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Relationship between Some Physiological Biomarkers in Obese Men and the Risk of Metabolic Syndrome

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ABSTRACT

Aims Obesity is associated with many diseases. Fat cells secrete biologically active substances known as biomarkers. This study aimed to assess the concentration of some biomarkers and take them as predictors of metabolic syndrome.

Instruments & Methods In the present, 88 blood serum samples were collected from male volunteers who have metabolic health in Basra Province, Iraq. 28 samples were taken from men with normal weight, and 60 samples from obese men. 5mm of venous blood was taken from each donor, and the concentration of biomarkers including paraoxonase enzyme-1, plasminogen activator inhibitor-1, oxidized low-density lipoprotein and endothelin-1 were measured. Then, the effect of BMI and waist circumferences on the concentration of biomarkers was investigated.

Findings A significant decrease in paraoxonase-1 concentration was observed in the obese group ($p \leq 0.01$), while plasminogen activator inhibitor-1 was significantly higher in the obese group compared to the normal weight group. There was no significant difference in the concentration of oxidized low-density lipoprotein and endothelin-1 between the two groups. There was a significant increase in the levels of plasminogen activator inhibitor-1 and endothelin-1 in the group with BMI>40 compared to the group with 40≥BMI≥35. There was no significant difference in the concentration of all biomarkers between the two waist circumference groups.

Conclusion Obesity is a major cause of the metabolic syndrome, and abnormal levels of paraoxonase-1 and plasminogen activator inhibitor-1 associated with obesity are early warning signs of metabolic syndrome.

Keywords Metabolic Syndrome; Obesity; Paraoxonase-1; Plasminogen Activator Inhibitor 1; Oxidized Low-Density Lipoprotein; Endothelin-1

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Introduction

Obesity is defined as an abnormal or excessive accumulation of fat that may cause harm to health [1]. Obesity and overweight are also associated with many diseases, which include cardiovascular diseases, high blood pressure, type 2 diabetes, stroke, asthma, back pain, joints, osteoporosis, and shortness of breath, and all of this leads to more than three million deaths annually [2]. Obesity is a vital indicator for predicting and preventing diseases of blood pressure, arteriosclerosis, and diabetes [3]. Fat cells secrete biologically active substances known as biomarkers, such as cytokines and adipokines. The accumulation of fat cells leads to irregular production of these substances, which contributes to the development of metabolic syndrome. [4, 5].

Paraoxonase-1 (PON-1) is an enzyme related to High Density Lipoprotein (HDL) and plays a key role in its work by protecting lipoproteins, biological membranes, and various body tissues from oxidative damage. It degrades lipid peroxides and prevents the accumulation of phospholipids in Low-Density Lipoprotein (LDL), which makes it have a protective role against heart disease and atherosclerosis [6]. The paraoxonase enzyme and HDL are synthesized in the liver and then excreted into the bloodstream, where they are closely related and together form a more active complex than the free enzyme [7]. Its low levels lead to the development of a wide range of diseases, including cardiovascular diseases, diabetes, rheumatic diseases, neurological diseases, and cancer [8]. In addition, PON-1 interacts with its receptors on macrophages, which inhibits the production of inflammatory cytokines such as Interleukin 6 (IL-6) and Tumor necrosis factor alpha (TNF-α) and enhances the anti-inflammatory effect [9]. The role of PON-1 as an antioxidant and anti-inflammatory makes it important in reducing the development of metabolic syndrome [10]. It was found that the levels of PON-1 were lower in patients with metabolic syndrome, and the low level of HDL in the blood plasma reduced the activity of the enzyme [11].

Plasminogen Activator Inhibitor (PAI-1) is a serine protease inhibitor that is the main inhibitor of plasminogen activators and a regulator of fibrinolysis and cell adhesion through its interactions with plasminogen activators, such as tissue-type-Plasminogen Activator (tPA) and Urokinase-type Plasminogen Activator (U-PA), so it plays an effective role in the infection of several diseases, such as cardiovascular diseases [12]. It was also found that 29.6% of people with cardiovascular diseases had elevated PAI-1 levels [13].

Metabolic syndrome is often associated with a chronic inflammatory state, characterized by increased secretion of inflammatory cytokines (IL-6, TNFα), which stimulate the secretion of PAI-1 from adipose tissue, leading to impaired fibrinolysis and an increased risk of cardiovascular disease in people with The metabolic syndrome [14].

Oxidized Low-Density Lipoprotein (OX-LDL) is a protein derived from LDL, found in the bloodstream and may contain peroxides or breakdown products of substances contained within the molecule LDL [15]. The process of oxidation of LDL leads to a change in its biological properties such as, size, density, and charge inside the bloodstream and in the walls of blood vessels, which increases the process of chemotaxis for monocytes, lymphocytes, T cells, and macrophages [16, 17].

Oxidative stress contributes to the pathophysiology of a number of chronic diseases, including metabolic syndrome, a characteristic of which is a disorder of blood lipid levels and an elevated LDL level, which has a strong tendency to oxidation [18]. The disturbance in blood fat levels and the high level of OX-LDL represent a risk factor for cardiovascular disease, which is one of the diseases associated with metabolic syndrome [19].

Endothelin (ET-1) is a vasoconstrictor peptide secreted by vascular endothelial cells that acts as a natural analogue of nitric oxide that dilates the blood vessels, contributes to the development of many pathological conditions such as bronchoconstriction, fibrosis, heart failure, high blood pressure, in addition to cardiovascular diseases [20] contributes to its production and release from a variety of body tissues, including the lungs and kidneys, as well as brain tissue, pituitary gland, and placenta, is in addition to the main source of its production, which is vascular endothelial cells, and it is also produced by fat cells [21, 22].

This study aimed to assess the concentration of some biomarkers and take them as predictors of metabolic syndrome, which are Paraoxonase-1 (PON-1), Plasminogen Activator Inhibitor-1 (PAI-1), Oxidized Low-Density Lipoprotein (OX-LDL) and Endothelin-1 (ET-1).

Instrument and Methods

The present study was conducted on fat men who enjoyed metabolic health in Basra Province, Iraq. 88 blood serum samples were collected from male volunteers in cooperation with private medical clinics. 28 samples were taken from men with normal weight, whose Body Mass Index (BMI) ranged between 18.5-24.5 and whose waist circumference was less than 102; and 60 samples from obese men, which were divided according to BMI into two categories. The first category included 24 samples of people who had obesity of the second degree, where their BMI ranged between 35-40. The second category included 36 samples of third-degree obese people whose BMIs were greater than 40, and they were divided based on waist circumferences into two categories. The first

category also included 28 samples of people with waist circumferences ranging from 110 to 125cm, while the second category included 32 samples of people with waist circumference greater than 125cm.

5 mm of venous blood was taken from each donor after visiting a specialist doctor in a private clinic and ensuring safety and no chronic disease. The blood was placed in a special type of tube called a gel tube to separate the serum from the cellular part of the blood. The blood was left to clot for 15 minutes. Then the tubes were placed in a centrifuge at a rotation rate of 3500 revolutions per minute for 15 minutes. After separation, the serum was placed in small Eppendorf tubes and kept at -20°C until the experiments.

The Enzyme-Linked Immunosorbent Assay (ELISA), as a well-known immunological method, was adopted using an ELISA Reader device (Mindray; Germany) and hormone kits (Elabscience; USA) to estimate the levels of biomarkers.

Data were analyzed using the pair t-test between the concentrations of samples of obese people and samples of people with normal weight at the probability levels of p≤0.05 and p≤0.01 by SPSS 21 software.

Findings

Table 1 shows some clinical measurements and biochemical tests for people suffering from obesity and for people with normal weight.

Table 1) The mean of clinical measurements and biochemical tests for the study samples

Variables	Obese men (n=60)	Men with normal weight (n=28)
Height (cm)	172.0±13.6	175.9±19.0
Weight (kg)	122.9±12.1	67.8±8.4
BMI (kg/m^2)	41.2±3.2	21.9±1.5
Waist circumference (cm)	126.1±14.5	80.6±7.8
Systolic pressure (mm/Hg)	119.2±10.1	115.3±9.9
Diastolic pressure (mm/Hg)	80.4±6.7	77.5±5.4
Glucose level (mg/dl)	110.0±9.5	85.9±9.3
Triglyceride level (mg/dl)	138.1±11.1	100.0±10.9
Cholesterol level (mg/dl)	122.1±15.7	94.2±8.2

There was a significant difference between the two groups in the concentration of PON-1 and PAI-1 biomarkers, as PON-1 was significantly lower in the obese group compared to the normal group, while PAI-1 was significantly higher in the obese group (p≤0.01). There was no significant difference in the concentration of OX-LDL and ET-1 biomarkers between the obese group and normal group (Table 2).

Table 2) Comparison of the mean concentration of biomarkers between the obese group and the normal group

Biomarkers	Obese (n=60)	Normal weight (n=28)	p-value
PON-1 (ng/ml)	0.747±0.293	4.489±1.787	0.0001
PAI-1 (ng/ml)	0.202±0.467	0.155±0.753	0.001
OXLDL (pg/ml)	425.590±200.113	413.633±174.435	0.787
ET-1 (ng/ml)	4.863±2.110	5.165±1.550	0.501

There was a significant increase in the concentration of the PAI-1 and ET-1 in the group with BMI>40 compared to the group with 35≤BMI≤40, while no significant difference was observed in the concentration of PON-1 and OX-LDL between the two groups (Table 3).

Table 3) The effect of BMI on the concentration of PON-1, PAI-1, OX-LDL, and ET-1 biomarkers

Biomarkers	35≤BMI≤40 (n=24)	BMI>40 (n=36)	p-value
PON-1 (ng/ml)	0.716±0.417	0.767±0.440	0.66
PAI-1 (ng/ml)	0.184±0.014	0.207±0.047	0.026
OX-LDL (pg/ml)	370.42±195.142	417.92±241.479	0.425
ET-1 (ng/ml)	2.173±0.825	6.518±2.204	0.0001

There was no significant difference in the concentration of PON-1, PAI-1, OX-LDL, and ET-1 biomarkers between the group with a waist circumference of 110-125cm and the group with a waist circumference of more than 125cm (Table 4).

Table 4) The effect of waist circumference on the concentration of PON-1, PAI-1, OX-LDL, and ET-1 biomarkers

Biomarkers	110-125cm (n=28)	>125cm (n=32)	p-value
PON-1 (ng/ml)	0.804±0.435	0.696±0.358	0.296
PAI-1 (ng/ml)	0.195±0.028	0.206±0.048	0.1
OX-LDL (pg/ml)	405.923±224.096	319.955±213.183	0.806
ET-1 (ng/ml)	4.943±2.177	4.168±1.907	0.147

Discussion

The current study showed that there is a significant decrease in the concentration of paraoxonase enzyme in the blood of obese people compared to its levels in the blood of people of normal weight. It also showed that there were no significant differences in the levels of the enzyme between the two groups of waist circumference and body mass index. These results are in agreement with the results obtained by other studies [23-26], which showed that the levels and activity of paraoxonase enzyme were low in people who suffer from obesity and enzyme levels were negatively correlated with body mass index and waist circumference. This decrease may be due to the high levels of cytokines and chemokines, which are prominent features of obesity [25]. These molecules affect the activity of the paraoxonase enzyme through several mechanisms, including the high levels of IL-6; as a result of the inflammatory response in the case of obesity, it reduces the gene expression of paraoxonase in hepatocytes [27, 28]. Also, IL-6 stimulates hepatic production of CRP, whose elevated levels due to obesity are inversely

related to PON-1 levels [29]. The leptin hormone can also be associated with the prescription of one of the hormones secreted by adipose tissue, which is a hydrophobic hormone with high-density lipoprotein and prevents it from binding to the paraoxonase enzyme [30]. In addition to leptin, it enhances oxidative stress through the formation of reactive oxygen species [31]. Fats may also be the target of these free radicals, as they work to oxidize them and produce lipid peroxides [32], which are inhibitors of enzyme activity [33].

The statistical analysis of the data indicates that there is a significant increase in the concentration of Plasminogen Activator Inhibitor (PAI-1) in the plasma of people who suffer from obesity compared to its concentration in the plasma of people with normal weight. The results also showed that there is a significant increase in the concentration of PAI-1 in the serum of the group with BMI >40 kg/m^2 compared to its concentration in the group with 35<BMI<40 kg/m^2. The results did not show a significant difference in the concentration of PAI-1 between the two groups of waist circumference. These results are in agreement with the results obtained by other studies [34-37], which showed that the increase in PAI-1 levels was positively associated with the increase in weight as well as with measurements of obesity such as waist circumference and body mass index.

This may be due to elevated levels of PAI-1 in the blood plasma of obese people. Obesity is a chronic inflammatory disorder that causes the secretion of inflammatory cytokines from fatty tissues [38]. In addition, adipose tissue in the case of obesity is characterized by an abundance of macrophages, as a result of the increased expression of MCP-1 [39]. Active macrophages, adipocytes, and preadipocytes secrete inflammatory cytokines such as TNF-α and IL-6 into the circulation, which works to enhance the inflammatory state in the liver and other sites in the body, including blood vessel cells [40]. So, working inflammatory cytokines regulate the expression of PAI-1 in adipose tissue [41]. Also, the increase in weight and the high level of free fatty acids increase the gene expression of PAI-1 in adipose tissue by macrophages, which leads to an increase in its level in the blood circulation [42].

The results showed that there was no significant difference in the concentration of oxidized low-density lipoprotein (OX-LDL) in the blood plasma between obese people and people of normal weight. It also showed that there was no significant difference in OX-LDL concentration between the two BMI groups, as well as between the two waist circumference groups. These results are in agreement with the results obtained by Tumova *et al.* [43], which showed that the levels of OX-LDL in obese people with healthy metabolism were similar to those in people of normal weight. The inflammatory state and increased oxidative stress are associated with metabolic health regardless of the presence or absence of obesity [44].

The results of the current study showed that there is no significant difference in the levels of the Endothelin-1 hormone (ET-1) in the blood plasma between obese people and people with normal weight. Also, there was no significant difference in hormone levels between the two waist circumference groups. These results are in agreement with the findings of Shulkina *et al.*'s study [45], which showed that there was no significant difference in the levels of Endothelin-1 between people who suffer from obesity and do not have diseases related to metabolic disorders and people of normal weight. This result may be due to normal endothelial cell function, as 50% of the Endothelin hormone found in blood circulation is produced by vascular endothelial cells [46]. Also, the results shown by Ahmed and Sulaiman that there is no significant difference in the levels of XO-LDL among the study samples may have a role in this result, as Endothelin is positively associated with increased oxidative stress [47] and high levels of OX-LDL stimulate ET-1 production from the vascular endothelium [48].

The results of the present study also showed a significant increase in the level of Endothelin hormone in the blood plasma of the group of people with a BMI of more than 40 kg/m^2 compared to another group with 40 ≥BMI ≥35 kg/m^2. These results are in agreement with the results of other studies [47, 49], which showed that there is a positive correlation between the level of the Endothelin hormone and body mass index. This result may be due to the increase in the number and size of fat cells that occurred in this group, as the Endothelin hormone, in addition to its production mainly by endothelial cells, is also produced by adipocytes [50]. Adipose tissue in obese individuals produces the Endothelin hormone 2-3 times more than that in people with normal weight [21]. Also, the Endothelin hormone is released into the blood circulation in response to several stimuli, including hypoxia [51]. Obesity is a chronic disease characterized by a lack of oxygen access to adipose tissue, and this may be one of the main factors in stimulating and producing Endothelin by adipocytes and endothelial cells, and consequently its high levels in blood plasma [52].

Conclusion

Obesity is a major cause of the metabolic syndrome, and abnormal levels of PON-1 and PAI-1 biomarkers associated with obesity are early warning signs of metabolic syndrome.

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