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ROLE OF LEPTIN, PLASMINOGEN ACTIVATOR INHIBITOR TYPE-1 IN THE OCCURRENCE OF ATHEROSCLEROSIS: NEW INSIGHTS INTO THE MECHANISM OF OBESITY-INDUCED ATHEROSCLEROSIS

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ABSTRACT

***Background and aim**: The most widespread pathological condition of peripherals and coronary artery disorders, as well as of cerebellar problems, is atherosclerosis (AS). Obesity is the most common nutritional disorder worldwide and is one of the major risk factors for atherosclerotic cardiovascular disease (ASCVD). Leptin, plasminogen activator inhibitor-1 (PAI-1) are released by adipose tissue, which is a tissue that is found throughout the body and is considered an important endocrine system, these are essential for the control of immunological and energy responses. **Methods**: A case-control study was used in the design of the current investigation. 100 male participants, comprising 60 atherosclerosis individuals, 30 obese patients, 30 normal weight patients, and 40 healthy people, 20 of whom were obese and 20 of whom were of normal weight. Age between (40-65). This work was done between November/2022 and May/2023. Patient from the Karbala Center for Cardiac Disease and Surgery. A 3 ml sample of venous blood was obtained from patients and was healthy. In addition, some information was taken from each person (age, height, weight). **Results**: There has been a significant increase in concentrations of each one of the hormones (Leptin, PAI-1) in all groups when compared with non-obese control. **Conclusion**: leptin and PAI-1 play a role in the development of atherosclerosis in obese individuals. A person's risk of developing atherosclerosis increases with rising body mass index. It was discovered that the hormone Leptin, which regulates metabolism, is rising, which might be an indicator that the metabolic problem in obese people is becoming more common.*

INTRODUCTION

Atherosclerosis

German physician Félix Marchand first used the term "atherosclerosis" (AS) in 1904; it is derived from the Greek words "adhere" and "sclerosis," which indicate gruel and hard, respectively, is the primary contributor to diseases of the coronary arteries, the brain, and the peripheral blood vessels (1). Cholesterol deposition and chronic inflammation are two crucial factors in the pathogenesis of AS, AS includes three main stages, including the generation of fatty streaks, the induction of atheroma, and atherosclerotic plaques (2). This condition begins when oxidized low-density lipoproteins (Ox-LDLs) build up in the artery intima (3). This resulted in the production of

proinflammatory oxidized lipids by the overlapping endothelial cells (ECs) (4). Within the intima of the artery, monocytes develop into proinflammatory the macrophages locally enhance the inflammatory reaction, eventually, macrophages ingest lipoproteins to produce foam cells rich in lipids, which cause early atherosclerosis lesions to appear (5).

Obesity

Obesity is a significant worldwide health problem linked to higher morbidity and mortality rates (6). According to the WHO, obesity is defined as “abnormal excessive fat accumulation that presents risk to health” (7). The buildup of too much body fat results in a variety of metabolic disorders and diseases, such as resistance to insulin and atherogenic dyslipidemia (8). Obesity poses a serious threat to public health since it adversely affects almost all bodily physiological processes and raises the chance of acquiring a number of disease conditions, including DM and CVD (9). By causing arterial inflammation and oxidative stress, proinflammatory adipocytokines and free fatty acids generated by malfunctioning fatty tissue can systematically accelerate atherosclerosis (10). Adipokines, such as leptin, PAI-1 are released by adipose tissue, which is a tissue that is found throughout the body and is considered an important endocrine system (organ), adipokines are essential for the control of immunological and energy responses (11).

leptin

leptin the obese gene encodes leptin, a single-chain 16 kDa protein that is mostly released by adipocytes but can also be generated by vascular smooth muscle cells and cardiomyocytes (12). In the 1990s, leptin was the first adipokine to be discovered, it is known to reduce food intake by reducing hunger and to regulate energy balance, including blood sugar and lipid metabolism (13). Produced mostly by adipose tissue in relation to the volume of fat reserves, with a key role in the management of lipid reserves (14). Leptin is a well-known proinflammatory adipokine that is thought to contribute together to a "low-grade inflammatory state" observed in overweight and obese people (15). Fasting Leptin levels between obese and lean individuals showed an inverse relationship with cerebral gray matter volume (16). The altered leptin transport over the blood brain barrier (BBB) into the hypothalamus caused by hypertriglyceridemia, together with peripheral leptin resistance central leptin resistance, must be emphasized since they may be key factors in the start and progression of obesity (17). Leptin levels and BMI are positively correlated, and it's thought that hyperleptinemia, which is linked to adipose tissue in obese people without the predicted hunger reduction, may signify a leptin resistance state (18). An increase in food intake and a decrease in energy expenditure are caused by a loss of leptin signaling, which can result from mutations in leptin or its receptors (19). Leptin levels may rise as a result of inappropriate or excessive fat storage in the context of obesity, resulting in a condition known as "leptin resistance" when leptin signaling is reduced. Leptin loses its ability to suppress feeding during this physiological resistance, increasing energy expenditure (20). Resistance to leptin's catabolic effects has been explained by a number of mechanisms, including issues with leptin transport across the blood-brain barrier, changes in development programming, and/or variations in leptin expression of receptors (21). Leptin is a proatherogenic substance that plays a special role in the pathogenesis of CVD (22). Human obesity-related hyperleptinemia or leptin resistance affects the endothelium cardiovascular structure and functioning, inflammation, and sympathetic nerve activity and may result in cardiovascular disease (23).

Plasminogen activator inhibitor type-1

PAI-1 is a single-chain glycoprotein with a 45-kDa mass and 379 or 381 amino acids (24). PAI-1 is primarily produced by Platelet precursor cells, megakaryocytes, although it is also produced by

endothelial, adipocyte, hepatocyte, and cardiomyocyte cells (25). Aging, obesity, diabetes, heart disease, and cerebrovascular illness are only a few of the conditions for which adipose-derived PAI-1 has been identified as a key mediator (26). Obesity and metabolic syndrome, including increased plasma levels of the PAI-1 (27). The fibrinolytic system consists of a balance between rates of plasminogen activation and fibrin degradation, both of which are finely regulated by spatiotemporal mechanisms, three distinct inhibitors of the fibrinolytic system that differently regulate these two steps are plasminogen activator inhibitor type-1 (PAI-1), α2-antiplasmin, and thrombin activatable fibrinolysis inhibitor (TAFI) (28). The primary protease of the fibrinolytic system, plasmin is essential for cell migration and remodeling of tissues because it can break down extracellular matrix proteins by activating metalloproteases, plasmin is produced from plasminogen by the endogenous enzymes tissue-type plasminogen activator (tPA) (29). Increased plasma levels of PAI-1 have been proven to have significant effects on the onset and progression of cardiovascular illnesses (30). In people, PAI-1 over-expression is associated with AS, especially in those who have the metabolic syndrome, which is marked by overweight or obese people, dyslipidemia, and high blood pressure (31). Hepatic lipid metabolism is also significantly regulated by PAI-1 (32). Fibrous deposit in plaques can be eliminated by plasminogen activators, and fibrinolytic imbalances contribute to the course of AS (33).

METHODOLOGY

Study design

A case-control study was used in the design of the current investigation. 100 participants, comprising 60 atherosclerosis individuals, 30 obese patients, 30 normal weight patients, and 40 healthy people, 20 of whom were obese and 20 of whom were of normal weight. In Karbala, Iraq, the work was finished during November 2022 and May 2023. Aging between (40-65).

Collection Data

The study's participants were all affected by the condition atherosclerosis. Their BMI was calculated based on their height and weight.

Collection samples

Each participant had their venous blood collected using a disposable syringe for a total of 3 milliliters (3ml) and left at room temperature for about 30 minutes to coagulate. The gel tubes were centrifuged at 4000 x g for five minutes to extract the serum. Serum was transferred to an Eppendorf tube and kept at a temperature of (-30oC). leptin, PAI-1 measurements were made using serum.

Ethical management of studies

The research adhered to the protocols for handling biological substances established by the Department of Clinical Laboratories at the University of Karbala's College of Applied Medical Sciences. The samples used in this study were taken from patients arriving at the Karbala Center for Cardiac Diseases and Surgery / Karbala Health Directorate after receiving the required consent from the hospital administration and patients.

Statical analysis

The computer application SPSS, version 12, was used for statistical analysis of the data. The data are shown as mean standard deviation (Sd). The results were deemed to have statistical

significance since they were calculated differences between groups using a T test, and the P value (i.e., the least significant difference) was discovered for the comparison between the groups.

RESULTS AND DISCUSSION

Table 1: Concentration of Leptin patients with AS and compare with control group.

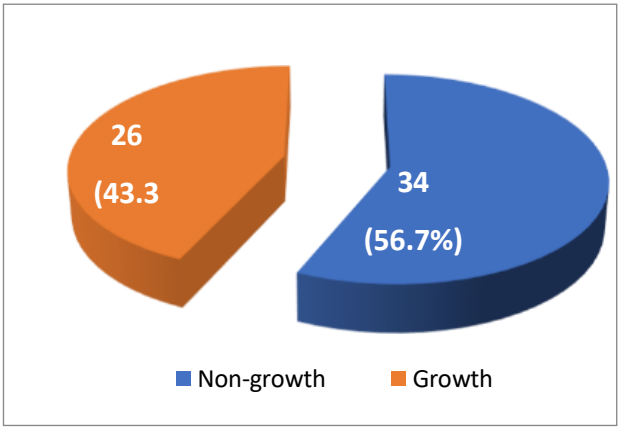
Groups	N	Mean	Std. Deviation
Athero Obese	30	657.84 a	32.04
Athero non-obese	30	545.32 c	92.18
Control Obese	20	599.80 b	75.52
Control non-obese	20	120.95 d	39.04

P value = 0.000* LSD= 25.981
* Means significant differences

Table 2: Concentration of PAI-1 patients with AS and compare with control group.

Groups	N	Mean	Std. Deviation
Athero Obese	30	8.207 a	0.886
Athero non-obese	30	7.296 b	0.972
Control Obese	20	4.171 c	0.807
Control non-obese	20	1.180 d	0.497

P value = 0.000* LSD= 0.201
* Means significant differences



Note: There are no significant differences between two groups if they share the same letter. There are significant differences between two groups if they have different letters.

Based on the results in the (**table 1)** showing a significant difference for average Leptin between;

- AS obese x AS non-obese (657.84 and 545.32).

- Control obese x control non-obese (599.80 and 120.95).
- AS obese x control obese (657.84 and 599.80).
- AS non-obese x control non-obese (545.32 and 120.95).

Numerous studies have been investigated and supported of the study's findings, which showed a significant difference in the level of leptin and increased body mass index. The obese individuals found high levels of leptin in circulation (20). Early investigations into the levels and expression of leptin in human organs indicated that serum leptin levels rise together with increases in body fat mass, supporting the idea that adipose tissue is a major source of this hormone (34). Primarily produced by adipose tissue in response to the amount of fat stores, and it plays a crucial part in the control of lipid reserves (14). It is believed that leptin has a role in the "low-grade inflammatory state" seen in overweight and obese individuals (15).

Studies have been and supported the study's findings, which showed a significant difference in concentration of leptin in the patient group when compared with control normal. Higher oxidative stress, atherogenesis, thrombosis, dysfunction of endothelial cells, and inflammation have all been linked to hyperleptinemia (13). Elevated leptin levels are associated with atherosclerosis and are thought to be a possible indication for problems associated with obesity (35). The first crucial stage in the development of atheroma has been identified as the binding of leptin with its receptor, hyperleptinemia, which is a characteristic of obesity, is one of the primary risk factors for AS (36). According to a recent study, leptin induces macrophages to take cholesterol, which causes the formation of atheromatous lesions (37).

Based on the results in the (**table 2**) showing a significant difference for average PAI-1 between;

- AS obese x AS normal (8.207 and 7.296).
- Control obese x control non-obese (4.171 and 1.180).
- AS obese x control obese (8.207 and 4.171).
- AS non-obese x control non-obese (7.296 and 1.180).

The findings presented in the table demonstrate a significant link between obesity and PAI-1, and this conclusion is consistent with previous research. In addition to increased levels of a serine protease inhibitor (PAI-1), being obese and the metabolic syndrome (27). BMI and plasma PAI-1 levels are significantly linked (32). Obesity, hypertension, and increased TGs, is characterized by elevated PAI-1 levels. (25). In addition, studies show BMI and PAI-1 are significantly related in obese and overweight persons (38). Preadipocytes, mature adipocytes, macrophages, endothelial cells, and smooth muscle cells (SMC) are among the cell types that produce more PAI-1 in adipose tissue, which is thought to be the cause of the relationship between PAI-1 and obesity (39). Individuals with obesity presented elevated PAI-1; however, we also found that subjects with metabolic alterations, both obese and lean, showed increased PAI-1 (40).

Additionally, a significant difference in concentration of PAI-1 between patient groups when compared with control non-obese. In accordance with past research, PAI-1 is reportedly involved in the etiology of AS, according to a recent large meta-analysis (41). Clinical studies have demonstrated elevated PAI-1 levels in individuals with early-stage and established atherosclerotic disease (42). A growing body of research has linked endothelial dysfunction and inflammation as major contributors to the development of atherosclerotic plaques, which is a chronic, systemic disease, endothelial dysfunction has the potential to alter the fibrinolytic system, which is crucial for the formation of atherosclerotic plaques (43). AS tends to exhibit increased PAI-1 expression

levels, PAI-1, which is the primary inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), is an inhibitor of fibrinolysis and plays a crucial role in AS (44).

Study Limitations

The participants chosen may not have been autoimmune disease (systemic lupus erythematosus,rheumatoid arthritic, et al), DM , liver diseases, Kidney Diseases.

CONCLUSION

There is a role for everyone (leptin, PAI-1) in the development of atherosclerosis in obese patients. A person with increased body mass index is more susceptible to development of atherosclerosis. The hormone Leptin, which controls metabolism, was found to be increasing, which may be a sign that the metabolic issue in obese individuals is becoming more common. Increased levels of PAI-1 have associations between obesity and atherosclerosis.

RECOMMENDATIONS

Study the relationship of the parameters in their occurrence of atherosclerosis in obese and non-obese females. Comparison of study parameters between male and female atherosclerosis patients. Comparison of study parameter with diabetic atherosclerosis and non-diabetic atherosclerosis.

ABBREVIATIONS

Atherosclerosis (AS), Atherosclerotic cardiovascular disease (ASCVD)**,** Plasminogen activator inhibitor-1 (PAI-1), Body mass index (BMI), oxidized low-density lipoproteins (Ox-LDLs), endothelial cells (ECs), Diabetes mellitus (DM), cardiovascular diseases (CVD), blood brain barrier (BBB), thrombin activatable fibrinolysis inhibitor (TAFI), tissue-type plasminogen activator (tPA), smooth muscle cells (SMC), urokinase plasminogen activator (uPA).

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