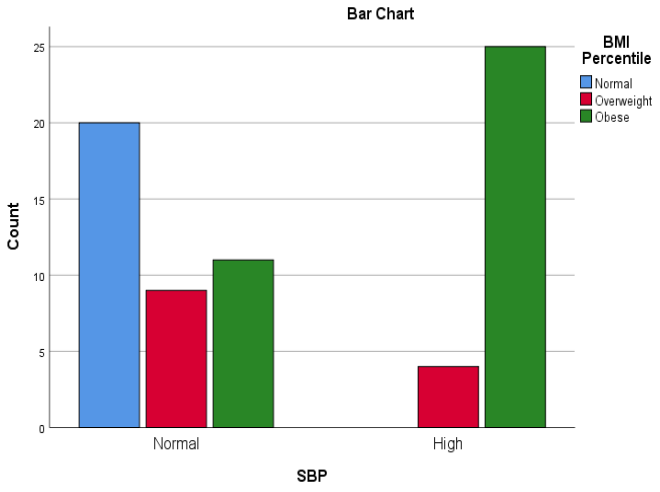


Figure (6 a)

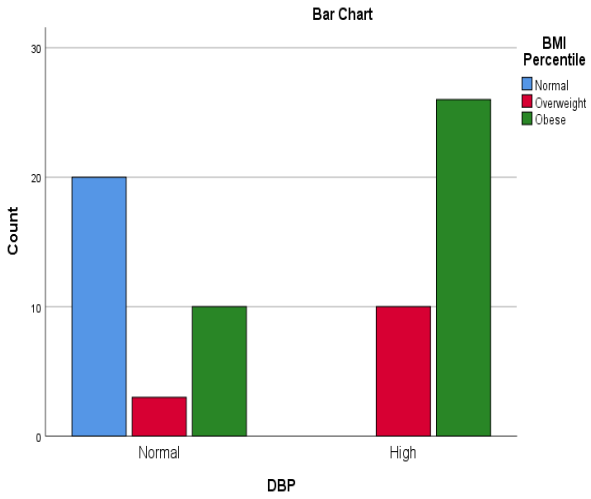


Figure (6 b)

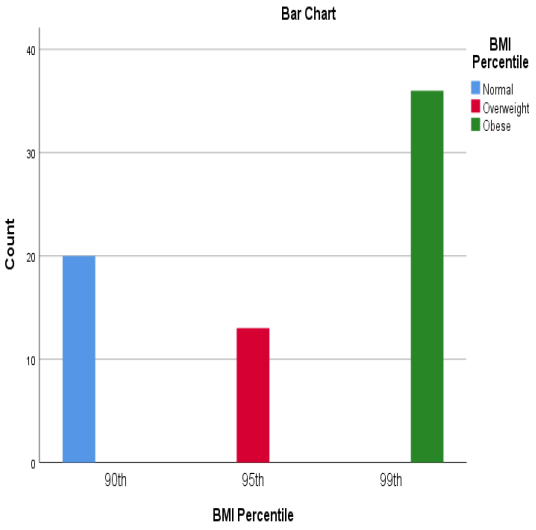
Figure(6 a & b) Distribution of systolic and diastolic blood pressure in the three groups

Table (4) & figure (6 a & b) showed that most of the overweight and the obese groups were hypertensive (had a highly significant proportions of high systolic and diastolic blood pressure P-value>0.001).

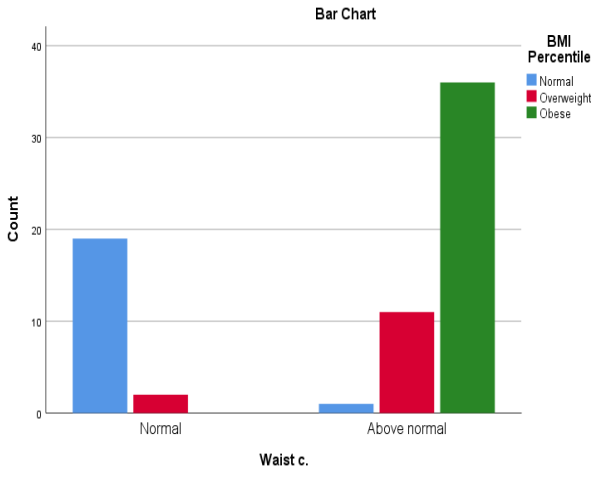
Table (5) General examination of the three studied groups:

Examination	Normal N=20 no.(%)	Overweight N=13 no.(%)	Obese N=36 no.(%)	P-value
Weight SD				
Below normal(<-2)	0(0)	0(0)	0(0)	
Normal (-2:+2)	20(100)	0(0)	0(0)	<0.001**
Above normal(>+2)	0(0)	13(100)	36(100)	
Mean±SD	35.8±13	57.9±11.4	69±22.3	<0.001**
Height SD				
Mean±SD	141.4±17.9	148.7±10.6	143.9±14.8	0.404
Waist circumference				
Normal	19(95)	2(15.4)	0(0)	<0.001**
Above normal	1(5)	11(84.6)	36(100)	
Mean±SD	67.4±8.6	93±17.1	100.6±14	<0.001**
Hip circumference	-----			
Mean±SD		101.6±11.2	105.7±15.9	0.518
W/H ratio				
Less than 1	-------	10(76.9)	27(75)	0.843
More than 1		3(23.1)	8(25)	
Mean±SD	-------	0.91±0.11	0.93±0.14	0.296

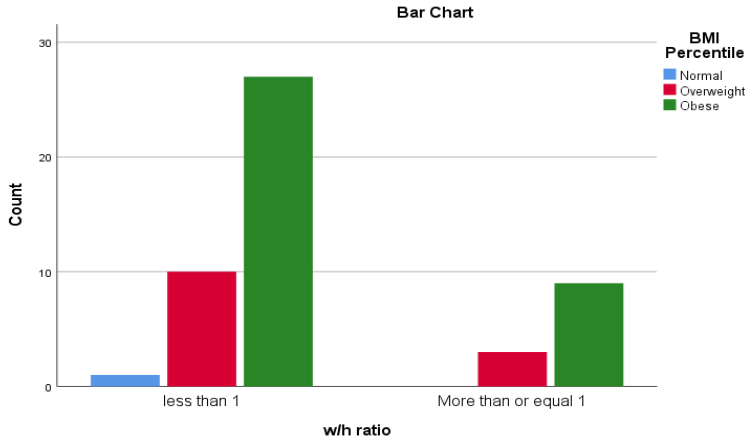
Scale data was presented as mean±SD& categorical data was presented as number (%)



(Figure 7 a)



(Figure 7 b)



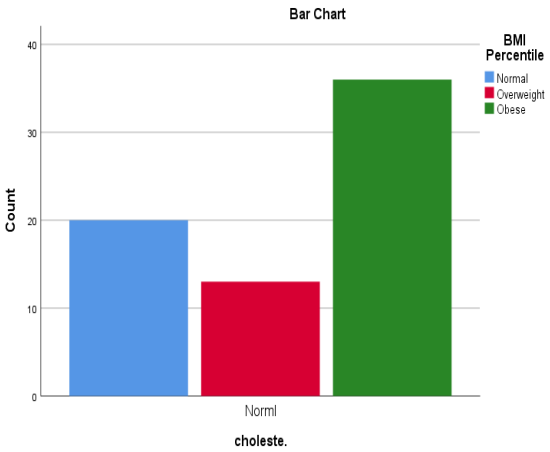
(Figure 7 c)

Table (5) and figure 7 (a, b, and c) showed that obese group had the highest weigh and waist circumference, significantly (P-value<0.001).

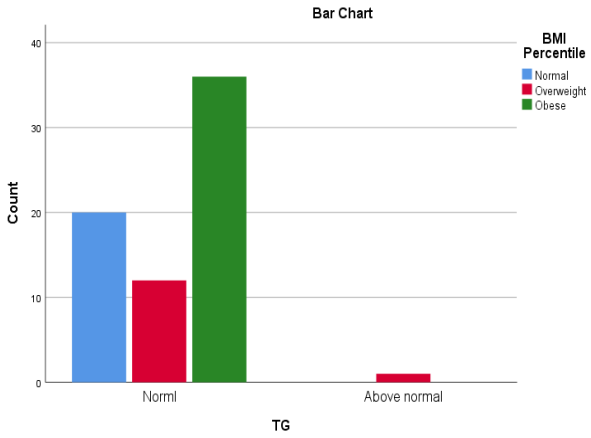
Table (6) Lipid profile of the three studied groups:

Lipid profile	Normal N=20 no.(%)	Overweight N=13 no.(%)	Obese N=36 no.(%)	P-value
Cholesterol Normal < 200 Mean±SD	 20(100) 137.4±13.76	 13(100) 140.9±25.4	 36(100) 152.7±24.9	 ---- 0.039*
Triglyceride Normal (35-160 mg/dl) Above normal Mean±SD	 20(100) 0(0) 93.7±6.3	 12(92.3) 1(7.7) 100.2±29.6	 36(100) 0(0) 115.7±23.9	 0.112 0.001*
HDL Normal (40-70 mg/dl) Below normal Mean±SD	 20(100) 0(0) 48.5±4.1	 10(76.9) 3(23.1) 45.7±6.3	 20(55.6) 16(44.4) 41.9±5.1	 0.002* <0.001**

Scale data was presented as mean±SD& categorical data was presented as number (%)



(Figure 8 a)



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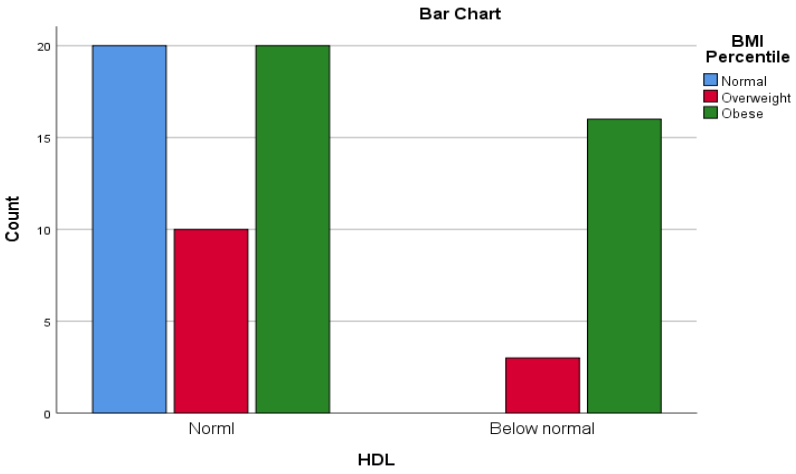


(Figure 8 c)

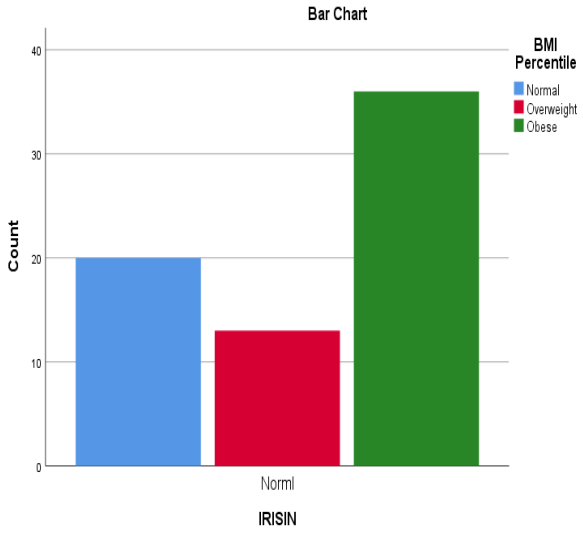
Table (6) & figure (8 a, b & c) showed that the obese group had a highest level of cholesterol and triglycerides and the lowest level of HDL significantly than the normal and the overweight groups (P-value<0.001).

Table (7) Hormonal profile, fasting glucose and glucose tolerance tests of the three studied groups:

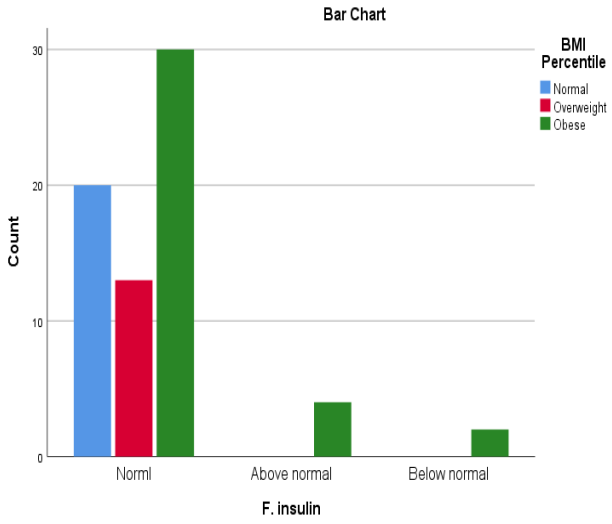
Parameters	Normal N=20 no.(%)	Overweight N=13 no.(%)	Obese N=36 no.(%)	P-value
Irisin Normal (7.8 up to 500) Mean±SD	 20(100) 64.8±30.2	 13(100) 63±19.3	 36(100) 110.8±63.4	 ---- 0.001*
Fasting insulin				

Normal (3-25)	20(100)	13(100)	30(83.3)	
Above normal	0(0)	0(0)	4(11.1)	0.197
Below normal	0(0)	0(0)	2(5.6)	
Mean±SD	10.7±5	7.4±4.5	11.1±8.5	0.258
Fasting glucose				
Normal (60-100 mg/dl)	20(100)	12(92.3)	31(86.1)	0.208
Above normal	0(0)	1(7.7)	5(23.9)	
Mean±SD	73.1±7.5	80.2±14.1	80.6±13.6	0.086
OGTT 3				
Normal (< 170 mg/dl)	20(100)	13(100)	36(100)	-----
Mean±SD	123.7±12.7	94.4±16.9	90.5±13.9	<0.001**
OGTT 4				
Normal (< 130 mg/dl)	20(100)	13(100)	36(100)	-----
Mean±SD	85.±17.7	75.5±18.5	69.8±11.3	0.002*

Scale data was presented as mean±SD& categorical data was presented as number (%)



(Figure 9 a)



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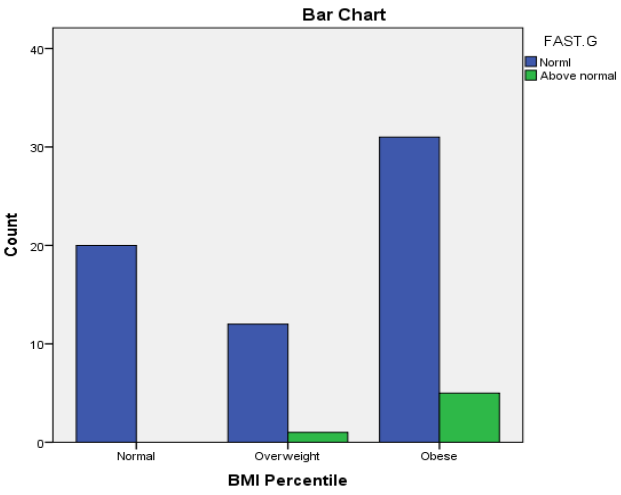
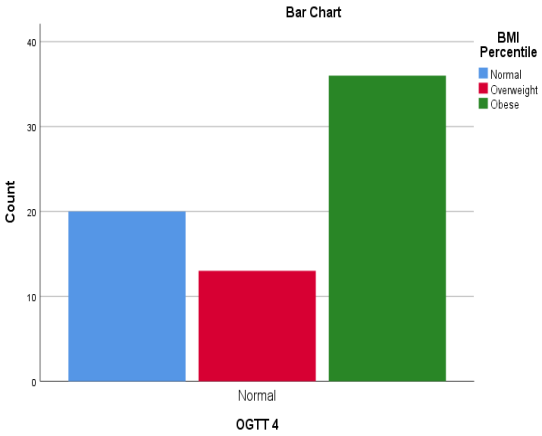
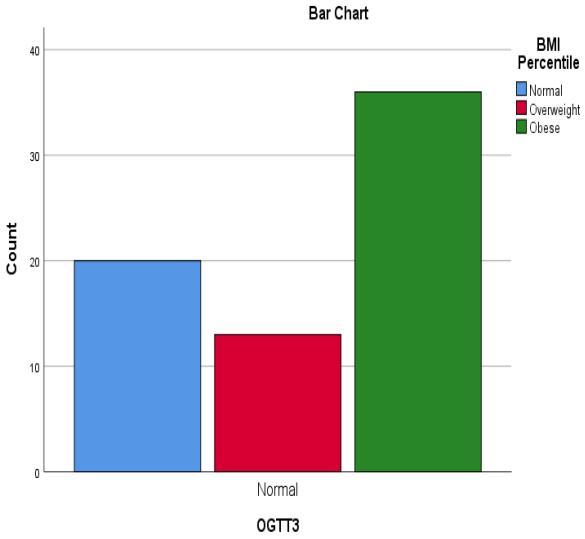


(Figure 9 c)



(Figure 9 e)



(Figure 9 d)

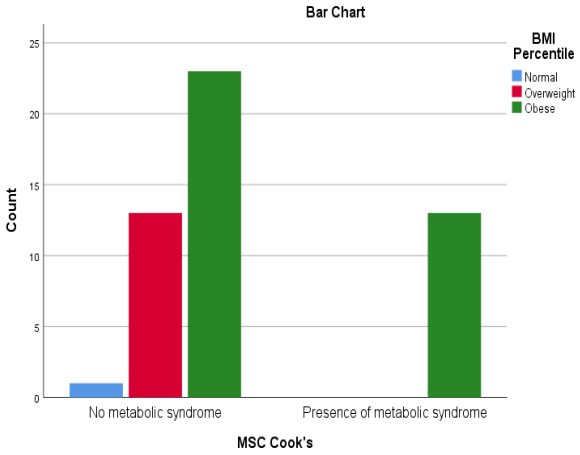
Table (7) & (figure 9 a, b, c, d & e) showed that the obese group had a higher level of Irisin than the normal and the overweight groups (P-value<0.001) but, the normal weight group had a higher level of oral glucose tolerance test 3 & 4 (P-value<0.001 and 0.002).

Table (8) Comparison between the overweight and obese group regarding presence of metabolic syndrome:

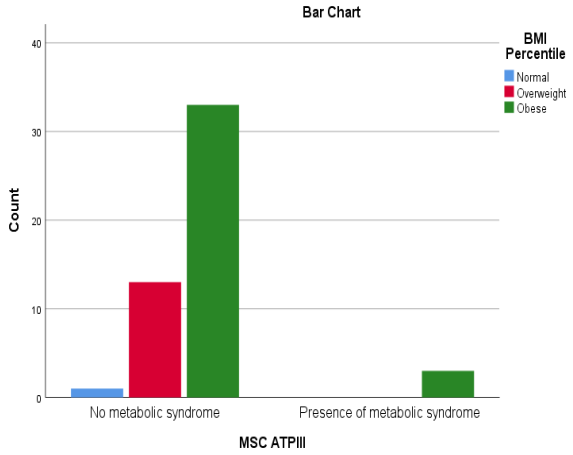
Metabolic syndrome criteria		BMI Percentile		P-value
		Overweight	Obese	
MSC	No metabolic syndrome	13	23	
Cook's		100.0%	63.9%	0.033*

	Presence of metabolic syndrome	0	13	
		0.0%	36.1%	
MSC ATPIII	No metabolic syndrome	13	33	0.538
		100.0%	91.7%	
	Presence of metabolic syndrome	0	3	
		0.0%	8.3%	
MSC deFerranti	No metabolic syndrome	11	13	0.007*
		84.6%	36.1%	
	Presence of metabolic syndrome	2	23	
		15.4%	63.9%	
MSC IDF	No metabolic syndrome	13	32	0.429
		100.0%	88.9%	
	Presence of metabolic syndrome	0	4	
		0.0%	11.1%	

Categorical data was presented as number (%)



(Figure 10 a)



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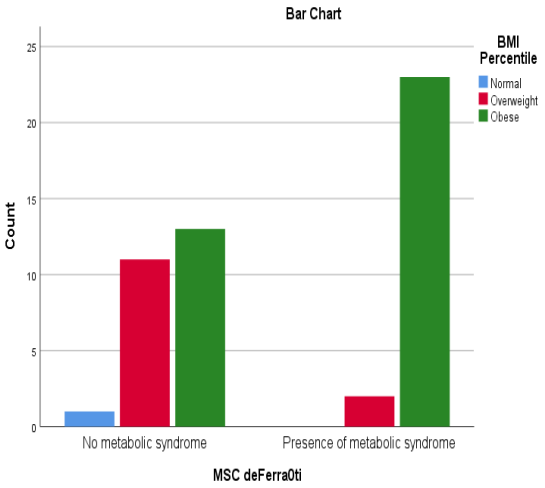
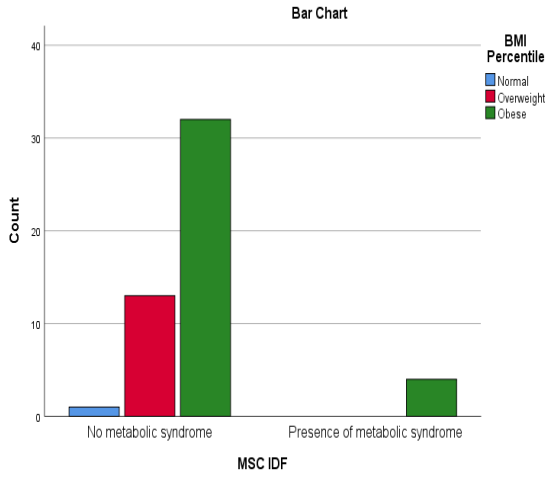


(Figure 10 c)



(Figure 10 d)

Table (8) & figure (10 a, b, c & d) showed that the obese group had a significant higher prevalence of metabolic syndrome regarding the MSC Cook's and the MSC deFerranti criteria only.

Table (9) Correlation between Irisin level and the other patient and laboratory criteria in obese, overweight and the normal groups:

Parameters		Irisin		
		Obese group	Overweight group	Normal
Age	Pearson Correlation (r)	0.159	0.666*	-0.375
	P-value	0.353	0.013	0.103
SBP	Pearson Correlation (r)	0.348*	0.652*	-0.226
	P-value	0.037	0.016	0.338
DBP	Pearson Correlation (r)	0.377*	0.500	-0.319
	P-value	0.023	0.082	0.170
BMI	Pearson Correlation (r)	0.530**	0.723**	-0.273
	P-value	0.001	0.005	0.244
w/h ratio	Pearson Correlation (r)	-0.034	0.476	.
	P-value	0.843	0.100	
Cholesterol	Pearson Correlation (r)	0.372*	0.424	-0.295
	P-value	0.026	0.149	0.207
TG	Pearson Correlation (r)	0.217	0.206	0.145

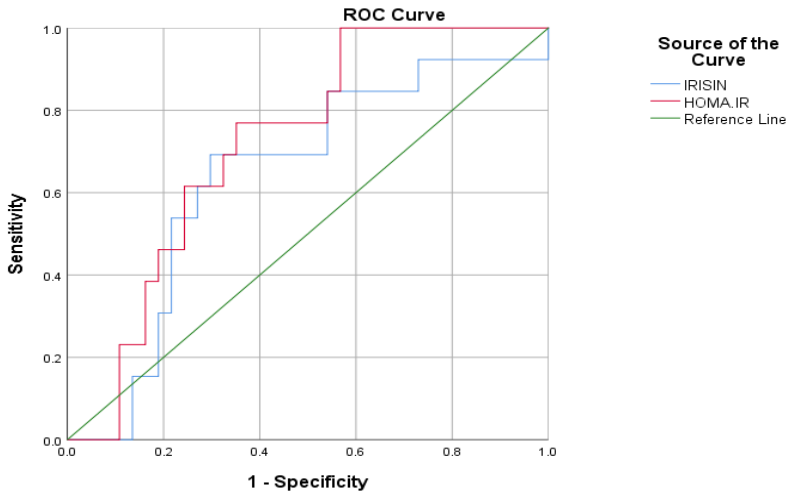
	P-value	0.204	0.499	0.541
HDL	Pearson Correlation (r)	0.174	0.388	0.259
	P-value	0.309	0.190	0.270
F. insulin	Pearson Correlation (r)	0.341*	0.599*	-0.342
	P-value	0.042	0.030	0.140
FAST. Glucose	Pearson Correlation (r)	0.344*	-0.119	-0.050
	P-value	0.040	0.698	0.833
OGTT3	Pearson Correlation (r)	-0.007	-0.422	-0.098
	P-value	0.969	0.151	0.680
OGTT4	Pearson Correlation (r)	-0.002	-0.109	-0.031
	P-value	0.992	0.724	0.898
MSC Cook's	Pearson Correlation (r)	-0.031	0.316	
	P-value	0.856	0.292	
MSC ATPIII	Pearson Correlation (r)	-0.015	0.635*	
	P-value	0.930	0.020	
MSC deFerranti	Pearson Correlation (r)	0.318	0.478	
	P-value	0.058	0.098	
MSC IDF	Pearson Correlation (r)	0.539**	0.697**	
	P-value	0.001	0.008	
HOMA.IR	Pearson Correlation (r)	0.491**	0.524	-0.316
	P-value	0.002	0.066	0.174

Correlation is significant at the 0.01 level (2-tailed).

Table (9) showed that in the obese group there was a significant linear positive correlation between the Irisin level and blood pressure, body mass index, cholesterol level, fasting insulin, fasting glucose, the number of criteria of metabolic syndrome of Metabolic Syndrome Components as regards International Diabetic Federation and the HOMA IR score.

In the overweight group, there was a significant linear positive correlation between the Irisin level and age, blood pressure, body mass index, fasting insulin and the number of criteria of metabolic syndrome of Metabolic Syndrome Components as regards International Diabetic Federation.

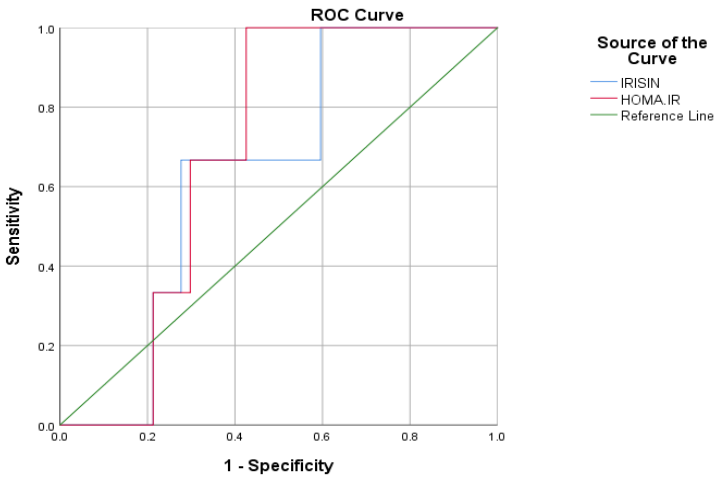
Figure (11) Prediction of presence of metabolic syndrome (regarding the Mc-cooks criteria) by using the IRISIN level and the HOMA-IR score:



Test Result Variable(s)	Area under the curve	Cut off value	Sensitivity	Specificity
IRISIN	0.640	70	84.6%	46%
HOMA-IR	0.717	1.1	100%	44%

Table (10) and figure (11) shows that the IRISIN can predict the presence of metabolic syndrome (regarding the Mc-cooks criteria) at a cut off 70 with sensitivity 84.6% and specificity 46% and HOMA-IR can predict the presence of metabolic syndrome (regarding the Mc-cooks criteria) at a cut off 1.1 with sensitivity 100% and specificity 44%.

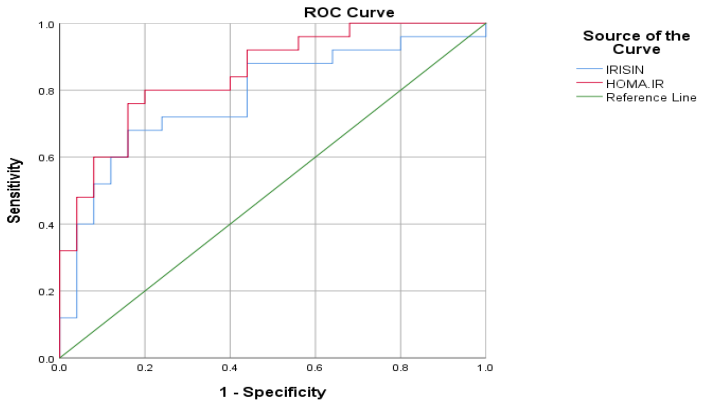
Figure (12) Prediction of presence of metabolic syndrome (regarding the MSCATPIII criteria) by using the IRISIN level and the HOMA-IR score:



Test Result Variable(s)	Area under the curve	Cut off value	Sensitivity	Specificity
IRISIN	0.638	70	100%	40%
HOMA-IR	0.688	1.1	100%	44%

Table (11) and figure (12) shows that the IRISIN can predict the presence of metabolic syndrome (regarding the MSC ATPIII criteria) at a cut off 70 with sensitivity 100% and specificity 40% and HOMA-IR can predict the presence of metabolic syndrome (regarding the MSC ATPIII criteria) at a cut off 1.1 with sensitivity 100% and specificity 44%.

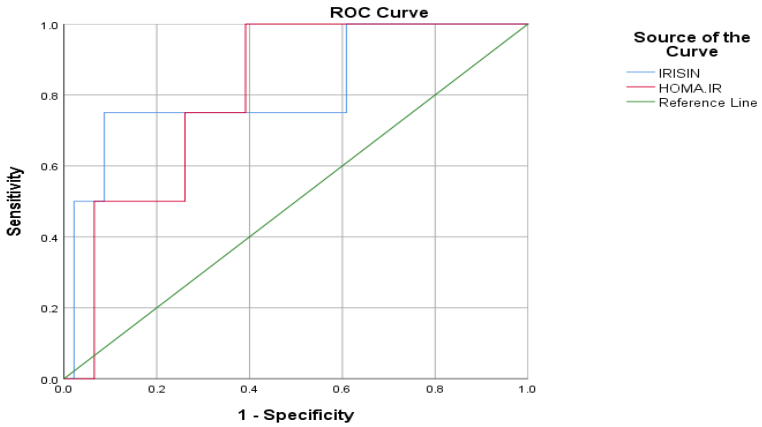
Figure (13) Prediction of presence of metabolic syndrome (regarding the MSCdeFerranti criteria) by using the IRISIN level and the HOMA-IR score:



Test Result Variable(s)	Area under the curve	Cut off value	Sensitivity	Specificity
IRISIN	0.779	70	80%	56%
HOMA-IR	0.850	1.1	92%	56%

Table (12) and figure (13) shows that the IRISIN can predict the presence of metabolic syndrome (regarding the MSC deFerranti criteria) at a cut off 70 with sensitivity 80% and specificity 56% and HOMA-IR can predict the presence of metabolic syndrome (regarding the MSC deFerranti criteria) at a cut off 1.1 with sensitivity 92% and specificity 56%.

Figure (14) Prediction of presence of metabolic syndrome (regarding the MSCIDF criteria) by using the IRISIN level and the HOMA-IR score:



Test Result Variable(s)	Area under the curve	Cut off value	Sensitivity	Specificity
IRISIN	0.815	70	75%	40%
HOMA-IR	0.804	1.1	100%	45%

Table (13) and figure (14) shows that the IRISIN can predict the presence of metabolic syndrome (regarding the MSC IDF criteria) at a cut off 70 with sensitivity 75% and specificity 40% and HOMA-IR can predict the presence of metabolic syndrome (regarding the MSCIDF criteria) at a cut off 1.1 with sensitivity 100% and specificity 45%.

4. Discussion:

Obesity, metabolic syndrome, and Irisin; three sides of one triangle. The amount of fat in the body, and their distribution as well as physical activity, are related to insulin resistance. Consequently, loss of weight and increased physical activity improve insulin resistance and metabolic syndrome as well [35].

Our study revealed a significant linear positive correlation between the Irisin level and BMI, also revealed a correlation between Irisin and body weight, waist circumference, and waist hip ratio. These results agree with Huh et al.,2012 in

a cross-sectional study of 117 healthy middle-aged women with BMI ranging from 20.0 to 47.7 kg/m2, and reported that circulating Irisin had positive associations with fat mass and a positive trend with BMI [36].

Similar results were reported by Stengel et al.,2013 in a study analyzed circulating Irisin levels over a broad spectrum of body weight in

40 patients with anorexia nervosa (mean body mass index, BMI 12.6±0.7 kg/m(2)), normal weight controls (22.6±0.9 kg/m(2)) and obese patients with BMI of 30-40 (36.9±1.2 kg/m(2)), 40-50 (44.9±1.1 kg/m(2)) and >50 (70.1±2.7 kg/m(2), n=8/group). Obese patients showed higher circulating Irisin levels compared to normal weight and anorexic patients ($p<0.05$) resulting in a correlation of Irisin with body weight ($r=0.47$, $p<0.01$) and BMI ($r=0.50$, $p<0.001$) [37].

Moreover, Pardo et al., 2014 reported that in 145 female patients, including anorexia nervosa patients, obese patients, and healthy normal weight subjects, the plasma Irisin levels were significantly elevated in the obese patients compared with the anorexia nervosa patients and normal weight subjects, and Irisin also positively correlated with body weight, BMI, and fat mass [38].

Similarly in a study done by [39], which involved 151 participants of (71 male and 80 female), it revealed that Irisin was positively correlated with BMI ($r = 0.22$), fat mass ($r = 0.21$), waist circumference ($r = 0.24$), and waist–hip ratio ($r = 0.20$).

On the other hand, the results from other studies have been controversial. Moreno-Navarrete et al., 2013 studied a subgroup of 69 non-diabetic subjects with BMI 27.61 ± 3.8, and reported that circulating Irisin decreased in association with obesity. In fact, they showed that circulating Irisin was negatively associated with BMI, percent fat mass, and waist to hip ratio [40].

Choi et al., 2013 found that plasma Irisin was negatively correlated with BMI in a study population included 104 subjects with normal glucose tolerance and 104 subjects with new-onset T2D [41].

Sanchis-Gomar et al., 2014 underwent a study involved 153 individuals divided into 20 controls and 133 patients. They did not find a positive or negative correlation between circulating Irisin levels and BMI [42].

The discrepancies in the above mentioned studies may be due to different populations analyzed in the studies, as some included obese subjects with metabolic diseases, which may influence plasma levels of Irisin.

Studies looking at patients undergoing interventions provide further evidence supporting the positive correlation between BMI and circulating Irisin levels.

One of those studies was that done by Huh et al., 2012 where blood samples were collected at baseline and 6 months after surgery in a subgroup of 14 obese subjects who were undergoing gastric banding or gastric bypass surgery. Circulating Irisin levels decreased significantly after 6 months, which was accompanied by significant weight loss [36].

Moreover, De la Iglesia et al.,2014 studied 93 Caucasian individuals diagnosed with metabolic syndrome, who followed an 8-week hypocaloric dietary strategy. They found that plasma Irisin levels were significantly reduced

at the end of the study accompanying the weight loss [43].

Consistent with this view, Crujeiras et al., 2014 reported in a group of 94 obese patients (BMI 35.66 ± 4.5 kg/m2), after a weight loss program consisting of 8 weeks of a hypocaloric diet and follow-up at 16-weeks. Irisin levels decreased paralleling body weight reduction after caloric restriction at 8 weeks, and returned to baseline levels at 24 weeks in those patients who regained the lost weight [44].

5. Conclusion and Recommendations:

Obese children exhibit a higher risk of getting involved in cardiovascular, cardiometabolic disorders and metabolic syndrome as well.

High level of Irisin in serum of obese children suggests its role as a protective hormone against harmful outcome of obesity, through enhancing process of metabolism , fat burning, energy expenditure, and keeping integrity of various body systems and organs.

Irisin as well as HOMA-IR can predict presence of metabolic syndrome with high sensitivity and specificity at different levels.

The study recommends applying further studies on therapeutic uses of synthetic Irisin molecule and how to benefit from its fat burning action.

6. References:

1. Han JC, Lawlor DA, Kimm SYS. Childhood obesity. Lancet 2010;375:1737-1748.
2. Lee EB. Obesity, leptin, and Alzheimer′s disease. Ann N Y Acad Sci 2011;1243:15-29.
3. Skinner A.C., Perrin E.M., Moss L.A., and Skelton J.A. Cardiometabolic risks and severity of obesity in children and young adults. N Engl J Med. 2015; 373: 1307–1317
4. Sawyer M.G., Harchak T., Wake M., and Lynch J. Four-year prospective study of BMI and mental health problems in young children. Pediatrics. 2011; 128: 677–684
5. Sorof J. and Daniels S. Obesity hypertension in children: a problem of epidemic proportions. Hypertension. 2002; 40: 441–447
6. Friedemann C., Heneghan C., Mahtani K., Thompson M., Perera R., and Ward A.M. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. BMJ. 2012; 345: e4759
7. Crowley D.I., Khoury P.R., Urbina E.M., Ippisch H.M., and Kimball T.R. Cardiovascular impact of the pediatric obesity epidemic: higher left ventricular mass is related to higher body mass index. J Pediatr. 2011; 158: 709–714.e1
8. Kaufman F.R., Hirst K., Linder B. et al., HEALTHY Study Group. Risk factors for type 2 diabetes in a sixth- grade multiracial cohort: the HEALTHY study. Diabetes Care. 2009; 32: 953–955
9. Zeitler P., Hirst K., Pyle L. et al. TODAY Study Group. A clinical trial to maintain

glycemic control in youth with type 2 diabetes. N Engl J Med. 2012; 366: 2247–2256

10. Spilsbury J.C., Storfer-Isser A., Rosen C.L., and Redline S. Remission and incidence of obstructive sleep apnea from middle childhood to late adolescence. Sleep. 2015; 38: 23–29
11. Verhulst S.L., Schrauwen N., Haentjens D. et al. Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution. Arch Dis Child. 2007; 92: 205–208
12. Papoutsakis C., Priftis K.N., Drakouli M. et al. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. J Acad Nutr Diet. 2013; 113: 77–105
13. Feldstein A.E., Charatcharoenwitthaya P., Treeprasertsuk S., Benson J.T., Enders F.B., and Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut. 2009; 58: 1538–1544
14. Pomerantz W.J., Timm N.L., and Gittelman M.A. Injury patterns in obese versus nonobese children presenting to a pediatric emergency department. Pediatrics. 2010; 125: 681–685
15. Yosipovitch G., DeVore A., and Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. (quiz 917-920)J Am Acad Dermatol. 2007; 56: 901–916
16. Legro R.S., Arslanian S.A., Ehrmann D.A...., and Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013; 98: 4565–4592
17. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. Lancet 2005; 366: 1059–1062.
18. Nagy P, Kovacs E, Moreno LA, Veidebaum T, Tornaritis M, Kourides Y et al. Percentile reference values for anthropometric body composition indices in European children from the IDEFICS study. Int J Obes (Lond) 2014; 38(Suppl 2): S15–S25.
19. Barba G, Buck C, Bammann K, Hadjigeorgiou C, Hebestreit A, Mårild S et al. Blood pressure reference values for European non-overweight school children:The IDEFICS study. Int J Obes (Lond) 2014; 38(Suppl 2): S48–S56.
20. De Henauw S, Michels N, Vyncke K, Hebestreit A, Russo P, Intemann T et al. Blood lipids among young children in Europe: results from the European IDEFICS study. Int J Obes (Lond) 2014; 38(Suppl 2): S67–S75.
21. Peplies J, Jiménez-Pavón D, Savva SC, Buck C, Günther K, Fraterman A et al. Percentiles of fasting serum insulin, glucose, HbA1c and HOMA-IR in prepubertal normal-weight

European children from the IDEFICS cohort. Int J Obes (Lond) 2014; 38(Suppl 2): S39–S47.

22. Boström P, Wu J, JedrychowskiMP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature. 2012;481:463–468.
23. Roca-Rivada A, Castelao C, Senin LL, Landrove MO, Baltar J, Belen Crujeiras A, Seoane LM, Casanueva FF, Pardo M. FNDC5/ irisin is not only a myokine but also an adipokine. PLoS One 2013; 8:e60563.
24. Aydin S., Koluglu T., Aydin S., Kalayci M., Yilmaz M., Cakmak T., et al. A comprehensive immuno-histochemical examination of the distribution of the fat-burning protein irisin in biological tissues Peptides, 61 (2014), pp. 130-136
25. Wrann C.D, White J.P, Salogiannnis J, Laznik B.D, Wu J, Ma D, Lin J.D, Greenberg M.E, Spiegelman B.M. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. Cell Metab. 2013, 18, 649–659.
26. Rana KS, Arif M, Hill EJ, Aldred S, Nagel DA, Nevill A, Randeva HS, Bailey CJ, Bellary S, Brown JE. Plasma irisin levels predict telomere length in healthy adults. Age (Dordr) 2014; 36: 995-1001.
27. Choi K. M., "The impact of organokines on insulin resistance, inflammation, and atherosclerosis," Endocrinology and Metabolism, vol. 31, no. 1, pp. 1–6, 2016.
28. Park M.J, Kim D.I, Choi J.H, Heo Y.R, Park S.H. New role of irisin in hepatocytes: The protective effect of hepatic steatosis in vitro. Cell Signal. 2015, 27, 1831-1839.
29. Schiaffino S, Dyar KA, Ciciliot S, Blaauw B, Sandri M. Mechanisms regulating skeletal muscle growth and atrophy. FEBS J 2013; 280 : 4294 – 4314.
30. Hecksteden A, Wegmann M, Steffen A, Kraushaar J, Morsch A, Ruppenthal S et al. Irisin and exercise training in humans — Results from a randomized controlled training trial. BMC Med 2013; 11: 235.
31. Ghali I, Salah N, Hussien F, Erfan M, El-Ruby M, Mazen I, Sabry M, Abd El-Razik M, Saad M, Hossney S, Ismaail and Abd El-Dayem S. Egyptian growth curves for infants, children and adolescents. Published in: Crecerenelmondo. Satorio A, Buckler JMH and Marazzi N (2008), Ferring Publisher, Italy
32. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. Arch Pediatr Adolesc Med 2003; 157: 821–827.
33. De Ferranti SD, Gauvreau K, Ludwig DN, Neufeld EJ and Newburger JW. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. Circulation; Vol. 110: pp2494-2497.

34. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes. 2007;8(5):299–306.
35. Inoue DS, De Mello MT, Foschini D, et al. Linear and undulating periodized strength plus aerobic training promote similar benefits and lead to improvement of insulin resistance on obese adolescents. J Diabetes Complicat. 2015;29(2):258–64.
36. Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE, Mantzoros CS. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism. 2012, 61 (12): 1725-38. 10.1016/j.metabol.2012.09.002
37. Stengel A, Hofmann T, Goebel-Stengel M, Elbelt U, Kobelt P, Klapp BF. Circulating levels of irisin in patients with anorexia nervosa and different stages of obesity–correlation with body mass index. Peptides. 2013, 39: 125-30.
38. Pardo M, Crujeiras AB, Amil M, Aguera Z, Jimenez-Murcia S, Banos R, Botella C, de la Torre R, Estivill X, Fagundo AB, Fernandez-Real JM, Fernandez-Garcia JC, Fruhbeck G, Gomez-Ambrosi J, Rodriguez R, Tinahones FJ, Fernandez-Aranda F, Casanueva FF. (2014): Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. Int J Endocrinol. 2014, 2014: 857270-
39. Park KH, Zaichenko L, Peter P, Davis CR, Crowell JA, Mantzoros CS. Diet quality is associated with circulating C-reactive protein but not irisin levels in humans. Metabolism. 2014, 63 (2): 233-41. 10.1016/j.metabol.2013.10.011
40. Moreno-Navarrete JM, Ortega F, Serrano M, Guerra E, Pardo G, Tinahones F, Ricart W, Fernandez-Real JM. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J Clin Endocrinol Metab 2013;98:E769-78.
41. Choi YK, Kim MK, Bae KH, Seo HA, Jeong JY, Lee WK, Kim JG, Lee IK, Park KG. Serum irisin levels in new-onset type 2 diabetes. Diabetes Res Clin Pract. 2013, 100 (1): 96-101. 10.1016/j.diabres.2013.01.007
42. Sanchis-Gomar F, Alis R, Pareja-Galeano H, Sola E, Victor VM, Rocha M, Hernandez-Mijares A, Romagnoli M. Circulating irisin levels are not correlated with BMI, age, and other biological parameters in obese and diabetic patients. Endocrine. 2014, 46 (3): 674-7. 10.1007/s12020-014-0170-9
43. De la Iglesia R, Lopez-Legarrea P, Crujeiras AB, Pardo M, Casanueva FF, Zulet MA, Martinez JA. Plasma irisin depletion under energy restriction is associated with improvements in lipid profile in metabolic syndrome patients. Clin Endocrinol (Oxf) 2014;81:306-11.

44. Crujeiras AB, Pardo M, Arturo RR, Navas-Carretero S, Zulet MA, Martinez JA, Casanueva FF. Longitudinal variation of circulating irisin after an energy restriction-induced weight loss and following weight regain in obese men and women. Am J Hum Biol. 2014, 26 (2): 198-207. 10.1002/ajhb.22493