Estimation of some biomarkers in obese men and their adoption as early risk predictors of metabolic syndrome

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Abstract---This study aimed to estimate the levels of the biomarkers ADP, IL-6, IGF-1 and MCP-1 in the serum of obese men and adopt them as early predictors of the occurrence of metabolic syndrome. A total of (88) samples from men, (and 60) samples from obese men, were divided according to body mass index (BMI) and waist circumference (WC) into two groups. The first group had BMI values between 35-40 kg/m^2 and WC 110-125 cm., while the 2nd group had BMI >40 kg/m^2 and WC >125 cm. A (28) samples were collected from healthy, with BMI values between 18.5-24.5 kg/m^2 and WC was < 102 cm. The results show that there is a significant increase level IL-6 at P ≤ 0.01 in the obese group compared with the healthy, and it was significantly higher in the group with WC > 125 cm. There was a significant decrease in the concentration biomarker IGF-1 in the obesity group, and it was significantly higher in the BMI ≥40 and WC 110-125 cm groups. It was also found the MCP-1 biomarker was significantly higher with the increase in BMI and WC values, Furthermore, the study showed there was no sign of BMI and WC on the ADP in obese group.

Keywords---Adiponectin, IL-6, IGF-1, MCP-1, Metabolic syndrome, Obesity.

1. Introduction

Obesity is a multifactorial chronic metabolic disease involving a complex interaction of genes, hormones and environmental factors. It is characterized by

an increase in fat stores of the body, so it is a gateway to the deterioration of health. It is one of the main causes of disability, cancer, cardiovascular disorders, respiratory disorders, metabolic disorders and death. In addition, it is a constantly growing social and economic burden on individuals, families and the health care system (Aktar *et al.*, 2017).

Obesity contributes to metabolic syndrome, as obesity is the main feature for this disease. In order to understand this relationship, the link between obesity and disease must be evaluated, as the accumulation of fat in tissues surrounding the viscera is directly related to the development of insulin resistance (Sironi *et al.*, 2004). It is believed that insulin resistance is a common factor in the development of metabolic syndrome. In addition, the inflammatory factors that are released by adipose tissue are also an important factor in the development of metabolic syndrome (Brooks *et al.*, 2010). Visceral fat deposits are also associated with the development of functionally disturbed fat cells (Huth *et al.*, 2016). These dysfunctional adipose tissues secrete pro-inflammatory biomarkers such as cytokines (Ellulu *et al.*, 2016 ; Akabi *et al.,* 2019), because of which a decrease in the levels of adiponectin happens, which makes the individual more susceptible to cardiovascular diseases (Golbidi *et al.*, 2012).

Metabolic syndrome has become a major public health problem and its prevalence is likely to increase to 20-30% of the adult population in most countries of the world. This prevalence depends on age, gender, race and diagnostic criteria (Eckel *et al.*, 2005). This disease has been associated with increased mortality rates because of cardiovascular disease, type II diabetes, and various other complications (Haffner, 2006).

Moreover, the assessment of metabolic syndrome and the risk of developing its complications depend on the test to determine the levels of biomarkers in the blood plasma (Mansoub *et al.*, 2006). Therefore, in many pathological cases, medicine relies on biomarkers to aid in diagnosis and follow-up when clinical signs are not clear. In addition, biomarkers also provide the ability to determine susceptibility, allowing the assessment of disease risks to population (Mayeux, 2004).

Adiponectin is a hormone derived from adipose tissue that makes up 0.01% of blood plasma proteins (Gil-Campos *et al.*, 2004). It plays an important role as a tool of communication between adipose tissue and other organs that are associated with metabolism (Wang and Scherer, 2016). It increases the oxidation of fatty acids and glucose uptake by muscle cells, as it was found that adiponectin increases the expression of glucose transport-4 (GLUT-4) (Ceddia *et al.*, 2005). Further, it reduces glucose produced by the liver (gluconeogenesis) and glycogenolysis by reducing the levels of enzymes that stimulate glucose production in the liver such as glucose-6-phosphatase (G6Pase) and Phosphoenolpyruvate Carboxy Kinase (PEPCK) (Frankenberg *et al.*, 2017). Adiponectin plays a protective role in preventing the development of insulin resistance, high blood pressure, atherosclerosis, and cardiovascular diseases. Therefore, this molecule could clarify the relationship between obesity and metabolic disorders (Shibata *et al.*, 2009 ; Jallod and Kata , 2019).

Interleukin-6 is a pleiotropic glycoprotein with broad biological activity that is secreted by white blood cells (macrophages) and T-cells, as well as by a number of other cells such as fibroblasts, osteoblasts, and endothelial cells, as well as tumour cell (Toumpanakis and Vassilakopoulos, 2007). The IL-6 is a non-specific biomarker that is associated with the inflammatory response and is not considered a diagnostic marker for any disease. However, the elevated concentrations of it are interpreted as an accompanying case of clinical signs of the disease. It is also referred to as a stimulating and anti-inflammatory cytokine because it has properties that work in both pathways (Kibe *et al.*, 2011).

The IL-6 has an inverse relationship with the level of HDL, which contributes to the occurrence of pathological complications that are associated with metabolic syndrome such as cardiovascular diseases, insulin resistance and diabetes, as one third of the total concentration of IL-6 in the blood circulation is released by fat tissue (Pietrzak *et al.*, 2020).

Insulin-like growth factor-1 (IGF-1) is a single-chain peptide with a structural framework that is similar to insulin. It has growth-stimulating activities as it works to regulate the growth and differentiation of many types of cells. Moreover, it plays an important role in regulating metabolic processes inside the body because it has metabolic effects which is similar to insulin (Kemp, 2009). This factor is mainly produced by the liver in response to its stimulation by growth hormone, and it can also be secreted from a number of other tissues, as 75% of the hormone present in the blood circulation is produced by the liver (Puche and Castilla-Cortazar, 2012).

The IGF-1 is one of the factors that change in obesity and many related diseases, as its short-term metabolic effect is similar to that of insulin, while the long-term effect is similar to that of growth hormone. The IGF-1 has many roles in the initiation and development of various diseases, because in some cases it prevents programmed cell death and in other cases it contributes to the increase in fat cells (Asgharihanjani and Vafa, 2019). IGF-1 is also an essential hormone in the pathophysiology of metabolic syndrome because of its relationship to fat and carbohydrate metabolism, as it can be one of the effective options in treating this globally growing disease by restoring the normal levels of this hormone (Aguirre *et al.*, 2016).

Insulin-like growth factor is a good predictor of metabolic syndrome, as its high levels are associated with a lower risk of developing metabolic syndrome (Sesti *et al.*, 2005). Also, its low levels were negatively associated with components of the metabolic syndrome such as type 2 diabetes, abdominal obesity, body mass index, and blood lipid disorders, which makes IGF-1 hormone of great importance in protecting against the development of metabolic syndrome (Juul *et al.*, 2002).

Monocyte-attracting protein (MCP-1) is a protein that regulates the migration and filtration of monocytes and phagocytes across the vascular endothelium to different tissues in response to the inflammatory state, where it, along with its receptors, contributes to causing many diseases (Deshmane *et al.*, 2009). Many types of cells are involved in the production and secretion of MCP-1, including monocytes, macrophages, fibroblasts, endothelial cells, smooth muscle cells, and

fat cells (Lockwood *et al.*, 2006). MCP-1 plays an important role in a number of pathological conditions such as cardiovascular diseases, brain, bone and joint diseases, cancers and respiratory infections, in addition to atherosclerosis and type 2 diabetes, through the activation of a number of pathways. In addition, it participates in protective immune responses during infection (Singh *et al.*, 2021).

2. Material and methods

The current study was conducted on obese men whose metabolic health is good in Basrah province/Iraq. The study aimed to evaluate the concentration of some biomarkers and take them as predictors of metabolic syndrome, which are adiponectin (ADP), interleukin-6 (IL-6), insulin-like growth factor (IGF-1), monocyte-attractive protein (MCP-1) as well as biochemical tests, represented by estimating the level of glucose, total cholesterol and triglycerides.

2.1 Design of experiment

The study involved the collection of (88) blood serum samples from men, including (60) samples from obese people, which were divided according to body mass index into two groups. The first group included (24) samples of people who had obesity of the second degree, where the values of their body mass index ranged between 35-39.9 kg / m². The second group included (36) samples of people who had obesity of the third degree if the values of the index of their body mass is greater than 40 kg/m². It was also divided based on the values of waist circumference into two groups. The first group also included (28) samples of people with waist circumference values ranging between 110 - 125 cm. The second group included (32) samples of people with waist circumference values greater than 125 cm. In addition, it was divided into two age groups (20-40) years old and (41-60) years old. Moreover, (28) samples were taken from healthy people (with normal weights), where their BMI values ranged between 18.5-24.5 kg/m² and waist circumference less than 102 cm. Samples were collected from volunteers in cooperation with private medical clinics.

2.2 Preparation of serum

Blood samples were drawn from the donors (who suffer from obesity and the healthy group) after they were presented to the specialized doctor in the private clinic. Five mL of venous blood was drawn from each donor after making sure of his safety and he does not suffer from any of the chronic diseases. The blood was placed in a special tube (Gel Tube) for the purpose of isolating the serum from the blood. The blood was left for 15 minutes for the purpose of coagulation. Then the tubes were placed in a centrifuge at a rotation rate of 3500 revolutions per minute for 15 minutes. The serum was placed in small Eppendrof tubes after separating it and store it at -20°C until tests are done.

2.3 Estimation of the concentration of biomarkers in serum

The well-known immunoassay (Enzyme-Linked Immunosorbeut Assay (ELISA)) was adopted using an ELISA reader device from Mindray Company (Germany),

and hormone kits that are prepared by Elabscience (USA), to estimate the levels of biomarkers.

2.4 Statistical Analysis

Statistical analysis of the data was carried out using the T-test between the concentrations of samples of obese people and samples of people with normal weight at the probability level of P≤ 0.05 and P≤ 0.01 and using the Statistical Science Package for the Social (SPSS) program version 21.

3. Results

Table (1) shows some clinical measurements and biochemical tests for men who suffer from obesity and for men of normal weight.

Table (1) Some clinical measurements and biochemical tests for the study samples

Feature	Obese people n = 60 the average	people with normal weight n = 28 the average
Height	172 cm	175.95 cm
Weight	122.93 kg	67.84 kg
BMI	41.17 kg/m2	21.91 kg/m2
Waistline	126.10 cm	80.63 cm
systolic pressure	119.2 mm/Hg	115.3 mm/Hg
diastolic pressure	80.4 mm/Hg	77.5 mm/Hg
Glucose	110.01 mg/m3	85.87 mg/m^3
Triglyceride	138.09 mg/m3	99.99 mg/m^3
Cholesterol	122.12 mg/m3	94.19 mg/m^3

3.1 The concentration of biomarkers in the blood serum of obese and healthy men (normal weight)

Table (2) shows that there was no significant effect in the level of ADP and MCP-1 hormone between the group of obese men and the healthy group, while there was a significant effect on the concentration of IL-6 and IGF-1 biomarkers between the two groups.

Table (2): Concentrations of biomarkers in the serum of the group of obese men compared to the healthy group

Biomarkers	Mean ± S.D		P-Value
	Obese people No. 60	Healthy people No.28	
ADP ng/ml	4.009 ±1.825	4.536 ±2.061	0.230
IL-6 pg/ml	2.057** ±0.915	0.175 ±0.240	0.000
IGF-1pg/ml	26.876 ±12.094	37.177** ±13.998	0.001
MCP-1ng/ml	856.088 ±260.312	776.873 ±154.443	0.140

** Significant difference at probability level P≤ 0.01

3.2 The effect of body mass index on the concentration of biomarkers in obese men

Table (3) shows that there is no significant difference between the group (39.9 ≥BMI≥35) and the group (BMI≥40) at the probability level of P≤0.05 in the concentrations of the biomarkers ADP and IL-6, while there was a significant increase in the concentration of the biomarkers IGF-1 and MCP-1 in the second group compared to the first group.

Table (3) Effect of BMI on biomarkers ADP, IL-6, IGF-1 and MCP-1

Biomarkers	Mean ± S.D		P.Value
	BMI=35-40 No.= 24	BMI> 40 No.=36	
ADP ng/ml	3.770 ±1.754	4.196 ±1.884	0.382
IL-6 pg/ml	2.273 ±0.860	1.969 ±1.093	0.240
IGF-1pg/ml	23.024 ±11.447	29.999* ±10.378	0.017
MCP-1ng/ml	701.358 ±161.562	970.353** ±358.268	0.001

* Significance at P≤0.05, ** Significant at P≤0.01

3.3 The effect of waist circumference on the concentrations of biomarkers in obese people

Table (4) shows that there is no significant difference in the concentrations of the biomarker ADP between the waist circumference group(125≥ WC ≥110) and the waist circumference group (WC > 125), while there were significant differences in the concentrations of biomarkers IL-6, IGF-1 and MCP-1 between the two groups.

Table (4): The effect of waist circumference on the concentration of biomarkers ADP, IL-6, IGF-1 and MCP-1

Biomarkers	Mean ± S.D		P-Value
	Waist circumference 110-125 cm No.= 28	Waist circumference > 125 cm No. = 32	
ADP ng/ml	4.325 ±1.948	3.763 ±1.798	0.250
IL-6 pg/ml	1.187 ±0.428	2.791** ±1.037	0.000
IGF-1pg/ml	31.116** ±11.548	22.851 ±10.281	0.005
MCP-1ng/ml	825.498 ±244.002	976.06* ±212.635	0.013

* Significance at P ≤ 0.05, ** Significant at P ≤ 0.01.

4. Discussion

The results of the current study showed that there were no significant differences in the concentration of the hormone adiponectin between the group of obese people and the healthy group. The study did not show a significant difference in the concentration of the hormone between the two groups of waist circumference and the two groups of BMI, and these results agreed with the results of the studies (Aguilar-Salinas *et al.*, 2008; Snehalatha *et al.*, 2008; Mente *et al.*, 2010; Kuo and Halpern, 2011; Awede *et al.*, 2018). These results are drawn because the samples taken in our study of obese people are among those who enjoy metabolic health. This is evident from the results of the biochemical analyzes that were conducted for them, which measured the levels of glucose, triglycerides and cholesterol, in addition to the clinical tests, which measured blood pressure levels. People who are obese and who are metabolically healthy obese are defined as people who have a body mass index greater than 30 kg/m² and do not have type 2 diabetes and high blood pressure (Aguilar-Salinas *et al.*, 2008).

The results of the current study showed that the levels of (IL-6) were significantly higher in the obese group compared to the healthy group (with normal weights). In addition, it showed a significant increase in the concentration of IL-6 in the waist circumference group that is greater than 125 cm compared to the other group. These results are in agreement with the results obtained by other studies (Bastard *et al.*, 2000; Khaodhiar *et al.*, 2004; Fenkci *et al.*, 2006; Wannnamethee *et al.*, 2007).

These results may be due to the expansion of adipose tissue in people who suffer from obesity, as adipose tissue contributes to the production of at least 35% of interleukin-6 present in the blood circulation (Kim *et al.*, 2009). Obesity is also associated with a state of chronic low-grade inflammation (Han *et al.*, 2020). This is a result of the lack of oxygen reaching the fat cells (Hypoxia) after the expansion of the fat tissues, which leads to programmed cell death (Roytblat *et al.*, 2000), which in turn generates signals to recruit macrophages and increase their infiltration into the fat tissues (Klover *et al.*, 2005). This in turn contributes

to an increase in the expression of IL-6 in the adipose tissue of obese people and an increase in its levels in the circulatory system (Han *et al.*, 2020).

It is clear from the results of the current study that there is a significant decrease in the concentration of (IGF-1) in the blood plasma of people with obesity compared to its concentration in the blood plasma of people of normal weight. It also showed a significant decrease in the concentration of IGF-1 in the group of people with a waist circumference greater than 125 cm compared to its concentration in people with a waist circumference less than or equal to 125 cm .There results agree with the results obtained by the studies (Schneider *et al.*, 2006; Gram *et al.*, 2006; Friedrich *et al.*, 2012; Savastano *et al.*, 2012).

The reason for the decrease in IGF-1 levels in obese individuals may be attributed to the chronic low-grade inflammatory state that is associated with obesity. This is characterized by increased production of inflammatory cytokines such as IL-6, which is one of the important factors that impair IGF-1 activity by affecting the regulation of IGF-1 carrier proteins (Witkowska-Sedek and Pyrzak, 2020). As inflammatory cytokines inhibit IGF-1 signaling pathways by 30-50% (Choukair *et al.*, 2014).

Furthermore, it, especially IL-6, stimulates hepatic C-Reactive protein (CRP) synthesis (a measure of systemic inflammation) which in turn is a limiting factor for IGF-1 production by hepatocytes due to its effect on hepatocyte expression of IGF-1 (Bermudez *et al.*, 2002). Also, low levels of IGF-1 in obese individuals may be a result of a decrease in functional hepatocytes producing insulin-like growth factor because of fatty degeneration of the liver associated with obesity (Garcia-Galiano *et al.*, 2007).

The results of the current study showed that there was a significant increase in the concentration of IGF-1 in the BMI group greater than 40 kg/m^2 compared to the BMI group of 35-40 kg/m^2. The reason behind this result may be that fat cells can produce IGF-1, and thus the higher the body mass index is, the greater the number of fat cells becomes, which leads to an increase in the level of IGF-1 in the blood circulation (Wabitsch *et al.*, 2000). Insulin also stimulates hepatic production of IGF-1, whose levels are usually high in obese people (Rajpathak *et al.*, 2009). In addition, insulin inhibits the secretion of IGF-1-carrying proteins by the liver, which increases the free concentration of IGF-1 in the blood circulation (Frystyk, 2004).

The results of the present study revealed that there is no significant difference in the level of mononuclear-attracting protein (MCP-1) in the blood plasma between obese people and people with normal weight. These results are in agreement with the results obtained by the study (Lee *et al.*, 2015). The reason for this may be due to the healthy metabolic health of the study samples for people who suffer from obesity.

The results of the current study also showed a significant increase in the concentration of MCP-1 in blood plasma with an increase in body mass index and waist circumference. These results are consistent with the results obtained by studies (Kim *et al.*, 2006; Breslin *et al.*, 2012), which showed that high levels of

MCP-1 were positively associated with the increase in the values of body mass index and waist circumference.

The reason for this may be due to the increase in the number and size of fat cells in the adipose tissue with an increase in the values of body mass index and waist circumference, as well as an increase in the accumulation of macrophages, which leads to a decrease in the oxygen supply and thus an increase in oxidative stress (Katsuki *et al.*, 2006). The MCP-1 is produced by many cell types such as fibroblasts, epithelial cells, vascular smooth muscle cells, as well as adipose tissue cells after induction by oxidative stress and inflammatory cytokines (Chen *et al.*, 2005).

5. Conclusion

The current study concluded that the altered levels of IL-6 and IGF-1 associated with obesity is a risk marker that predicts the development of metabolic syndrome in obese men.

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