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Impact of Obesity on Metabolic Hormones and Interleukins in Obese Individuals with and without Metabolic Syndrome

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Abstract

Obesity is a medical condition that occurs when the body mass index (BMI) is ≥ 30 kg/m^2. Many factors cause obesity, such as unhealthy lifestyle, socioeconomic status, and genetic factors. Chronic low-grade inflammation is one of the hallmarks of obesity, and genetic factors also cause it. Obesity affects many different organ systems. This study aimed to investigate the impact of obesity on metabolic hormones and interleukins in obese individuals with and without metabolic syndrome (MetS). The study includes 140 Iraqi participants' (60 males and 80 females), who were divided into 65 obese individuals with MetS, 50 obese individuals without MetS, and 25 healthy controls during their attendance at the Endocrinology and Diabetes Consultation/ Al-Imamain Al-Kadhimain Medical City / Baghdad / Iraq, from the period (January 2023 to July 2023). The average age of participants ranged from 20 to 60 years. Blood samples (5ml) were collected from all study participants by intravenous phlebotomy. Metabolic hormones (leptin, resistin, and adiponectin) and [interleukin-10 (IL-10), interleukin-13 (IL-13), and interleukin-18 (IL18)] were measured using enzyme-linked immunosorbent assay (ELISA) kits (sandwich method). The results revealed a significant ($P<0.05$) increase in leptin, and resistin in the obese with MetS and without MetS groups compared with the control group, and a significant decrease in adiponectin level in the obese with MetS group and without MetS groups compared with the control group. According to interleukins, there was a significant decrease in the mean value of IL-10 level in the obese with MetS group and without MetS group compared with the control group, and a significant increase in IL-13 and IL-18 levels in the obese with MetS group and without MetS group compared with the control group. In conclusion, obesity affects the levels of metabolic hormones and interleukins. Some hormones and interleukins increase while others decrease with obesity.

Keywords: Interleukins, Metabolic hormones, Metabolic Syndrome (MetS), Obesity.

تأثير السمنة على الهرمونات الأيضية والإنترلوكينات لدى الأفراد المصابين بالسمنة مع و بدون متلازمة التمثيل الغذائي

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الخلاصة

السمنة حالة طبية تحدث عندما يكون مؤشر كتلة الجسم (BMI ≥ 30 كجم/م^2). هناك العديد من العوامل التي تسبب السمنة، مثل نمط الحياة الغير صحي، والوضع الاجتماعي والاقتصادي، والعوامل الوراثية. يعد الالتهاب المزمن منخفض الدرجة أحد السمات المميزة للسمنة، وتؤثر السمنة على العديد من أجهزة الأعضاء المختلفة. هدفت هذه الدراسة إلى التحقيق في تأثير السمنة على الهرمونات الأيضية والإنترلوكينات لدى الأفراد المصابين بالسمنة مع أو بدون متلازمة التمثيل الغذائي (MetS). شملت الدراسة 140 مشاركًا عراقيًا (60 ذكرًا و 85 أنثى)، تم تقسيمهم إلى 65 فردًا مصابًا بالسمنة مع متلازمة التمثيل الغذائي، و 50 فردًا مصابًا بالسمنة بدون متلازمة التمثيل الغذائي، و 25 من الأصحاء أثناء حضورهم استشارة الغدد الصماء والسكري / مدينة الإمامين الكاظمين الطبية، من الفترة (يناير 2023 إلى يوليو 2023). تراوح متوسط أعمار المشاركين من 20 إلى 60 عامًا. تم جمع عينات الدم (5 مل) من جميع المشاركين في الدراسة عن طريق السحب الوريدي. تم قياس الهرمونات الأيضية (اللبتين والريزيستين والأديبونيكتين) والإنترلوكينات (IL−10 وIL−13 وIL−18) باستخدام تقنية الاليزا. كشفت النتائج عن زيادة كبيرة ($P < 0.05$) في الليبتين والريزيستين في مجموعات السمنة مع متلازمة التمثيل الغذائي وبدون متلازمة التمثيل الغذائي مقارنة بمجموعة الاصحاء، وانخفاض كبير في مستوى الأديبونيكتين في مجموعة السمنة مع متلازمة التمثيل الغذائي وبدون مجموعات متلازمة التمثيل الغذائي مقارنة بمجموعة الاصحاء. وبحسب الإنترلوكينات، كان هناك انخفاض معنوي في متوسط قيمة مستوى IL−10 في مجموعة السمنة مع متلازمة التمثيل الغذائي والمجموعة غير المصابة بمتلازمة التمثيل الغذائي مقارنة بمجموعة الاصحاء، وارتفاع معنوي في مستويات IL−13 وIL−18 في مجموعة السمنة مع متلازمة التمثيل الغذائي والمجموعة غير المصابة بمتلازمة التمثيل الغذائي مقارنة بمجموعة الاصحاء. وبالنتيجة، تؤثر السمنة على مستويات الهرمونات الأيضية والإنترلوكينات، حيث ترتفع بعض الهرمونات والإنترلوكينات بينما تنخفض أخرى مع السمنة .

1. Introduction

Since 1980, the global prevalence of overweight and obesity has doubled, resulting in roughly one-third of the world's population being classed as overweight or obese. Obesity negatively impacts nearly all physiological functions of the body and poses considerable public health issues [1]. The body considers obesity as inflammation, which leads to stimulating the immune system and secreting cytokines known as adipokines, some of which are pro-inflammatory and some of which are anti-inflammatory. Obesity is highly associated with various metabolic disorders, including insulin resistance (IR), atherogenic dyslipidemia, non-alcoholic fatty liver disease (NAFLD), or metabolic syndrome (MetS) [2,3]. There are several criteria for MetS diagnosis, and the International Diabetes Federation criteria are focused on the central obesity [4]. In obesity, modifications of adipokines and other cytokines are thought to contribute to a low-grade inflammation within the adipose tissue (AT), impacting the progression of many secondary diseases such as MetS, (IR), diabetes, arterial hypertension, and asthma [5]. Research indicates that fat tissue exerts important endocrine functions, which are facilitated by a complex network of different soluble factors produced by adipocytes known as adipocytokines, including tumor necrosis factor a (TNF-α), Interleukins (ILs), leptin, adiponectin and resistin. Some adipokines play a major role in IR and cardiovascular complications associated with obesity, especially central or visceral obesity [6]. Obesity can occur at any age, and it has increased in both adults and children of all ages, regardless of geographical locality, ethnicity or socioeconomic status. In low-income nations, obesity is generally more common among middle-aged adults from wealthy and urban environments (especially women), whereas, in high-income countries, it impacts all ages and both genders, but its prevalence is disproportionately higher among disadvantaged groups [7]. Adipose tissue secretes the adipokine leptin, which is then transported to the brain via the blood-brain barrier by leptin transporters, known as obesity receptors. Leptin stimulates the brain to control energy balance, decrease hunger, and decrease food intake [8]. Obesity is associated with leptin

resistance, which manifests as hyperleptinemia with pro-inflammatory effects and possible involvement in the activation of immune cells [9]. Resistin was first suggested as a potential connection between obesity and diabetes and is associated with the development of atherosclerosis and cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), rheumatoid arthritis, cancer, asthma, inflammatory bowel disease, and chronic kidney disease [10].

Anti-inflammatory cytokines are regulated by obesity, and IL-10 is upregulated in the pro-inflammatory macrophages of obese and IR individuals [11]. IL-18 is a primary immune response regulator, responsible for immunological-mediated illnesses and regulates both innate and adaptive immune responses. Many studies have linked IL-18 to dyslipidemia, hypertension, obesity, and IR [12]. Individuals with MetS have been found to have higher circulating levels of IL-18, which is closely linked to the syndrome's components, predicts cardiovascular events and mortality in MetS populations, and occurs before type 2 diabetes mellitus (T2DM) develops [13]. IL-13 plays a direct role in preserving glucose homeostasis in obesity. Similar to IL-10, IL-13 is necessary to maintain insulin activity and glucose homeostasis [14].

The current study was prepared to find out the impact of obesity on some physiological and immunological parameters in obese subjects with and without metabolic syndrome.

2. Materials and Methods

2.1 Study design

This study included 140 Iraqi participants, (60 males and 85 females), who were divided into 65 obese individuals with MetS, 50 obese individuals without MetS (divided according to MetS criteria), and 25 healthy controls during their attendance at the Endocrinology and Diabetes Consultation / Al-Imamain Al-Kadhimain Medical City / Baghdad / Iraq, from the period (January 2023 to July 2023). The average age of participants ranged from 20 to 60 years. Information including both descriptive and clinical data, was obtained from each participant according to the study protocol. Blood samples (5ml) were drawn from all study subjects' by intravenous phlebotomy and, then placed in a gel tube to allow the blood to clot at room temperature. It was then centrifuged at 4000 rpm for 10 min to collect the serum, which was transferred to an Eppendorf tube and kept at −20 °C until use for the rest of the analyses.

2.2 Measuring the metabolic hormones and interleukins

Metabolic hormones (Leptin, resistin, and adiponectin) and Interleukins (IL-10, IL-13, and IL-18) were measured by Sandwich ELISA. The sandwich ELISA kit (Cloud-Clone Crop/USA), consists of a plastic microplate multi-well plate with 96 wells that is pre-coated with a specific antibody. Sera is then added to the appropriate microplate wells with a specific biotin-conjugated antibody. Then, avidin conjugate to horseradish peroxidase (HRP) was added to each microplate well and incubated. After 3,3′,5,5′-Tetramethylbenzidine (TMB) substrate solution was added, only those wells that contain specific antibodies, biotin-conjugated antibodies, and enzyme-conjugated avidin will display a color alteration. sulphuric acid solution was used to terminated the enzyme-substrate reaction and the color change was measured spectrophotometrically at a wavelength of 450 nm [15].

3. Statistical analysis

Data analysis was carried out using the available statistical package of IBM SPSS-29 (IBM Statistical Packages for Social Sciences- version 29, Chicago, IL, USA). Data were presented using simple measures of frequency, percentage. The significance of the difference of different percentages (qualitative data) was tested using the Pearson Chi-square test (2-test). One-way ANOVA with post hoc analysis was used to investigate differences between the three groups. Statistical significance was considered whenever the P value was equal to or less than 0.05.

4. Results

4.1 Distribution of the study groups according to the age

Figure-1 shows the distribution of the studied groups according to age, and it can be stated that most obese patients with and without MetS were in the age category (35-50 years). Regarding the other age categories and when a comparison was made between the two patient groups, the findings revealed that the obese with MetS was more than obese without MetS in the age category (>50 years), while the obese without MetS was more than obese with MetS in the age category (<35 years).

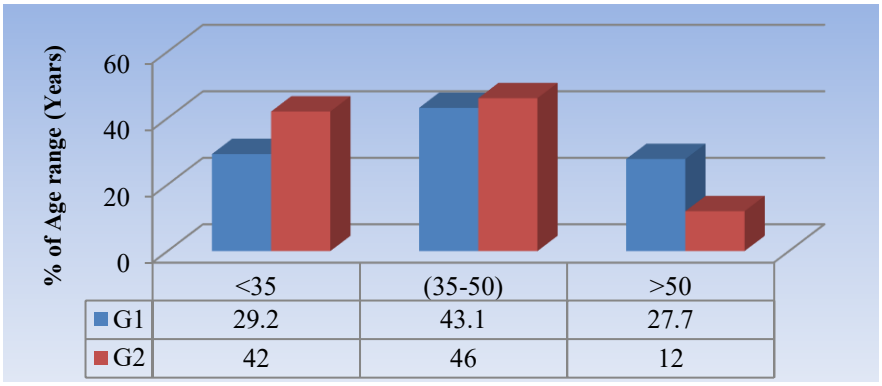

Figure 1: Distribution of the study groups according to the age

4.2 Levels of metabolic hormones of the study groups

Table-1 shows the levels of metabolic hormones in the study groups. There was a significant ($P<0.05$) increase in leptin levels in the obese with MetS group (3.14±1.35 ng/ml) and the non-MetS group (2.70±0.70 ng/ml) compared with the control group (1.52±0.54 ng/ml). In addition, there was a significant ($P<0.05$) increase in the mean value of the obese in the MetS group compared to that of without MetS group. The mean value of adiponectin was significantly ($P<0.05$) lower in the obese with MetS group (1.48±0.88 ng/ml) and without MetS group (3.24±2.43 ng/ml) compared with control (4.62±0.35 ng/ml); and significant ($P<0.05$) decrease in the mean value of obese with MetS group than without MetS group. The results showed that the mean value of resistin was significantly ($P<0.05$) higher in the obese with MetS group (3.60±1.89 ng/ml) and without MetS group (3.61±1.69 ng/ml) compared with control group (1.07±0.25 ng/ml); while between the obese groups, non-significant differences were found. The results revealed a significant ($P<0.05$) increase in mean value of Leptin/Adeponectin (L/A) ratio in obese with MetS group (0.95±0.37 ng/ml) and obese without MetS group (0.93±0.19 ng/ml) compared with control group (0.69±0.30 ng/ml), while non-significant differences were found between obese with and without MetS.

Table 1: Levels of metabolic hormones of the study groups

Metabolic hormones (Mean±SD)	Groups			*P. value*
	Control	Obese with MetS	Obese without MetS	
Leptin (ng/ml)	1.52±0.54	3.14±1.35[a, b]	2.70±0.70 [a]	≤0.001
Adiponectin(ng/ml)	4.62±0.35	1.48±0.88[a, b]	3.24±2.43 [a]	≤0.001
Resistin (ng/ml)	1.07±0.25	3.60±1.89[a]	3.61±1.69 [a]	≤0.001
L/A Ratio	0.69±0.30	0.95±0.37[a]	0.93±0.19[a]	≤0.001
*a: statistically significant compared with the control. *b: Statistically significant when compared with obese without MetS group				

4.3 Levels of interleukins in the study groups

Results in Table 2 show the levels of interleukins; there was a significant (P<0.05) decrease in the mean value of IL-10 in the obese with MetS group (102.32±72.87 Pg/ml) and without MetS group (92.50±46.62Pg/ml) compared with the control group (409.92±121.24 Pg/ml), and non-significant differences between obese groups. According to IL-13, the mean value of IL-13 in the obese with MetS group (410.19±84.76 Pg/ml) and without MetS group (441.04±164.36 Pg/ml) was significantly (P<0.05) higher than in control group (323.83±44.95 Pg/ml), and non-significant differences between obese groups. The results also showed a significant (P<0.05) increase in the mean value of IL-18 in obese with MetS group (570.28±207.94 Pg/ml) and without MetS group (572.15±149.87 Pg/ml) compared with the control group (173.10±39.80 Pg/ml), and non-significant differences between obese with and without MetS groups.

Table 2: Levels of interleukins of the study groups

Interleukins (Mean±SD)	Groups			*P. value*
	Control	Obese with MetS	Obese without MetS	
IL-10 (Pg/ml)	409.92±121.24	102.32±72.87[a]	92.50±46.62 [a]	≤0.001
IL -13 (Pg/ml)	323.83±44.95	410.19±84.76[a]	441.04±164.36 [a]	≤0.001
IL 18 (Pg/ml)	173.10±39.80	570.28±207.94[a]	572.15±149.87 [a]	≤0.001

*a: statistically significant compared with the control. *b: Statistically significant when compared with the obese without MetS group.

4.4 Effect of age on metabolic hormones in obese with and without metabolic syndrome

Table 3 shows the effect of age on metabolic hormones. The results revealed a significant (P<0.05) decrease in levels of L/A ratio with an increase in the age of the group of obese with MetS. The results of the obese without MetS group revealed a significant (P<0.05) decrease in leptin and L/A ratio levels with an increase in age.

Table 3: Effect of age on metabolic hormones in obese with and without metabolic syndrome

Metabolic hormones (Mean±SD)	Obese with MetS (Years)			*P. value*
	>35	35-50	>50	
Leptin (ng/ml)	3.54±2.30[a]	3.17±0.66[a]	2.85±0.58[a]	0.23
Adiponektin (ng/ml)	3.25±0.99[a]	3.47±0.85[a]	3.73±0.78[a]	0.24
Resistin (ng/ml)	3.20±2.02[a]	3.95±1.93[a]	3.47±1.67[a]	0.39
L/A ratio	1.11±0.60[a]	0.86±0.16[b]	0.84±0.17[b]	0.03
Metabolic hormones (Mean±SD)	**Obese without MetS (Years)**			***P. value***
	<35	**35-50**	**>50**	
Leptin (ng/ml)	3.91±0.69[a]	2.97±0.56[b]	2.23±0.97[c]	0.04
Adiponektin (ng/ml)	3.73±0.78[a]	4.91±3.43[a]	3.45±0.27[a]	0.19
Resistin (ng/ml)	3.67±1.82[a]	3.68±1.75[a]	3.12±1.07[a]	0.73
L/A ratio	0.91±0.14[a]	0.70±0.21[b]	0.64±0.27[c]	0.04

*Means in row carrying different small letters indicate a significant difference (P<0.05).
*Means in row carrying similar small letters indicate a non-significant difference (P<0.05).

4.5 Effect of age on interleukins in obese with and without metabolic syndrome

Table 4 shows the effect of age on interleukins. The results revealed a significant (P<0.05) decrease in IL-18 levels with an increase in the age of obese without MetS group.

Table 4: Effect of age on interleukin in obese with and without metabolic syndrome

Interleukins (Mean±SD)	Obese with MetS (Years)			*P. value*
	>35	35-50	>50	
IL-10 (Pg/ml)	121.38±96[a]	98.94±68.15[a]	87.45±46.89[a]	0.35
IL-13 (Pg/ml)	411.47±93.06[a]	408.59±83.93[a]	411.33±81.74[a]	0.99
IL-18 (Pg/ml)	557.98±269.17[a]	557.98±174.01[a]	602.38±190.96[a]	0.74

Interleukins (Mean±SD)	Obese without MetS (Years)			*P. value*
	<35	35-50	>50	
IL-10 (Pg/ml)	96.78±40.11[a]	94.81±56.52[a]	68.72±5.05[a]	0.14
IL-13 (Pg/ml)	440.19±127.21[a]	432.89±202.20[a]	475.24±135.70[a]	0.85
IL-18 (Pg/ml)	608.20±126.01[a]	570.94±156.72[b]	438.17±156.46[c]	0.04

*Means in row carrying different small letters indicate a significant difference (P<0.05).
*Means in row carrying similar small letters indicate a non-significant difference (P<0.05)

5. Discussion

The current results regarding the increase in metabolic hormones in the obese groups compared to the control group are in agreement with those of another study [16], which showed a link between elevated blood leptin levels and obesity. Increased serum leptin levels should be interpreted as a warning indication of an energy imbalance, inadequate nutrition, hyperinsulinemia, IR, or alterations in other metabolic risk variables that are closely linked to T2DM and CVD, especially in obese individuals [17]. The findings revealed that the level of leptin in the obese with MetS group was significantly higher than that in the non-MetS group, which is in agreement with the results of [18], who demonstrated a high correlation between leptin and central obesity and BMI, as well as with T2DM risk variables, such as HOMA index and insulin. According to adiponectin, the current results showed a decrease in obese groups, which is in agreement with the results of [19], who showed that adiponectin levels are reduced in obesity. Adiponectin has significantly decreased in obese individuals with MetS compared to those without MetS, possibly because adiponectin acts as a primary regulator of lipid and glucose homeostasis by means of its insulin-sensitizing characteristics. Adiponectin levels seem to decrease as the number of MetS components increases, and in MetS, the development of T2DM and IR leads to a decrease in adiponectin levels more than in the absence of MetS, although it is also slightly decreased in obese individuals without MetS [20]. The finding of resistin agrees with the finding of Shaheen *et al.,* who showed that overall circulating resistin concentrations were significantly higher in all categories of obesity than in healthy lean subjects, and resistin levels were observed to be the highest in subjects with obesity and diabetes simultaneously [21]. The decrease in levels of IL-10 agrees with the result of Kakar *et al.,* who showed a decreased production capacity of IL-10 in association with T2DM and MetS [22]. IL-10 modulates inflammation and maintains cellular homeostasis. The results for IL-13 are in agreement with the findings of Bantulà *et al.,* who reported that levels of IL-13 increased in the sera of obese patients' compared to the control [23]. The current finding regarding the increase in IL-18 in obese patients is compatible with a previous study [24], which reported that obese patients and those with T2DM had considerably higher levels of IL-18. In contrast, [25] showed that IL-18 concentration decreases with weight reduction. Ahmad *et al.,* reported that changes in plasma IL-18 are more closely linked to IR rather than changes in obesity in general because the expression of IL-18 is increased in obesity but not affected by weight loss; and plasma IL-18 is associated with traits of the MetS (BMI, waist circumference, TG, HDL (inversely), fasting glucose, and insulin) [26].

The current study showed a high prevalence of obesity in the second age category (35-50 years), which is in agreement with another study conducted in Saudi Arabia that reported that adult Saudi males and females have a high prevalence of obesity, and that as people age, they become much more overweight and obese [27]. The study of Pengpid and Peltzer, reported that individuals aged 40–49 years had considerably greater odds of obesity compared to those aged18–39 years; however, this difference was no longer significant for those aged 50 years and above [28]. The current study shows that obesity with MetS was higher than without MetS in the age category (>50 years) and vice versa in the age category (<35 years), because aging is a major risk factor for developing and progressing metabolic diseases in older adults. Due to various physiological changes that occur with age, these changes affect metabolic regulation and contribute to the increased risk of metabolic disorders [29]. Aging is linked to falling serum leptin levels independent of BMI, and with the development of leptin resistance, circulating leptin was inversely correlated with age and decreased by 53% in participants aged ≥60 years [30]. The L/A ratio decreases with increasing age because leptin is affected by an increase in age, which leads to a decrease in the L/A ratio in obese patients with and without MetS. According to IL-18, the current results showed a significant decrease with age in obese individuals without MetS, which agrees with Hung *et al.,* who showed that IL-18 is weakly associated with age [31]. Reduced insulin sensitivity is linked to increased levels of pro-inflammatory cytokines. Chronic low-grade inflammation causes IR, which leads to a transition from metabolically normal obesity to MetS [32]. The immune system's metabolic alterations are a major factor in many illnesses. Nutrient excess in obesity causes inflammatory reactions in skeletal muscles, adipose tissue, and other organs, which leads to diabetes and systemic insulin resistance [33].

6. Conclusion

In conclusion, regarding the findings of metabolic hormones, increased levels of leptin in obese people with MetS and increased levels of adiponectin in obese people without MetS could explain the overall variability of metabolic changes in both groups. Obesity is associated with significantly decreased levels of IL-10 and significantly increased levels of IL-13 and IL-18. While non-significant differences were found between the two groups of obese in all studied interleukins. Obesity affects the body by causing inflammatory and physiologic changes, such as hypertension, dyslipidemia, T2DM, and IR. One of the recommendations for the present is the study of genetic predisposition to obesity and MetS in obese people, and it describes the genetic causes of obesity, including monogenic, and polygenic causes associated with obesity.

Ethical approval

This study was approved on September 26, 2022, by the ethics committee of the Department of Biology, College of Science, University of Baghdad (Ref.No. CSEC/0922/0090).

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Conflict of interest

There is no conflict of interest.

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