Original Article

The relationship between obesity and plasma level of factor V and fibrinogen

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Abstract:

Background: Obesity is a medical condition in which excess body fat has accumulated to the extent that it has an adverse effect on health.. It measured by BMI (body mass index), obesity is considered when the BMI is ≥ 30 kg/m2.It increases the risk of coronary heart disease, Diabetes Mellitus and Cancer. Chronic inflammation and impaired fibrinolysis in obesity may induce thrombosis.

Aim of study: assess the effect of BMI (body mass index) on plasma level of Factor V and fibrinogen in obese and normal weight subjects.

Methods: This study was started on December 2015 and completed on June 2016, and included 51 obese attended alyarmouk Teaching Hospital. As well 25 non-obese subjects, were recruited as a control, age range from18to 50 years old .The hemostatic parameters done for them included the prothrombin time, activated partial thromboplastin time, FV activity, fibrinogen level, and platelet count.

Results: There were insignificant difference in the means of prothrombine time (PT),activated partial thromboplastine time(aPTT), Factor V activity(FV) and Platelet count(PLT)of obese group compared to control group with P value (0.63, 0.902, 0.44, 0.484) respectively. There was significant difference in the mean of fibrinogen of obese group compared to control group with P value (0.006).The correlation between BMI and (PT, PLT, FV and fibrinogen)in obese and control study groups were statistically insignificant with ($P > 0.05$) , but a significant positive correlation between BMI and PTT in obese group was found with ($P=0.037$). There was a significant negative correlation between FV and PT in obese and control groups ($P =0.001$).There was insignificant positive correlation between fibrinogen and PT in obese and control groups ($P > 0.05$).

Conclusions: Significant difference in the mean of plasma level of fibrinogen concentration between obese group and normal weight group was found. Insignificant difference in the means of PT, aPTT, platelet count and FV activity between obese group and normal weight group were found.

Keywords: obesity, FV, fibrinogen.

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Introduction:

Obesity is an independent risk factor for venous thromboembolism. It increases the risk of thrombosis two-fold [1, 2, 3].A high BMI is recognized as a major risk factor for thrombotic disorders such as cardiovascular disease, stroke, and venous thromboembolism. Obesity is an established predictor of myocardial infarction independent of sex, age, and ethnicity [4, 5]. Obesity cause chronic inflammation and impaired fibrinolysis that lead to thrombosis. It increase the levels of the pro-inflammatory cytokines IL-6 and tumor necrosis factor alpha (TNF-α), acute phase proteins, inflammation may cause thrombosis indirectly by inducing oxidative stress and endothelial dysfunction. High level plasminogen activator inhibitor-1(PAI-1) levels impede the normal clearance of fibrin and consequently promote thrombosis.

The initiation of coagulation cascade begin when Tissue Factor (TF) is exposed to blood and binds with factor VIIa .Obese patients have increased adipocyte and monocyte TF expression [6, 7, 8]. Factor V is a coagulation protein, referred to as proaccelerin or labile factor, it is not active as enzyme but work as a cofactor. The synthesis of FV occurs in the liver. The molecule circulates in plasma as a single-chain molecule with a plasma half-life of 12–36 hours. Deficiency leads to hemorrhage, while some mutations (most notably factor V Leiden) predispose for thrombosis. It is activated by thrombin, activated factor V (now called FVa) is a cofactor of the prothrombinase complex: The activated factor X (FXa) enzyme requires calcium and activated factor V to convert prothrombin to thrombin on the cell surface membrane. [9, 10 -13]. Fibrinogen (factor I) is a glycoprotein that helps in the formation of blood clots. The synthesis occur in liver .The coagulation cascade activates the prothrombin by converting it into the serine protease thrombin. Thrombin then converts the soluble fibrinogen into insoluble fibrin strands. These strands

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are then cross-linked by factor XIII to form a blood clot. It has important role in clotting, fibrinolysis, inflammation and wound healing.Fibrinogen is an acute-phase reactant and its synthesis can be increased up to 20-fold with a strong inflammatory stimulus. [9].

Aim of study:

Through measurement of FV level and fibrinogen concentration and coagulation parameters(PT,PTT andPLT), this study aims to assess the effects of BMI on plasma level of FV and fibrinogen and coagulation parameters in obese and normal weight persons.

Patients, Materials and Methods:

This prospective case control study was done over a period of 6 months, started on December 2015and completed on June 2016. This study included 76 subjects with age range 18−50, 51obese subjects who BMI≥30 as study group and25normalweight subjects who BMI< 25 as control group were attending Al yarmok teaching Hospital as healthy patient's relative. This research was approved by Department of Pathology College of Medicine University of Baghdad. All obese and non-obese controls were informed about the nature of this study and oral consents were obtained from them. Full history was taken for each subjects including name, age, medical history (hypertension, diabetes mellitus, rheumatoid arthritis, previous thrombosis), surgical history (if present, the time for the last surgical procedure), drug history, smoking history, recent trauma, prolonged air travel, symptoms of pulmonary embolism (shortness of breath, cough with bloody mucus, chest pain, fainting spells, dizziness), symptoms of DVT (redness, warmth, tenderness, and swelling of the leg),all above questionnaire was considered as exclusion criteria. Weight was measured with electronic balance, bare foot. Height was measured with the subject barefooted and his back facing the wall using a calibrated rod. BMI was calculated for each subjects by dividing his weight in kilograms by the square of his height in meters (kg/m2). By a clean aseptic venipuncture 4.3 ml of blood were drawn from each patient and control groups. The sample was then divided between two tubes:

- 2.5 ml of blood in dipotassium ethylene diamine tetra-acetic acid (K2-EDTA) tube for platelet count (PLT) which were performed using automated analyzer (Cell-DYN, RUBY ABBOTT Diagnostic, USA)
- 1.8 ml of blood in disposable capped plastic tube containing 0.2 ml of 109 mmol/l trisodium citrate dihydrate (32 g/l) and gently mixed well by inverting several times.Platelets poor plasmas (PPP) were prepared by centrifugation of blood at 2000 g for 15 minutes [14]. Then 0.3 ml of PPP was obtained from the upper part of the separated plasma for performance of prothrombin time (PT), activated partial thromboplastin time (APTT), and for factor V activity and fibrinogen level within 2 hours of blood collection using STart4® semi-automated coagulometer (DiagnosticaStago, France).

Methods:

- PT: This test depends on reaction with factors V, VII and X, II and on the fibrinogen concentration of the plasmaand indicates the overall efficiency of the extrinsic clotting system. This test was performed using a commercially available kit NEOPLASTINE® CI PLUS 5 (DIAGNOSTICASTAGO/ France), which contains:

Reagent 1: lyophilized thromboplastin prepared from fresh rabbit cerebral tissue.

Reagent 2: Aqueous solvent containing calcium.

A vial of reagent 2 was shaken well and the entire content was transferred into a vial of reagent 1 and left for 30 minutes at room temperature (18 -25 oC) then, the Reagent 1 vial swirled gently to obtain a homogeneous suspension(170). The test was performed using STart4® semi-automated coagulometer. Exactly 0.1 ml of control or patient's PPP was poured in a cuvette in which steel ball was put and left to be warmed at 37oC in STart4® for 2 minutes then 0.2 ml of prewarmed reagent 1 and 2 mixture was added, the clotting time was recorded in seconds .Normal PT range established in the laboratory was (12-14) seconds. [14]

- APTT: The test depends not only on the contact factors, factors VIII and IX, but also on the reaction with factors X, V, prothrombin and fibrinogen .and indicates the overall efficiency of the intrinsic pathway. APTT was determined using a commercially available kit C.K.PREST®2(DIAGNOSTICA STAGO, France) which contains:

Reagent 1: cephalin, prepared from rabbit brain, lyophilized.

Reagent 2: activator, buffered suspension of kaolin

STA®-CaCl2 0.025M (DIAGNOSTICA STAGO, France).

A vial of reagent 2 was shaken well and the entire content was transferred into a vial of reagent 1 and left for 30 minutes at room temperature (18-25oC) then swirled gently to obtain a homogeneous suspension. The test was performed using 0.1 ml of control or patient>s PPP poured in a cuvette in which a steel ball was put then 0.1 ml of prewarmed reagent 1 and 2 mixture is added to cuvette to be left for exactly 3 minutes at 37oC in STart4® then 0.1 ml of prewarmed CaCl2 was added, the clotting time was recorded in seconds. Normal APTT range established in the laboratory was 28-40 seconds. [14]

- FV ASSAY: The assay of factor V is based on the PT. The assay compares the ability of dilutions of the patient's plasma and of a standard plasma to correct the PT of a substrate plasma.

PPP from patient or control.Standard,unicalibrator STA®: citrated normal human plasma, Lyophilized Neoplastine® CI Plus 5 STA

STA® - Deficient V: lyophilized citrated human plasma from which factor V has been removed by selective immuno-adsorption.

STA® - Owren-Koller.

Each vial was reconstituted with 1 ml of distilled water and left to stand at room temperature (18-25 °C) for 30 minutes. Then the vial was swirled gently to obtain a homogenous solution. Three dilutions of the standard and the test plasma in Owren-Koller buffer were prepared as follow: 1:10 (put 0.1 of ppp and 0.9 buffer) , 1:20(put 0.5 of first dilution and 0.5 of buffer), and 1:40(put 0.5 of second dilution and 0.5 of buffer) , representing

100%, 50%, and 25% activity of factor V, respectively then 0.1 ml of each dilution was poured to a cuvette (in which a steel ball was put) added to it 0.1 ml of deficient V reagent and left to be warmed at 37°C in STart4® for 2 minutes then 0.2 ml of prewarmed Neoplastine® CI Plus reagent was added, the clotting time was recorded in seconds. The clotting time (PT) of each dilution of the test, and standard determined and plotted on a log-log paper as factor V activity (%) versus clotting time in seconds. The parallel straight lines obtained from plotting the clotting times of the three dilutions of the standard and that of the test plasma on log-log paper were considered as the parallel line bioassay of factor V activity. [14]

- Fibrinogen assay: PPP from patient or control.

STA® -FIBRI PREST:lymphosized titrated human calcium thrombin (approximately ,80 NIH unit ml)containing a specific heparin inhibitor to allow the assayof fibrinogen in heparinized plasma samples.STA® - Owren-Koller.Each vial from STA® -FIBRI PREST with 2 ml distilled water. Then, allow the reconstituted material to stand at room temperature (18-25 °C) for 30 minutes. Swirl the vial gently before use. One dilution of the the test plasma in Owren-Koller buffer were prepared as follow: 1:10(add 100 microliter of PPP of test or control to 900 microliter of Owren-Koller buffer then 100 micron of this dilution was poured to a cuvette (in which a steel ball was put) then incubate for 2 minutes in 37°C added to it 0.1 ml of STA® -FIBRI PREST reagent. The clotting time (PT) of each tests were recorded in seconds then from calibration table inside the kit that convert the PT in seconds to concentration in (g/ l), normal range of fibrinogen 2-4 g/ l. [14].

Statistical analysis: Statistical analysis was done by using SPSS (statistical package for social science) version 17.Mean±SD was used to describe quantitative variables, number of percentage were used to describe qualitative variables, Student's t-test was used to compare study groups (obese and control) for PT,aPTT,PLT,FV,fibrinogen . Pearson correlation test was used to detect the relation of FV and fibrinogen with other variables. The value less than 0.05 was considered significant.

Results:

Hemostatic parameters: The hemostatic parameters that were included in this study were: PT, APTT, FV activity, fibrinogen concentration, and Platelet count.Age:The obese group was aged matched with the control, the mean age of obese persons in this group was 35.0784 ± 9.68472 years and 30.3200 ± 7.79273 years in control, with statistically significant difference, P value = 0.036.table(1)

Table (1) the mean of age in obese and control:

	Group	N	Mean	Std Deviation	Std Error Mean
Age	Obese	51	35.0784	9.68472	1.35613
	Control	25	30.3200	7.79273	1.55855

*Significant using independent samples t- test at 0.05 level.

Table (2) the baseline of hemostatic parameter of obese and control:

	Group	N	Mean	Std Deviation	Std Error Mean	P value
PT second	Obese	51	11.8020	1.56569	0.21924	0.630
	Control	25	11.6320	1.12758	0.22552	
aPPT second	Obese	51	33.1922	5.24511	0.73446	0.902
	Control	25	33.0480	3.64567	0.72913	
Platelet X 10^9	Obese	51	258.6667	50.96966	7.13718	0.483
	Control	25	268.1600	62.91375	12.58275	
Factor V %	Obese	51	144.8824	45.72249	6.40243	0.440
	Control	25	137.4000	21.26813	4.25363	
Fibrinogen g/l	Obese	51	4.7351	1.22843	0.17202	0.006*
	Control	25	4.0564	.83347	0.16669	

*Significant using independent samples t-test at 0.01 level

PT (prothrombin time):the mean was 11.8020 ± 1.56569 seconds in obese and the mean was11.6320 ± 1.12758 seconds in control with statistically insignificant difference, P value=0.630 (Table 2).APTT:the mean was33.1922 ± 5.24511 seconds in obeseand themean was33.0480±3.64567 in control with statistically insignificant difference, P value= 0.902(Table 2).Platelet count: the mean was258.6667 ±5.24511 X 10^9 in obese and the mean was 268.1600±62.91375 X 10^9in control with statistically insignificant, P value=0.483 (Table 2).Factor V% activity: the mean was 144.8824±45.72249 %in obese and the mean 137.4000±21.26813% in control with statistically insignificant, P value=0.440 (Table 2).Fibrinogen: the mean was 4.7351±1.22843mg|L in obese andthe mean4.0564±0.83347mg|L in control with statistically significant P value=0.006 (Table 2).The correlation between BMI and PT: There was insignificant negative correlation between PT and BMI in obese group and insignificant positive correlation in control group. Table (3), table (4), figure (1).

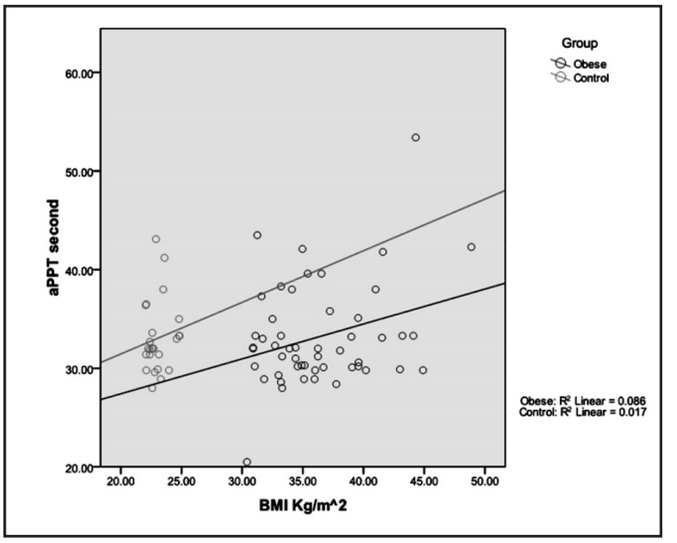


Figure (1) the correlation between BMI and PT.

The correlation between BMI and aPTT:There was significant positive correlation between aPTT and BMI in obese group (Pvalue=0.037) and there was insignificant positive correlation between aPTT and BMI in control group. Table (3), table (4), figure (2).

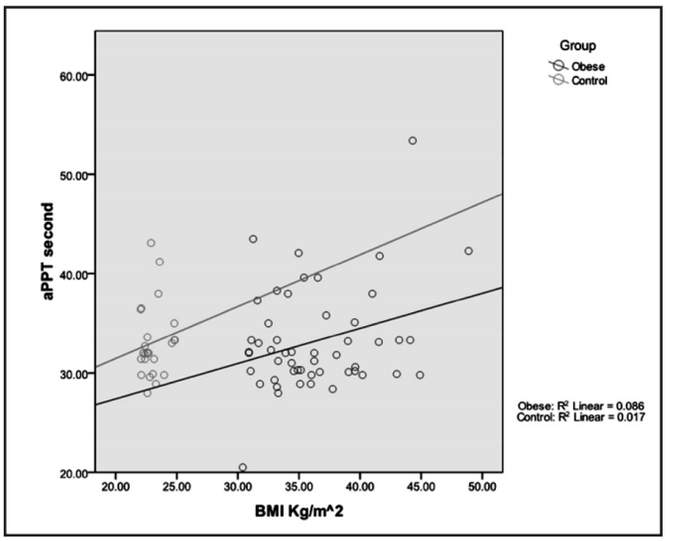


Figure (2) the correlation between aPTT and BMI in obese and control.

The correlation between platelet count and BMI: There was insignificant positive correlation between platelet count and BMI in obese. There was insignificant negative correlation between plateletcount and BMI in control. Table (3), table (4), figure (3). The correlation between FV activity and BMI:There was insignificant negative correlation between FV and BMI in obese group. There was insignificant positive correlation between FV and BMI in control group. . Table (3), table (4), figure (4).

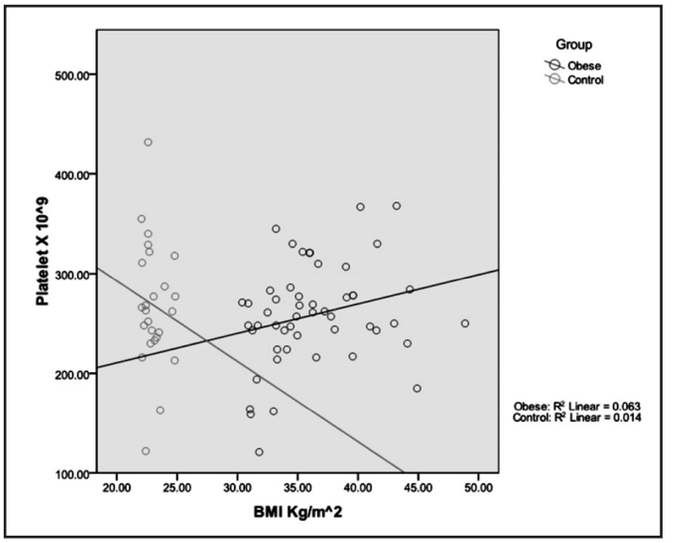


Figure (3) the correlation between platelet count and BMI obese and control.

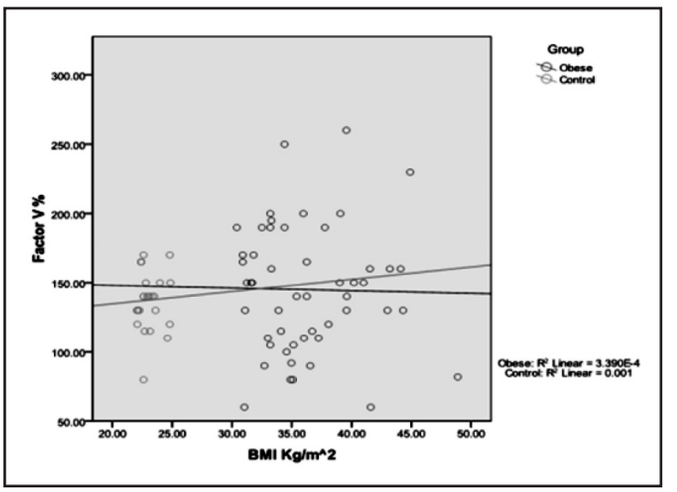
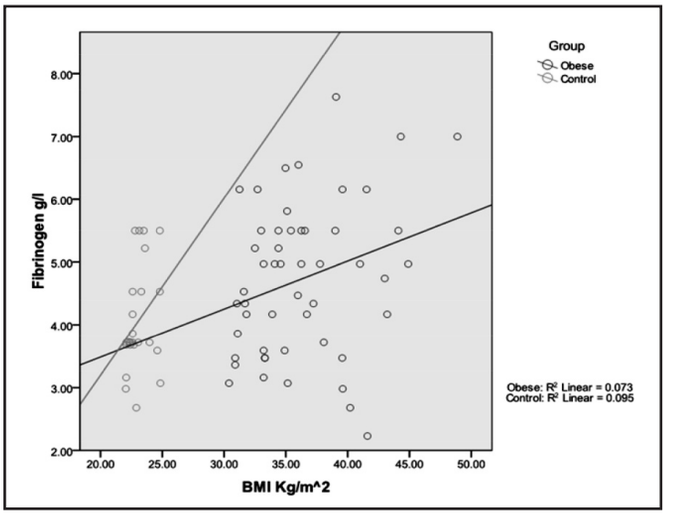


Figure (4) the correlation between factor V activity and BMI in obese and control.

The correlation between FV activity and PT: There was significant negative correlation between FV and PT in obese and control groups Pvalue =0.001. Table (3), table (4). The correlation between Fibrinogen concentration and BMI:There was insignificant positive correlation in obese and control groups. . Table (3), table (4), figure (5)

Figure (5) the correlation between fibrinogen concentration and BMI in obese and control.



The correlation between Fibrinogen concentration and PT: There was insignificant negative correlation in obese group and positive insignificant correlation in control group. Table (3), table (4) .

Table (3): The correlation of obese group

Parameters	Correlation	BMI Kg/m^2	PT second	aPPT second	Platelet X 10^9	Factor V %
PT second	Pearson Correlation	-.0187				
	Sig. (2-tailed)	0.190				
	N	51				
aPPT second	Pearson Correlation	0.294*	0.008			
	Sig. (2-tailed)	0.037	0.955			
	N	51	51			
Platelet X 10^9	Pearson Correlation	0.251	-0.174	0.024		
	Sig. (2-tailed)	0.076	0.223	0.867		
	N	51	51	51		
Factor V %	Pearson Correlation	-0.018	-0.455**	-0.246	-0.104	
	Sig. (2-tailed)	0.898	0.001	0.082	0.466	
	N	51	51	51	51	
Fibrinogen g/l	Pearson Correlation	0.271	-0.208	0.362**	-0.057	-0.053
	Sig. (2-tailed)	0.054	0.143	0.009	0.691	0.712
	N	51	51	51	51	51

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table (4): correlation of control group

Parameters	Correlation	BMI Kg/m^2	PT second	aPPT second	Platelet X 10^9	Factor V %
PT second	Pearson Correlation	0.033				
	Sig. (2-tailed)	0.876				
	N	25				
aPPT second	Pearson Correlation	0.131	-0.216			
	Sig. (2-tailed)	0.534	0.300			
	N	25	25			
Platelet X 10^9	Pearson Correlation	-0.117	0.390	-0.184		
	Sig. (2-tailed)	0.579	0.054	0.379		
	N	25	25	25		
Factor V %	Pearson Correlation	0.038	-0.604**	-0.131	-0.518**	
	Sig. (2-tailed)	0.857	0.001	0.532	0.008	
	N	25	25	25	25	
Fibrinogen g/l	Pearson Correlation	0.308	0.040	-0.020	-0.237	-0.025
	Sig. (2-tailed)	0.134	0.849	0.924	0.255	0.905
	N	25	25	25	25	25

**. Correlation is significant at the 0.01 level (2-tailed).

Discussion:

The difference in the mean PT between obese group and control group didn't show statistical significance with (P value 0.630) ,which was similar to Sharma S et al. (London UK)who observed that insignificant difference in PT in four study groups{ obese pregnant (OP),lean pregnant(LP),non pregnant obese(NPO),non pregnant lean(NPL)}[15].In contrast to the study of Kopp CW et al (Austria) who observed that PT was reduced after 14 months after gastroplasty [16] and Stoppa-Vaucher S et al. (Geneva) who observed that PT was reduced in obese children compared with lean children. This difference between the results may be propably due to difference in age of study group, sample size and geographical variation [17].In this study the observed aPTT mean of obese group compared to lean was statistically insignificant with (P 0.902), that is compatible with Sharma S et al. (London UK) who observed that insignificant difference in aPPT in four study groups{ obese pregnant (OP),lean pregnant(LP),non pregnant obese(NPO),non pregnant lean(NPL)} [15] and with study of Kopp CW et al (Austria) who observed that there was insignificant difference of aPTT before and after 14 months of gastroplasty[16],also in agreement with Stoppa-Vaucher S et al. (Geneva)who observed that there was insignificant difference of a PTT in obese children compared

with lean children[17]. The mean platelet count of obese group compared to control group in this study was statistically insignificant with p value=0.483 and there was insignificant positive correlation between platelet count and BMI, while SamochaBonet D et al observed that there was significant elevation of platelet counts in overweight, obese and morbid obese ($P < 0.0001$) compared with normal-weight females and significant correlation between BMI and platelet counts ($P < .0001$) was found among females[18].These difference may be probably due to difference in sample size and gender of study group. The mean of difference factor V activity was statistically insignificant in obese compared to control (P value=0.440).In this study, the observed mean fibrinogen concentration of obese group were statistically higher than that in the control group with P value=0.006. That's in agreement with Bowles LK et al who observed there were significant association of BMI with fibrinogen ($P = 0.002$) and strong positive associations of BMI with fibrinogen ($r = 0.57$, $P < 0.0001$) in women also Bowels LK study stated that there was positive significant association with BMI and FVIII, FXII,antithrombin activity and protein C[19]. These results differ from those obtained by Abdollahi M et al (Iran) who observed that obese individuals had higher levels of factor VIII and factor IX, but not of fibrinogen. The same study stated that the effect on risk of obesity was not changed after adjustment for coagulation factors levels (fibrinogen, F VIII, F IX, D-dimer) [3].De Pergola G et al (Italy) whostate that several studies have shown that obese patients have higher plasma concentrations of all pro-thrombotic factors (fibrinogen, von Willebrand factor (vWF), and factor VII), as compared to non-obese controls, with a positive association with central fat. Similarly plasma concentrations of plasminogen activator inhibitor-1 (PAI-1) have been shown to be higher in obese patients as compared to non-obese controls and to be directly correlated with visceral fat [20].Azevedo WF etal who observed that Serum fibrinogen levels were elevated in 28.3% of individuals (p=0.003) in his cross sectional study on 128 obese children and adolescents [21].Ditschuneit HH etal, he studied sixty patients (44 female, 16 male) after 9.5 ± 6.2 month of dieting. He observed that fibrinogen level correlated with the body mass index, the waist circumference, the hip circumference and the waist to hip ratio. In patients with extreme overweight and high fibrinogen levels, who reduced their BMI by 7.4 ± 1.24 kg/m2, the weight loss correlated with the decrease in fibrinogen [22].Rillaerts E etal. results are based on a study of 90 obese subjects (36 men, 54 women) and 90 non-obese, he observed the link between obesity and hyperviscosity may have been mediated by fibrinogen levels, which were on average 40% higher in the obese group than in healthy controls[23].Obesity could impair the fibrinolysis by production of PAI-1 and could enhance the coagulation by production of Tissue factor(TF) by adipose tissue .obesity also create a hypercoagulable state by affecting the hepatic synthesis of several factors like fibrinogen, FVII,FVIII and TF. The production of adipose tissue hormones (adipokines) could cause prothrombotic state and also interfere with platelet function [24].

Conclusions: Significant difference in the mean of plasma level offibrinogen concentrations between obese group and normal weight group was found. Insignificant difference in the means ofPT, aPTT, platelet count, FV activity between obese group and normal weight group were found.

Reference:

1. Rosendal FR, Van HylckmaVlieg A, Tanis BC etal. Estrogens, progestogens and thrombosis. J ThrombHaemost 2003; 1(7):13711380-.

2. Murthy AS. Obesity and contraception: emerging issues. SeminReprod Med 2010; 28(2): 156–163

3. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. ThrombHaemost 2003; 89(3): 493498-.

4. Wolk R, Berger P, Lennon RJ, et al. Body mass index, a risk factor for unstable angina and myocardial infarction in patients with angiographically confirmed coronary artery disease. Circulation. 2003; 108:2206–2211.

5. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27000 participants from 52 countries: a case-control study. Lancet. 2005; 366:1640–1649.

6. Kanda H, Tateya S, Tamori Y, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. J Clin Invest. 2006; 116:1494–1505.

7. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994; 372:425–432.

8. Wallace AM, McMahon AD, Packard CJ, et al. Plasma leptin and the risk of cardiovascular disease in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation. 2001; 104:3052–3056.

9. Hoffbrand AV, Moss PAH. Platelets, blood coagulation and haemastasis. Essential Haematology. 5th ed. Oxford OX4 2DQ, UK: Blackwell Publishing 2006; 264to 307.

10. Huang NJ,Koerper MA .Factor V deficiency :aconcise review . Hemophilia2008 ; 14 (6|):1164– 1169

11. Oliver JA, Monroe DM, Church FC, et al: Activated protein C cleaves factor Va more efficiently on endothelium than on platelet surfaces. Blood (2002) ; 100:539,

12. Gould WR, Silveira JR, Tracy PB: Unique in vivo modifications of coagulation factor V produce a physically and functionally distinct platelet-derived cofactor: Characterization of purified platelet-derived factor V/Va. J BiolChem, 2004; 279:2383.

13. Hayward C: Multimerin: A bench-to-bedside chronology of a unique platelet and endothelial cell protein—Fromdiscovery to function to abnormalities in disease. Clin Invest Med 1997; 20:176

14. Laffan M, Manning R. Investigation of haemostasis. In: Bain BJ, Bates I, Laffan MA, Lewis SM (eds.) Dacie and Lewis Practical Haematology. 11th ed. Philadelphia: Churchill Livingstone Elsevier 2011;399_445

15. Sharma S, Uprichard J, Moretti A, Boyce H, Szydlo R, Stocks G. Use of thromboelastography to assess the combined role of pregnancy and obesity on coagulation: a prospective study. Int J ObstetAnesth. 2013 Apr; 22(2):1138-.
16. Kopp CW1, Kopp HP, Steiner S, Kriwanek S, Krzyzanowska K, Bartok A, Roka R, Minar E, Schernthaner G. Weight loss reduces tissue factor in morbidly obese patients. Obes Res. 2003 Aug; 11(8):9506-.
17. Stoppa-Vaucher S1, Dirlewanger MA, Meier CA, de Moerloose P, Reber G, Roux-Lombard P, Combescure C, Saudan S, SchwitzgebelVM.Inflammatory and prothrombotic states in obese children of European descent .Obesity (Silver Spring). 2012 Aug; 20(8):16628-. doi: 10.1038/oby.2012.85. Epub 2012 Apr 9.
18. Samocha-Bonet D1, Justo D, Rogowski O, Saar N, Abu-Abeid S, Shenkerman G, Shapira I, Berliner S, Tomer A. Platelet counts and platelet activation markers in obese subjects.Medi atorsInflamm.2008;2008:834153.
19. Bowles LK, Cooper JA, Howarth DJ, Miller GJ, MacCallum PK. Associations of haemostatic variables with body mass index: a community-based study .Blood Coagul Fibrinolysis. 2003 Sep; 14(6):56973-.
20. De Pergola G, Pannacciulli N. Coagulation and fibrinolysis abnormalities in obesity, J Endocrinol Invest. 2002 Nov; 25(10):899904-.
21. Azevedo WF, Cantalice AS, Gonzaga NC, Simões MO, Guimarães AL, Carvalho DF, Medeiros CCJ. Fibrinogen: cardiometabolic risk marker in obese or overweight children and adolescents. Pediatr (Rio J) 2015 Sep-Oct; 91(5):46470-.
22. Ditschuneit HH, Flechtner-Mors M, Adler G. Fibrinogen in obesity before and after weight reduction. Obes Res. 1995 Jan; 3(1):438-.
23. Rillaerts E1, van Gaal L, Xiang DZ, Vansant G, De Leeuw I. Blood viscosity in human obesity: relation to glucose tolerance and insulin status. Int J Obes. 1989;13(6):73945-
24. Faber DR, de Groot PG, Visseren FL. Role of adipose tissue in haemostasis, coagulation and fibrinolysis.Obes Rev. 2009 Sep; 10(5):55463-.