IS There an Impact of PAI-1 on the Thrombotic Episode in Iraqi Obese Patients with Corona Virus -19

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Abstract

Objective: firstly To assess the incidence of Corona Virus -19 covid-19 as risk factors in obese individuals leading to thrombotic episode, and secondly to compare the effects Plasminogen activator inhibitor-1 (PAI-1) on the occurrence of this thrombotic status in obese and normal body weight individuals. The pathogenesis of Coronavirus disease 2019 (COVID-19) is gradually demonstrated and explained around the world A high and a great number of thrombotic episodes are reported, in present study can be consider the COVID-19 as a prothrombotic disease.

Design and Methods: The experiments comparing the PAI-1 in 90 obese and 30 normal body weight participants aged 32-62 years. The obese patients subdivided to three groups: first group consisted from 30 over weight individuals and the second group comprised from 30 obese patients, while third group consisted from 30 morbid obesity patients. All participants underwent to the medical examinations to make sure they were infected with covid-19. The activity of PAI-1and tissue plasminogen activator (t-PA) was determined by applied ELISA method by certain kit in all study groups individuals.

Results: Three study groups (overweight, obese, and morbid obesity) elicited significant ($p< 0.05$) elevation in metabolic characteristics such as fasting blood glucose (FBG), fasting insulin and lipids variables, as well as increasing in insulin resistance (HOMA-IR) and D-dimer fractions, in addition to there were significant augmentation in PAI-1 and t-PA in three study groups when comparing with those of normal or healthy body weight

The present results show a positive relationship between PAI-1 and body mass index, t-PA, D-dimer and metabolic characteristics which include fasting blood glucose, fasting insulin and lipids fractions, also HOMA-IR**.**

Key Words: *Covid-19, Obesity, PAI-1 , t-PA, thrombosis*

Introduction

Coronaviruses are a great family of viruses which cause diseases in animals and humans. Seven coronaviruses can leading to infection in people around the world but commonly people have infected with these four human coronaviruses [1]. The main organ which effected is a respiratory system, the infection ranging from the common cold to more severe comorbidities such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) and the most recently discovered coronavirus (COVID-19) causes infectious disease [1]. The virus is spread rapidly between individuals through respiratory droplets during coughing[2].As of 13 September 2020, 210 Countries and Territories around the world have reported over 28.946.628 confirmed cases and 924.610 deaths of COVID-19,only in Iraq show 286.778 coronavirus cases and 7.941 deaths.

There are very few available data on impact of (body mass index) BMI for patients with COVID-19 infections, the obesity in the COVID-19 epidemic plays a major role in the pathogenesis of COVID-19 infection. It is believed the immune system, which is an essential player in the pathogenesis of COVID-19, also plays an substantial role in obesity which enhanced inflammation

in adipose tissue. The metabolic dysfunction is a main cause of inflammation in adipose tissue which potentially leading to dyslipidaemia, insulin resistance, diabetes mellitus, hypertension, and cardiovascular disease CVD [3]. In previous research the case of influenza A, was the obesity increases the duration of virus and severity ; the complication of having virus in patients with obesity was 42% longer than persons who do not have obesity[4]. Another study indicated that in H1N1 influenza, obesity is consider as risk factor for hospitalization and death[5].

Several investigators revealed that BMI was significantly higher in patients with a severe form of COVID-19 infection[6]. The published of retrospective analysis on 112 patients with COVID-19 infection demonstrated that BMI of the critical group with range (23.0-27.5 kg/m^2) was significantly higher than that of the general group with range(20.0-24.0 kg/m^2), then critical group were subdivided into two groups, survivors (84.8%) and non-survivors (15.18%). Among the non-survivors, 88.2% of patients had a BMI > 25 kg/m^2 [7]. Thrombotic events were an aggravating cause of death. Thromboembolic risk is known to be higher in patients with obesity than in the general population. It logically follows that obesity can be an aggravating risk factor for death from COVID-19 infection[8].

Plasminogen activator inhibitor-1 (PAI-1) play an important role in inhibition of plasminogen activators which included tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA), additionally, it regulates the fibrinolytic system as well as PAI-1 have a pivotal role in acute thrombotic phenomenon such as deep vein thrombosis (DVT) and myocardial infarction (MI). PAI-1 have more biological effects beside to the role in thrombosis including its central role in fibrotic disorders, atherosclerosis, renal and pulmonary fibrosis, diabetes mellitus , and cancer [9].

PAI-1 is produce in adipose tissue, and its levels in plasma are increased in obesity and reduced with weight loss[10]. In a great epidemiological studies, the high level of PAI-1 has been established as a predictor of myocardial infarction[11]. It is important to mention that effect of PAI-1 eliminates after adjustment metabolic syndrome components[12]

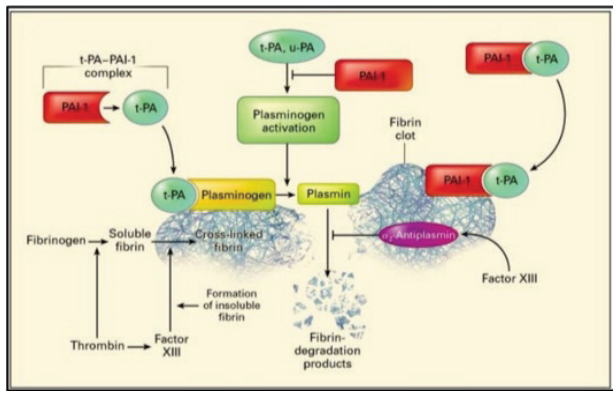

Figure (1): The role of PAI-1 in inhibition of fibrinolysis [13]

Abnormalities in coagulation factors and imbalance illustrated the link between obesity and thrombosis which occur in both arterial and venous[14]. Several studies have shown that patients with BMI higher than 30 kg/m^2 have higher concentrations of all pro-thrombotic factors (fibrinogen, vonWillebrand factor (vWF), and factor VII), when compared to normal BMI controls, with a positive correlation with central obesity, in the same way, the concentrations of plasminogen activator inhibitor-1 (PAI-1) have been elevated levels in obese patients when compared with non-obese controls, as well as,it is correlated directly with visceral fat. Likewise , patients with obesity are characterized by higher plasma levels of anti-thrombotic factors, which include, tissue-type plasminogen activator (t-PA) and protein C, when compared with non-obese individuals, the enhancing these factors may be represent a protective role to counteract the increase in pro-thrombotic factors[15,16]. Just as mentioned earlier the adipose tissue participate directly in product of plasma PAI-1, then stimulating other cells to produce PAI-1. In addition to, the adipose tissues secreted interleukin-6 (IL-6) which linked with the actions to produce tumor necrosis factor-α (TNF-α) in obesity, these findings could explain the association of insulin resistance with endothelial dysfunction, coagulopathy, and coronary heart disease. Recent studies mentioned the role of leptin in impairing balance and enhancing thrombosis, so the abnormalities value of some hormones such as (androgen, catecholamines) likely to combined with the accumulation of body fat may be leading to the impairment of coagulative pathway in obesity[14]. Some investigators demonstrated to be efficient method to improving the obesity combined with pro-thrombotic risk profile[17,18].

Systemic inflammation, endothelial dysfunction, disturbances of lipid and glucose metabolism, and IR contribute to the hypercoagulable state and the impaired fibrinolysis found in obesity[15]. However, obesity is characterized by the elevation of several clotting factors and PAI-1 directly affecting coagulation and fibrinolysis independent of genetic factors[19]. Moreover, a recent study has reported that subcutaneous adipose tissue shows a stronger relationship with functional measures of hypercoagulability as compared to visceral adipose tissue, suggesting that the anatomic location of adipose deposition may influence the type of thrombotic event, with visceral adipose tissue being associated with arterial thrombosis whereas subcutaneous adipose tissue predisposing to venous thrombosis[20].

Materials and Methods

Study Design

In this study, 120 hospitalized individuals with covid-19 infection aged 32-62 years were recruited during the period April–May 2020. The 90 obese patients subdivided to three groups: first group consisted from 30 over weight individuals (BMI 25.0-29.9 kg/m^2) and the second group comprised from 30 obese patients(BMI 30.0-39.9 kg/m^2), while third group consisted of 30 extreme obesity patients (BMI >40 kg/m^2) while the fourth group comprised from 30 covid-19 patients with healthy body weight (BMI 18.5-24.9 kg/m^2), The questionnaire in the present study was prepared in accurately depending on the opinion of the specialist, including medical swap, D- dimers analysis and CT-scan in addition to the demographic characteristics such as height, weight, and vital signs such as systolic and diastolic blood pressure, all this information was provided through oral interviews with patients and supervising physicians.

Blood Biochemistry Analysis:

All blood sampling was carried out under sterile conditions. Blood glucose measurements which included fasting blood glucose, post prandial blood glucose using certain kits from Spinract, Spain , fasting insulin levels using ELISA kit from Calbiotech, USA then determined HOMA-IR by certain equation. In addition to the measurement of blood lipid profiles were carried out, that included total cholesterol, HDL-cholesterol and triglycerides were obtained between 8 and 10 am following a 10-h fast, using kits from Biolabo, France. Estimates of LDL-cholesterol were calculated using the Friedewald equation. Plasminogen activator inhibitor 1 (PAI-1), tissue-type plasminogen activator (t-PA), and D-dimers were measured using ELISA method by Elabscience, China kit.

Statistical Analysis

The statistical analysis was achieved by the statistical package for the social science (SPSS) software for windows, version 20.0. the result were represented as mean ± standard deviation (Mean ± SD**)**. Two - way Analysis of variance was used to compare variables in different studied groups. Pearson's correlation was applied to determine the relation among the measurable factors of the present study, significant was determined regression. The confidence interval was set at 95%, thus p values less than 5% ($p<0.05$) were considered statistically significant.

Result and Discussion

A total of 120 patients (77 males and 43 females) were participate in current study with a mean age of 51.2 ± 16.4 . sixty –two patients were entered to intensive care unit (ICU) ; most of them were obese or they have extreme obesity. Table (1) illustrated patient characteristics and laboratory data.

18 (29%) of ICU patients developed thrombosis (10 pulmonary embolisms, 6 deep vein thromboses, and 2 acute aortic thrombosis) diagnosed with computational tomography scan (CT scan) and other laboratory tests such as (D-dimers analysis). D-dimers were increased in 80% of overweight, obese, and extreme obesity patients when compared with healthy weight individuals, most of them were admitted to (ICU) in hospital. ICU patients from three groups (overweight, obese, and extreme obesity) presenting with an aggressive form of Covid-19 disease who had significantly higher levels of t-PA, PAI-1 ($p=0.000$) of each other when compared with ICU patients who had healthy weight.

Plasminogen activator inhibitor PAI-1 is the primary inhibitor of both tissue-type (t-PA) and urokinase-type (u-PA) plasminogen activators, which inhibits fibrinolysis and has causative relationship with various vascular complications [40]

In addition to PAI-1 is the dominant inhibitor of the fibrinolytic system. Increased concentration of PAI-1 in the circulation enhanced hypofibrinolysis which is a state of impairment of removal the thrombi from the vascular system, by degradation cellular matrix, migration of smooth muscle cell and angiogenesis, as well as PAI-1 may affect in the development of atherosclerotic lesions[21].

High PAI-1 levels are correlated with an cardiovascular risk of atherothrombosis, dyslipidemia, hyperinsulinemia, and hypertension [22]. PAI-1 has important role in acute thrombotic events such as fibrotic disorders including atherosclerosis and renal and pulmonary fibrosis . Tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) directly effect thrombus formation and degradation leading to risk for arterial thrombosis[23]. PAI-1 is a procoagulant, proinflammatory, and profibrotic molecule. The PAI-1/ tissue plasminogen activator (tPA) ratio uses as a tool of a patient's fibrinolytic balance which can indicate thrombus and stroke risk[24].

The present study finding agreed with the study which mentioned that levels of (t-PA) are increased in obese diabetic patients and the major episode behind atherosclerosis is inhibition of fibrinolysis due to enhanced plasminogen activator inhibitor-1 (PAI-1) levels, marker of ineffective fibrinolysis leading to increased thrombus formation and produce the unstable plaque. Additionally high serum glucose concentration also has been shown to be associated with elevated PAI-1 levels. Increased PAI-1 levels have been encountered in many disease conditions, including metabolic syndrome, diabetes, and obesity[25]. The results of the prospective cardiovascular study indicated that PAI-1 play important role in adipose tissue development and insulin signaling in adipocytes . PAI-1 is the primary inhibitor of both tissue-type and urokinase-type plasminogen activators, which inhibits fibrinolysis and has causal relationship with various vascular complications[26].

The outcomes showed a significant increase in blood sugar levels and insulin concentration in overweight, obese and extreme obesity patients comparing with healthy weight patients, the aim of evaluate fasting blood sugar and fasting insulin was to determine the insulin resistance by certain equation by HOMA-IR formula, table (1) shows highly significant increase in HOMA-IR values in obese and extreme obesity groups, while did not show significant differences between obesity and extreme obesity.

The study reported a significant increase in the levels of triglycerides, and very low density lipoprotein binding cholesterol (vLDL-c) of patients with overweight, obesity and morbid obesity comparison to healthy weight individuals group. In addition to the present study shows that high density lipoprotein binding cholesterol (HDL-C) in serum of obese and extreme obesity groups is significantly decreased ($p<0.05$) compared with that of healthy weight group show Table (1).

Table (1): Levels (Mean ± SD) of characteristics and some laboratories biomarker in Sera of Studied Groups

variables	Healthy weight	Over weight	Obese	Extreme obesity	p- value
BMI kg/m2	23.56±10.23	28.54±12.66	36.43±12.76	44.56±14.34	0.070 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.003 For 2 vs 3 0.000 For 2 vs 4 0.012 For 3 vs 4
Fasting blood glucose mg/dL	86.54±15.51	120.60±15.59	130.23±69.98	135.61±81.24	0.010 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.063 For 2 vs 3 0.000 For 2 vs 4 0.153 For 3 vs 4

Cont... **Table (1): Levels (Mean ± SD) of characteristics and some laboratories biomarker in Sera of Studied Groups**

Fasting insulin µIU/L	14.45±3.65	18.77±5.78	24.89±8.35	27.83±8.80	0.061 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.003 For 2 vs 3 0.000 For 2 vs 4 0.173 For 3 vs 4
HOMA-IR	1.413±0.578	2.343±1.123	3.019± 1.45	3.333±1.366	0.070 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.032 For 2 vs 3 0.000 For 2 vs 4 0.353 For 3 vs 4
Triglyceride mg/Dl	133.33±300.24	169.92±85.00	228.75±90.11	235.55±48.98	0.045 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.033 For 2 vs 3 0.000 For 2 vs 4 0.193 For 3 vs 4
HDL mg/Dl	68.25±22.89	43.67±17.59	34.890±6.45	33.95±8.05	0.000 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.013 For 2 vs 3 0.009 For 2 vs 4 0.653 For 3 vs 4
vLDL mg/Dl	38.40±7.19	45.395±16.50	66.606±18.03	67.32±20.09	0.060 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.023 For 2 vs 3 0.000 For 2 vs 4 0.754 For 3 vs 4
PAI-1 ng/mL	52.67±10.28	74.67±30.18	82.56±39.34	96.35 ± 35.13	0.000 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.053 For 2 vs 3 0.000 For 2 vs 4 0.050 For 3 vs 4
t-PA ng/mL	14.82 ± 7.57	22.97 ±11.86	43.9 ± 19.5	61.44±30.54	0.067 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.000 For 2 vs 3 0.000 For 2 vs 4 0.000 For 3 vs 4
D-Dimers ng/mL	798.8±398.8	864.6 ± 439.2	3412.7±1332.5	3677.5 ± 1641.2	0.047 For 1 vs 2 0.000 For 1 vs 3 0.000 For 1 vs 4 0.000 For 2 vs 3 0.000 For 2 vs 4 0.905 For 3 vs 4

1:Healthy weight 2: Over weight 3:Obese 4: Extreme obesity

As shown in Table (2),serum (PAI-1) concentration were positively correlated with BMI, fasting blood glucose, fasting insulin, HOMA-IR, triglyceride, vLDL , t-PA, and D-dimers, while inversely correlated with HDL, these correlation indicated (PAI-1) levels effecting on the independent risk factors which proved that (PAI-1) might be participated in thrombosis occurrence.

Previous studies provides more evidences that PAI-1–dependent mechanisms may attribute to the pathogenesis of insulin resistance and type 2 diabetes mellitus. For example, in the IRAS study (Insulin Resistance Atherosclerosis Study, a longitudinal cohort of 1047 subjects followed for 5 years), PAI-1 was a mainly predictor for the evolvement of diabetes mellitus, even after adjusting for adipose tissue distribution, and insulin sensitivity[27]. Another study revealed that visceral and subcutaneous adipose tissue PAI-1 mRNA expression were positively correlated with BMI in severe obesity (r=0.043/0.56, respectively[28]. Moreover, there are more information for that weight reduction virtually reduces plasma PAI-1 in obese humans[29]. These previous findings are in line with present results which correlating serum PAI-1 with adipose tissue BMI. Furthermore, another study demonstrated that PAI-1 which secreted from omental adipose tissue is greater than that from subcutaneous adipocytes. [30]. Thus, increased omental fat secretion of PAI-1 may be contribute to the enhanced atherothrombotic risk of human central obesity.

In epidemiological studies, there are a direct link between PAI-1 and lipid parameters (e.g., triglyceride and HDL-C levels) in healthy young adults[31]. Also, recent studies supposed that very low density lipoprotein (VLDL) was responsible for increasing the PAI-1 level by increasing a VLDL response element localized to the promoter region of the PAI-1 gene and mediating VLDL which induced PAI-1 transcription in endothelial cells [32, 33].

A previous in vitro research also showed that small-sized HDL, but not large-sized HDL, enhanced PAI-1 release in the murine 3T3 adipocyte cell line; however, to date, there are limited data on the association of PAI-1 with the functional and structural properties of the different lipoprotein fractions[34].

Table 2: Correlation of TPA-1 levels to the Evaluated Parameters in the Studied Groups

	Parameters	PAI-1 Healthy Weight	PAI-1 Over weight	PAI-1 obese	PAI-1 Extreme obesity
r	BMI	0.248	0.525**	0.785**	0.825**
p		0.079	<0.001	<0.001	<0.001
r	Blood Glucose	0.058	0.189	0.463**	0.567**
p		0.653	0.194	0.001	0.001
r	Insulin	0.012	0.155	0.459**	0.659**
p		0.893	0.284	0.001	0.001
r	HOMA-IR	0.250	0.760**	0.431**	0.731**
p		0.080	<0.001	0.002	0.002
r	Triglyceride	0.120	0.691**	0.622**	0.822**
p		0.420	<0.001	<0.001	<0.001
r	HDL-C	0.071	0.619**	0.719**	0.881**
p		0.660	<0.001	<0.001	<0.001
r	VLDL-C	0.011	0.340*	0.431	0.531
p		0.949	0.016	<0.001	<0.001
r	t-PA	0.111	0.382*	0.664**	0.860**
p		0.481	0.012	<0.001	<0.001

**Correlation is significant at the 0.01 level, *Correlation is significant at the 0.05 level .

The pathophysiology of Covid-19-related thrombosis is incompletely understood. In Covid 19 the Inflammation status promotes releasing tPA and PAI-1 from endothelial cells[35]. In addition, the ctivation of platelets in covid-19, also release large amounts of PAI-1 because the platelets are the major circulating pool of PAI-1 that can contribute to a high local concentration of PAI-1 at the location of a growing fibrin clot. Increased PAI-1 is responsible for hypofibrinolysis and fibrin persistence. Interestingly, increased PAI-1 plasma levels were observed in patients during the SARS-CoV epidemic in 2002[36]. Persistent fibrin deposition in lung parenchyma and alveolar spaces of Covid-19 patients strongly suggests that despite increased levels of tPA, high PAI-1 levels can overcome local tPA release. In addition, plasma hypofibrinolysis from elevated levels of PAI-1 and TAFI is a risk factor for venous thrombosis[35].

Conclusion

There are much evidences about the impact of PAI-1 on thrombosis formation in covid-19 patients who suffered from three types of obesity and the sever of disease associated with increment of BMI. In addition to the analysis of our data established that the homeostasis between coagulation and fibrinolysis is not found in patients with Covid-19 infection, who suffered from hypercoagulability and hypofibrinolysis at the same time which correlated with high PAI-1 and increased t-PA levels. Additionally, in present study concluded this severity of covid -19 increase with increase the number of metabolic syndrome components such as hyperglycemia, hyperinsulinemia and dyslipidemia.

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Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Kufa University and all experiments were carried out in accordance with approved guidelines.

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