Leptin and Adiponectin in Relation to Body Mass Index and Anemia

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Abstract- Obesity/its comorbidities occasionally exist alone, but actually, this is a dynamic network of cross morbidities that are often regarded as separable entities. Obesity is nowadays viewed as an escalating risk factor for iron deficiency, and various theories have been proposed since then explaining their relation. We aimed to determine the relationship of increased body mass index (BMI) with adiponectin, leptin, and iron profile in a sample of middle-aged and older adults with and without iron deficiency anemia. An observational study was performed among 90 participants classified into three groups. Group I included healthy subjects with normal BMI; as a control. Group II included subjects with increased BMI, and group III included subjects with increased BMI and iron deficiency anemia. After overnight fasting, fasting blood glucose, triglycerides, total cholesterol, iron, total iron-binding capacity, complete blood count, serum leptin, and adiponectin were measured. There were significantly higher mean values of BMI among those with anemia, higher mean values of serum leptin, and significantly lower mean values of adiponectin. A significant positive correlation of serum leptin with BMI and a significant negative correlation of serum leptin with iron in Group III were reported. The adiponectin/leptin ratio of (0.8) was correlated with iron and homeostatic model assessment in Group III, and a ratio of (1.1) was significantly correlated with BMI and hemoglobin level in Group II. This could suggest that interventions aimed at increasing the adiponectin/leptin ratio may help in resolving anemia among obese populations by increasing their serum iron and hemoglobin.

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Keywords: Obesity; Iron deficiency; Adiponectin; Leptin; Adiponectin/leptin ratio

Introduction

Overweight and/ or obesity (ow/ob), as well as iron deficiency (ID), affect billions all over the world (1). For certain parts of the world, obesity prevalence is high. In general, the prevalence of adult obesity is rising with age. In most developed nations, the highest prevalence is about 50 and 60 years old; and earlier in many developing countries (2,3). The World Health Organization considers obesity a chronic disease and one of the great threats to public health (4,5). At almost the same level, anemia is one of the world's most prevalent micronutrient deficiency diseases. The prevalence of anemia has been shown to rise with age. However, the association between obesity and iron deficiency was firstly mentioned in 1962 (6,7).

Various theories have been proposed since then, explaining the relation between obesity and iron deficiency as; imbalanced nutrition in obese subjects, an increase in iron requirements due to increased blood volume, or decreased level of myoglobin that helps bind iron in the muscles due to decreased activity (8,9). Genetic predisposition is another interpretation; decreasing iron uptake from the duodenum in obese regardless of iron intake (10). Obesity and iron deficiency have been linked as each one affects the other; in other words, as obesity increases, it induces inflammatory mediators, which by turn increases ferritin, promoting the uptake of iron by macrophages and causing a reduction of iron absorption in the gut. As well, iron deficiency anemia may reduce mitochondrial and cellular homeostasis, which decreases activity and increases the sense of fatigue in obese subjects (11).

Adipokines are known for their pivotal role in the

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pathophysiological link between dysfunctional adipose tissue and metabolic alterations (12). Leptin was the first adipokine discovered, reporting its direct effect on the hypothalamus to reduce appetite and control food intake. Leptin is primarily produced by adipose tissue in proportion to the amount of fat stores, which is important in the regulation of energy homeostasis and other physiological processes (13). Leptin concentration is usually increased in obese subjects, but unfortunately, the target cells become resistant to its action; and as leptin shows resistance in obesity, hyperleptinemia occurs, yet the mechanism is still unclear (14).

Adiponectin is an adipocyte-derived peptide that circulates in high concentrations and is shown to have insulin-sensitizing activity, anti-inflammatory, antiatherogenic and antiapoptotic properties according to experimental tests (15). Its concentrations are decreased in obesity, insulin resistance (IR), and hyperinsulinemia (16). Low adiponectin levels are also associated with type 2 diabetes and decreased free fatty acids (FFA) entering the subcutaneous adipocyte, leading to an increased incidence of metabolic syndrome (17). As regards the relation between hemoglobin and adiponectin, several studies reported a negative correlation (18). Other studies emphasize a great direct effect between iron, ferritin, leptin, and feeding behavior (19). Both leptin and adiponectin have been related to cardiometabolic risk factors (20). The adiponectin/leptin ratio (Adpn/Lep R) has been proposed as a marker of adipose tissue dysfunction in several studies, as both of them affect metabolism, whether central or peripheral (21).

The aim of the present work is to determine the relationship of increased body mass index (BMI), i.e., ow/ob, with adiponectin, leptin, and iron profile in middle-aged and older adults Egyptians with and without iron deficiency anemia (IDA).

Materials and Methods

This observational study was conducted in the outpatient therapeutic nutrition clinic of Saint Tekla Hospital Alexandria-Egypt, between September 2019 and February 2020. The study was approved by the hospital's ethics review committee and included 90 participants. The informed written consent of each subject was collected personally.

Sample size

To estimate sample size, we conducted an a priori test for sample size calculation using the G*Power 3.1.9.2 software. We assigned an alpha of 0.05, a power (1-β) of 90 %, and detection of moderate effect size; a total sample size of 90 subjects was needed for the 3 groups (30 in each group) based on ANOVA statistical test.

A total of 90 Egyptian subjects, 45 males and 45 females (age range 40-65 years), were enrolled in this study and classified into three groups. Group I included 30 apparently healthy volunteers with normal body mass index; as a control group (Gp 1) with comparable age, sex, and socioeconomic status as patient groups. Group II included subjects with increased body mass index (Gp II), and group III included subjects with increased body mass index and iron deficiency anemia (Gp III) (22).

Subjects with clinically diagnosed acute or chronic inflammatory diseases, endocrine, cardiovascular, hepatic, renal diseases, hormonal contraception, and unusual dietary habits were excluded from the study.

Anthropometric measurements.

Bodyweight and height were assessed. BMI was calculated as weight in kilograms divided by the square of height in meters.

Laboratory tests

All subjects were subjected to the following: full history taking, full clinical examination, and investigations after overnight fasting, including fasting blood glucose (FBG), triglycerides (TG), total cholesterol, Iron (Fe), Total iron-binding capacity (TIBC); using fully automated chemistry analyzer Cobas-C and Cobas. Ferritin was done using Immuilte (2000/XPi). HBA1c was done using Nephlometer Siemens.

Complete blood count (hemoglobin) was analyzed using an automated blood cell counter (XE 2100).

Serum leptin levels were measured using quantitative determination of leptin in human serum by an enzyme immunoassay method, Alpco Immunoassays.

Serum adiponectin was measured by enzyme-linked immunosorbent assay (ELISA, Abcam's Human).

Statistical analysis

Analysis of statistics was done with version 18.0 of the Statistical Package for the Social Science (SPSS). Baseline data was interpreted as mean±SD. To evaluate the categorical variable, a Chi-square test has been used and ANOVA for differences between 3 means. Pair-wise comparison between every 2 groups was made using Post Hoc Test (Tukey). Correlation of adipokines with anthropometric and different parameters was done by Pearson correlation analysis. A statistical significance was considered at a value of $P<0.05$.

Results

The study included 90 subjects with a mean age of 49±6.3; divided into three groups according to their BMI. Group I included 30 normal weights, with a mean BMI of 22.1±1.3, as controls (12 males and 18 females) (Gp1), and group II included 30 ow/ob subjects with a mean BMI of 31.2±6 (14 males and 16 females) (Gp II), and group III included 30 ow/ob with iron deficiency anemia with mean BMI 35.5±6.9 (19 males and 11 females) (Gp III) with significant differences between the three groups. Other demographic criteria and basic biochemical tests were comparable for all, with no significant differences Table 1.

Table 1. Comparison between the studied groups according to demographic data and basic biochemistry

Parameters		Control (n=30)	ow/ob (n=30)	ow/ob+IDA (n=30)	Test of Sig (*P*)	P_1	P_2	P_3
Gender	**Male** **Female**	12(40%) 18(60%)	14(46.7%) 16(53.3%)	19(63.3%) 11(36.7%)	χ^2=3.467 (0.177)	–	–	–
Age (years)	**Mean SD.**	50.6 ± 6.3	48.3 ± 6	48.6 ± 6.7	F=1.188 (0.310)	–	–	–
Weight	**Mean±SD.**	64.3^{c} ± 7.8	84.1^{b} ± 19.6	100.5^{a} ± 10.1	F=54.01* (<0.001*)	<0.001*	<0.001*	<0.001*
Height	**Mean±SD.**	1.7 ± 0.1	1.7 ± 0.2	1.7 ± 0.1	F=0.106 (0.900)	–	–	–
BMI	**Mean±SD.**	22.1^{c} ± 1.3	31.2 ^{b} ± 6	35.5 ^{a} ± 6.9	F=83.81* (<0.001*)	<0.001*	<0.001*	<0.001*
HbA1c	**Mean±SD.**	5.5 ± 0.3	5.5 ± 0.3	5.4 ± 0.3	F=0.430 (0.652)	–	–	–
HOMA-IR	**Mean±SD.**	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.1	F=0.290 (0.749)	–	–	–
Cholesterol	**Mean±SD.**	222.8 ± 52.1	227.1 ± 49.6	228 ± 42	F=0.102 (0.903)	–	–	–
TG	**Mean±SD.**	191.4 ± 64.7	205.4 ± 81.9	211.2 ± 73.9	F=0.571 (0.567)	–	–	–
HDL	**Mean±SD.**	37.5 ± 6.9	38.4 ± 8.5	39.7 ± 6.9	F=0.679 (0.510)	–	–	–
LDL	**Mean±SD.**	121.4 ± 26.9	123.7 ± 30.9	122.8 ± 28.4	F=0.052 (0.950)	–	–	–

Means with Common letters are not significant (i.e., Means with Different letters are significant)
χ^2: Chi-square test
F: F for ANOVA test, Pair-wise comparison bet. every 2 groups were done using Post Hoc Test (Tukey)
p: *P* for comparing the studied groups
p_1: *P* for comparing Control and OW/OB
p_2: *P* for comparing between Control and OW/OB +ID
p_3: *P* for comparing OW/OB and OW/OB +ID
*: Statistically significant at $P \leq 0.05$
BMI (Min.–Max.) (18.5 – 24.9) (25.2 – 37.2) (27.2 – 48.9)

There were significantly lower mean values of hemoglobin, serum iron, and higher TIBC among those with anemia **(**ow/ob+IDA), while ferritin was comparably low in both ow/ob and ow/ob+IDA with a statistically significant difference between cases and controls.

Mean values of serum leptin were 13.6 ng/ml, 18.8 ng/ml, and 20.3 ng/ml, respectively. The mean values of adiponectin were 21.8 µg/ml, 18.3 µg/ml, and 16.2 µg/ml, respectively. A statistically significant difference between the three groups was found. The mean serum leptin among ow/ob+IDA was significantly higher than in the non-anemic ow/ob group and showed significant positive correlations with BMI and significant negative correlations with serum iron Table 2.

In Gp II, BMI range (25.2-37.2), leptin was inversely correlated with BMI (Figure 1). There was a significant negative correlation of serum leptin with hemoglobin levels in Gp II (r= -0.852, P<0.001) (Figure 2). Adpn/Lep R in Gp II was positively correlated with weight, BMI, and hemoglobin.

A significant positive correlation of serum leptin with BMI [range (27.2-48.9)] (Figure 3) and a significant negative correlation of serum leptin with iron in Gp III (r= -0.431, P=0.017) (Figure 4).

However, there was no significant correlation between serum leptin and serum ferritin or total iron-binding capacity in all groups. Adpn/Lep R was

correlated with iron and homeostatic model assessment (HOMA-IR) in Gp III (r=0.500, *P*=0.005) and (r=0.405, *P*=0.027) respectively Table 3.

Table 2. Comparison between the three studied groups according to iron profile and adipokines

Parameters		Control (n = 30)	ow/ob (n = 30)	ow/ob +IDA (n = 30)	Test of Sig (p)	p_1	p_2	p_3
Fe	**Mean ± SD.**	$0.8^a \pm 0.3$	$0.7^a \pm 0.3$	$0.3^b \pm 0.2$	F=28.489* (<0.001*)	0.121	<0.001*	<0.001*
Ferritin	**Mean ± SD.**	$78.6^a \pm 42.8$	$24.7^b \pm 4.6$	$23.5^b \pm 3.9$	F=47.717* (<0.001*)	<0.001*	<0.001*	0.982
TIBC	**Mean ± SD.**	$3.2^b \pm 0.7$	$3.3^b \pm 0.6$	$5.1^a \pm 0.5$	F=93.953* (<0.001*)	0.740	<0.001*	<0.001*
Hemoglobin	**Mean ± SD.**	$13.7^a \pm 1.2$	$13.9^a \pm 1.2$	$10.6^b \pm 0.6$	F=92.106* (<0.001*)	0.838	<0.001*	<0.001*
Leptin	**Mean ± SD.**	$13.6^c \pm 1.9$	$16.8^b \pm 1.8$	$20.3^a \pm 1.7$	105.966* (<0.001*)	<0.001*	<0.001*	<0.001*
Adiponectin	**Mean ± SD.**	$21.8^a \pm 1.8$	$18.3^b \pm 1$	$16.2^c \pm 1.1$	137.850* (<0.001*)	<0.001*	<0.001*	<0.001*
Adiponectin/ Leptin	**Mean ± SD.**	$1.6^a \pm 0.3$	$1.1^b \pm 0.1$	$0.8^c \pm 0.1$	153.663* (<0.001*)	<0.001*	<0.001*	<0.001*

Means with Common letters are not significant (i.e., Means with Different letters are significant)
F: F for ANOVA test, Pair-wise comparison bet. every 2 groups were done using Post Hoc Test (Tukey)
p: *P* for comparing the studied groups
p_1: *P* for comparing Control and OW/OB
p_2: *P* for comparing Control and OW/OB +ID
p_3: *P* for comparing OW/OB and OW/OB +ID
*: Statistically significant at $P \leq 0.05$

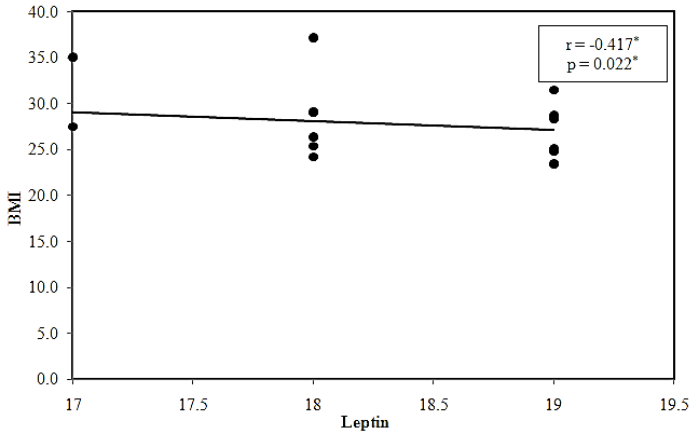

Figure 1. Correlation between Leptin with BMI in ow/ob group

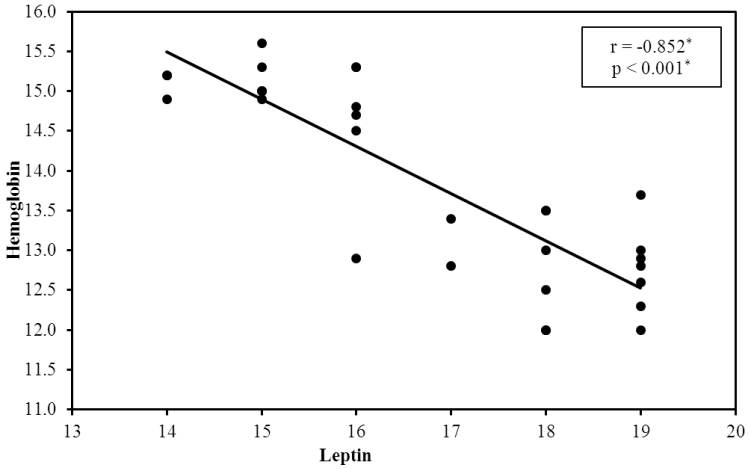

Figure 2. Correlation between Leptin with Hemoglobin in ow/ob group

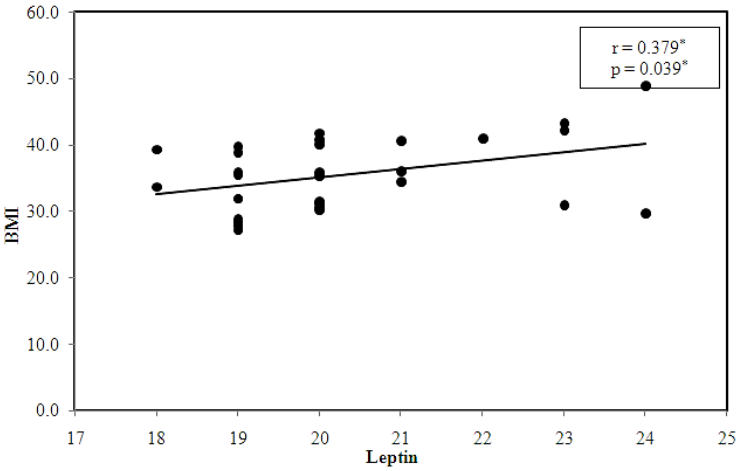

Figure 3. Correlation between Leptin with BMI in ow/ob +IDA group

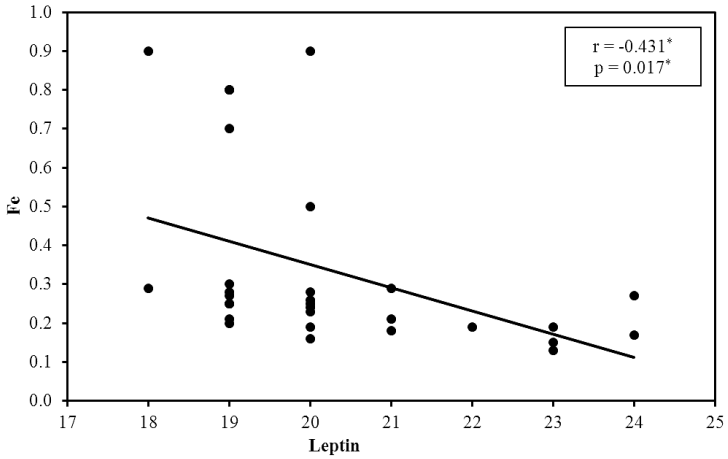

Figure 4. Correlation between Leptin with Fe in ow/ob +IDA group

Table 3. Correlation between Leptin and Adiponectin with different parameters in OW/OB & OW/OB+ID

Parameters		ow/ob			ow/ob +IDA		
		Leptin	Adiponectin	Adpn/Lep R	Leptin	Adiponectin	Adpn/Lep R
BMI	r	-0.417*	0.040	0.384*	0.379*	-0.071	-0.343
	P	0.022*	0.835	0.036*	0.039*	0.708	0.063
HOMA-IR	r	0.103	0.014	-0.081	-0.301	0.300	0.405*
	P	0.587	0.943	0.670	0.106	0.108	0.027*
Fe	r	-0.183	0.265	0.267	-0.431*	0.243	0.500*
	P	0.334	0.157	0.154	0.017*	0.196	0.005*
Ferritin	r	0.153	-0.253	-0.265	-0.048	0.097	0.102
	P	0.420	0.177	0.156	0.800	0.609	0.592
TIBC	r	0.172	0.042	-0.153	0.013	0.055	0.003
	P	0.364	0.824	0.420	0.944	0.775	0.989
Hemoglobin	r	-0.852*	0.018	0.773*	0.207	-0.223	-0.327
	P	<0.001*	0.923	<0.001*	0.271	0.237	0.077

r: Pearson coefficient
*: Statistically significant at $P \leq 0.05$

Discussion

Although obesity has become a socioeconomic burden in developed countries, the intake of energy-dense-nutrient poor foods and sedentary lifestyles have been increasing in developing countries (23). In Egypt,

the percentage of adults who are overweight (BMI≥25 kg/m^2) is 63.0%, while the percentage who are obese (BMI≥30 kg/m^2) is 35.7% in both sexes, according to the STEPwise Survey 2017 (24). Iron deficiency anemia is one of the most serious nutritional deficiencies in the world today, and in Egypt, iron deficiency remains a significant public health problem (25).

Obesity is related to abnormal iron homeostasis, poor iron absorption, and decreased iron reserves, in spite of sufficient dietary intake, in adults as well as children. Iron deficiency in obese patients is significantly higher than in non-obese. Adipose tissue generates several proinflammatory cytokines that affect the homeostasis of iron (26-27).

We investigated the relations between levels of leptin, adiponectin, and Adpn/Lep R with BMI, iron profile, and HOMA-IR in ow/ob middle-aged and older adults Egyptians with and without iron deficiency anemia. Serum leptin was negatively associated with hemoglobin in non-anemic ow/ob (Gp II), and this correlation was statistically significant and strong; r= -0.852. On the other hand, adiponectin was negatively associated with hemoglobin in ow/ob+IDA (Gp III), but this correlation was not statistically significant and weak; r= -0.223, Table 3. In ow/ob+IDA (Gp III), leptin was significantly higher as their BMI was higher than the non-anemic Gp II, while adiponectin was significantly lower in ow/ob+IDA, particularly for the same reason, Table 2.

Paradoxically in stage 5 chronic kidney disease patients, a significant positive correlation between serum leptin and hemoglobin and body mass index was found, suggesting that leptin acts synergistically with erythropoietin. Hyperleptinemia, which is often found in obesity, is a stimulating factor for erythropoiesis in hemodialysis patients (HD). Previous studies found that increased leptin levels are positively correlated with BMI, whether in chronic kidney disease patients or controls. Anemia was evidently improved in postoperative parathyroidectomy patients with elevated leptin. The notion was a hypothesis that stronger anemia management might be a link between obesity and greater survival in HD. These findings raise the possibility of leptin supplementation to protect against renal anemia (28-31).

Lewerin *et al*, (18) found that hemoglobin level was negatively correlated with adiponectin concentration, independent of age and body composition. Our study showed a negative correlation between adiponectin with hemoglobin level within the ow/ob+IDA group but was not statistically significant r= -0.223.

Honda *et al.*, found that in elderly anemic women with a mean age of 77yrs, anemia was associated with hyperadiponectinemia, whereas, in young and middle-aged women, there was no change in the level of adiponectin whether anemic or not (32). This was contradictory to our results as there was significant hypoadiponectinemia within the ow/ob +IDA group in comparison with ow/ob and controls Table 2.

Several studies suggested that adiponectin decreases obesity, causing insulin resistance and metabolic syndrome, while adiponectin supplementation may provide an effective therapeutic option for obesity-related metabolic syndrome (33). It was obvious in our study that adiponectin showed a statistically significant low level in ow/ob and ow/ob +IDA than in the control group Table 3.

Adpn/Lep R as a new biomarker corresponds more efficiently with the resistance to insulin than adiponectin and leptin alone, or HOMA-IR, and it decreases with the growing number of metabolic risk factors and is suggested as a prognostic indicator for the metabolic syndrome. From this perspective, an enhancement of this ratio was linked to a decreased risk of chronic diseases. Adpn/Lep R above 1 is considered normal; a ratio between 0.5 and 1 could indicate a medium risk increase, and a ratio below 0.5 suggests a severe metabolic risk (21). In the current study; Adpn/Lep R of (0.8) was significantly correlated with iron and (HOMA-IR) in Gp III (r=0.500, *P*=0.005) and (r=0.405, *P*=0.027) respectively. On the other hand, an Adpn/Lep R of (1.1) was significantly correlated with BMI and hemoglobin level in Gp II, Table 3. This could suggest that interventions aimed at increasing Adpn/Lep R may help in resolving anemia among ow/ob populations.

From a clinical point of view, adiponectin and leptin could be relevant factors in planning the management of high BMI subjects. Although there were no definitive studies confirming the therapeutic role of adiponectin or leptin, the Adpn/Lep R may have an influence on preventive medicine and prognostic surrogate markers for obesity-related comorbidities.

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