



Estimation of Fibrinogen, Stable factor, and Antihemophilic Factor Concentrations in Patients complained from Diabetes Mellitus Type2 of both sex in Babylon province

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Abstract : The present study was applied to estimate specific clotting factors included in extrinsic and common pathway of patients affected with type-2 diabetes mellitus from both sexes (men and women).

The study included 180 subjects, of those, ninety subjects (45 men, 45 women) were affected with type-2 diabetes mellitus. The others remaining number (90) were used as a healthy control sample (45 Men, 45 Women). According to age, all subjects of the study (patients, control) were subdivided into three subgroups; (40-49) , (50-59) , and (60-69) years old. All patients of the present study were recording elevation ($P < 0.05$) in the level of glucose concentration when matched with their health counter parts. Regarding results of clotting factors, values of fibrinogen, the final components of common pathway, did explain a marked drop ($P < 0.05$) in most patient groups matching with the healthy groups.

About results of stable factor (F VIII), the essential components of extrinsic pathway, did explain a remarks heightening ($P < 0.05$) in most of diabetic patient groups when compared with healthy control groups.

Results of anti-hemophilic factor (principal factor of intrinsic pathway) were significantly decreased ($P > 0.05$) in most patients groups of both sexes matching with healthy groups.

From results which are explained above it can be concluded that extrinsic pathway of blood clotting appears more active in relative to intrinsic pathway through increased concentration of factor (VIII) which in turns can render the diabetic patients who are highly susceptible to thrombotic events.

Key words : Clotting factors , diabetes mellitus , thrombosis.

Introduction

Diabetes mellitus is a syndrome resulted from a complex of factors. The disease is caused by many genetic and acquired changes in insulin production or its actions on target tissues. Deficiency of insulin or its action may cause several abnormalities of another nutrients such as carbohydrate, lipids, and proteins¹.

Moreover, type 2 – diabetes disease appears step by step. In early stays, the disease seems masked as the clinical symptoms are not enough to give a complete diagnosis of disease, then after, loss of physical activities, overweight, and aging render the clinical signs and symptoms of disease are more prominent².

Diabetes mellitus is condition characterized with increase hypercoagulability. Hypercoagulability is a condition resulted from more fibrinogen concentration, down regulation of proteins and increase synthesis of vWF by endothelium .These changes are associated with drop of fibrinolysis through elevated PA – 1³.

Recently, it was found that cardiovascular events were found to associate with high level of plasma fibrinogen and also the same association was occurred between level of fibrinogen and coronary disease⁴. In post food intake, the production of fibrinogen is increased because of insulin over production. Inversely, release of albumin in response to insulin release remain normal regardless of metabolic balance^{5,6}.

Experimental

The subject of the study

This study is established in different locations including Marjan Teaching Hospital / Center of Diabetes in Babylon , laboratories of College of Science for Women and College of Science in Babylon University during the period ranged from October 2015 to May 2016 . The total number of patient subjects that included in this study was 90 diabetic patients from both sexes (45 men and 45 women) . According to age , the patients were divided into three subgroups as follows :(40-40) years , (50-59) years, and (60-69) years .Each age group including 15 patients divided according to gender . Ninety (90) healthy control individuals (45 women and 45 men) were included in the study and were also subdivided according to age and gender factor . All patients attended to diabetic center in Marjan Hospital to take management and treatments. The blood samples were drawn from patient before intake food and therapies in the morning. The excluding criteria of patients involve thyrotoxicosis, tumors, smoking, asthma, and cardiovascular disease.

Women including in this study were not pregnant and without hormonal replacement therapy and without contraceptive drugs.

Blood Sample Collection

The blood samples were collected in the morning (8 o'clock).The anti-cubical vein of left arm was employed .Before sampling , the skin was clean with alcohol solution (70 %) and then left to dry .Sets of tubes were prepared , the first one has trisodium citrate as anti-coagulant to perform special analyses involve in determination of clotting factors .

Determination of Fibrinogen(FI)

Principle of Test

Method which are used in the determination of fibrinogen (FI) involves prominent fact which means that high level of thrombin (FII) in sample of pre – diluted plasma. The clotting time is inversely proportionated to the levels of fibrinogen in the sample (according to instructions of Biolabo company).

Measurement of Stable Factor (VII) levels

Principle of Test

ELISA kit that provided by Elabscience company was used to estimation of FVII level in plasma .Spectrophotometer was used with wave length 450 nm.

Measurement of Antihemophilic Factor (FVIII) levels

Principle of Test

ELISA kit supplied by Elabscience company was conducted to determine concentration of FVII .This test depends on interactions of antigen – antibodies and the final products are spectrophotometrically measured at 450 nm wave length .

Statistical Analysis

The results in this study were statistically analysed by application of specific computer program called spss program. The differences among studied groups were examined by student's – test. The level $p < 0.05$ was depended as lower significant line. All results of the present study were represented means \pm standard deviation⁷.

Results

Results of Blood Sugar Levels in Patients Men

The level of blood sugar in male affected with diabetes mellitus in figure (1) were markedly increased ($p < 0.05$) of different groups of males diabetic patients in a comparison with those of control groups.

There are non - significant difference ($p > 0.05$) among age groups of male patients (second group , third group) except there is a significant difference (3.7) in first group .

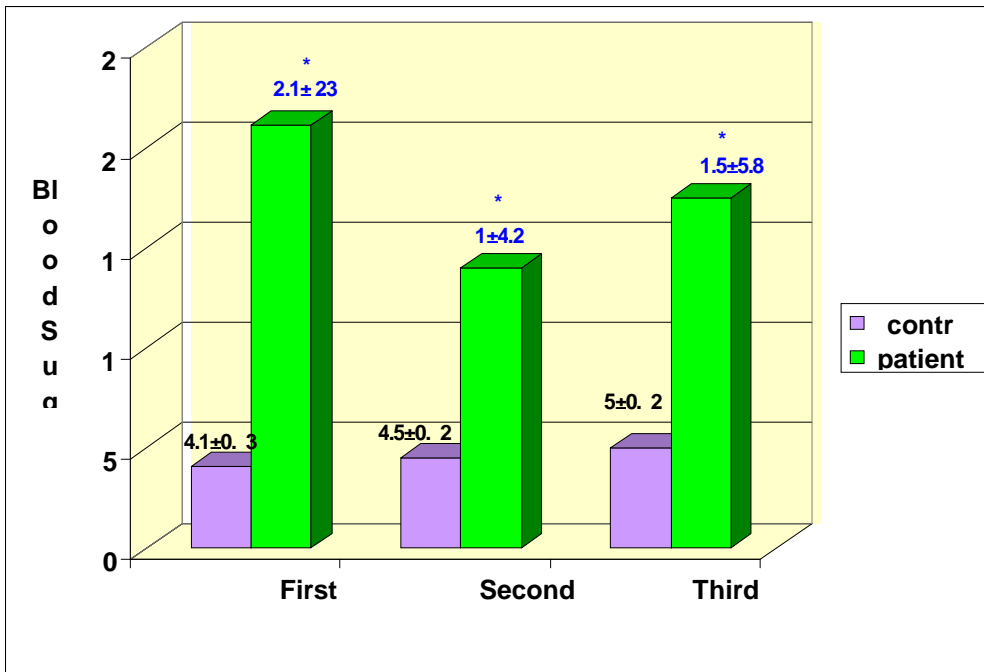


Figure (1) The mean of blood sugar (mmol/ L) in male of diabetic patients .

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably different ($p < 0.05$)

Values of Blood Sugar Levels of Patients Women

The level of blood sugar in diabetic female which are present in figure (2) indicated a marked heightening ($p < 0.05$) in different tests of female diabetic patients in a comparison to those of control groups.

There are non - significant difference ($p > 0.05$) among age groups of female patients (second group, third group) except there is a significant difference (2.4) in first group .

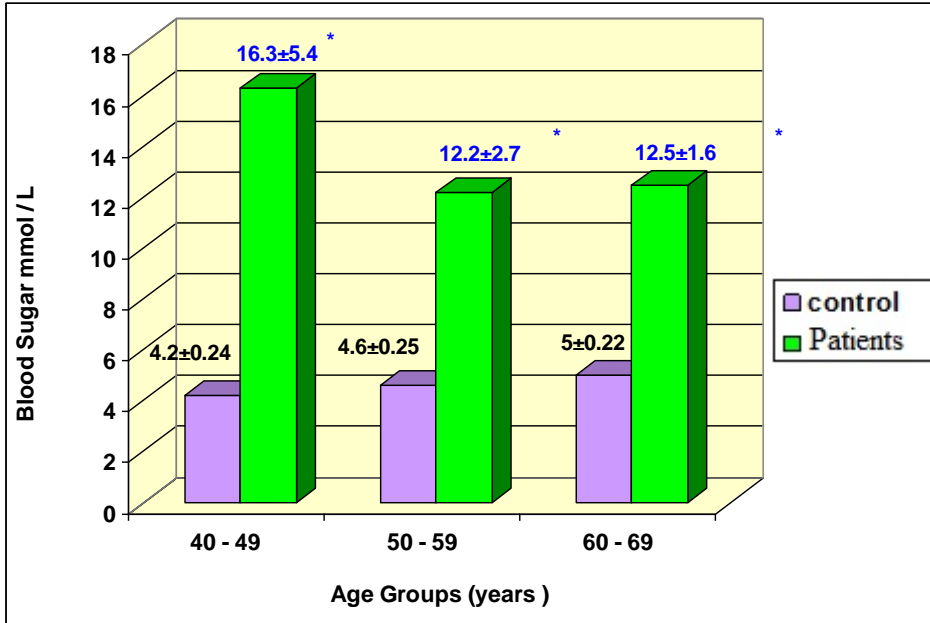


Figure (2) The mean of blood sugar (mmol / L) in women with diabetes mellituse.

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably different (p<0.05)

Fibrinogen Levels Concentration (Factor I) in diabetic Men

The level of fibrinogen affected with type 2 diabetes mellitus in figure (3) revealed marked drop (p<0.05) are of two age groups (second group , third group) of diabetic patients when compared with those control groups and confirmed non – significant fall (p>0.05) in first group of diabetic patients in matching with control group. There are non - significant differences (p> 0.05) among age groups of men patients .

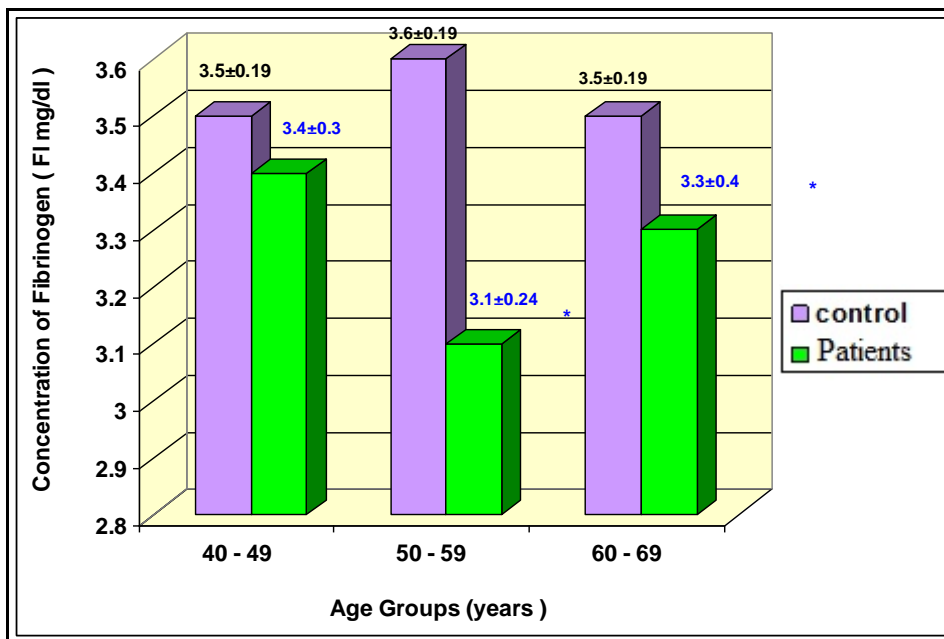


Figure (3) The result of F1levels (F1 mg / dl) in male affected with type2 diabetes mellitus.

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably different (p<0.05)

Fibrinogen Levels (Factor I) in Diabetic Women

The level of F1 in diabetic female are explained below (figure 4) prominent fall ($p < 0.05$) of two age tests(first group, third group) of female diabetic patients when matched comparison with this control groups and there is no differences ($p > 0.05$) in age group (second group) of diabetic females patients in a comparison with healthy group.

There are non - significant difference($p > 0.05$) among two age groups of female patients(second group, third group) and there is a significant difference (1.1) in first group .

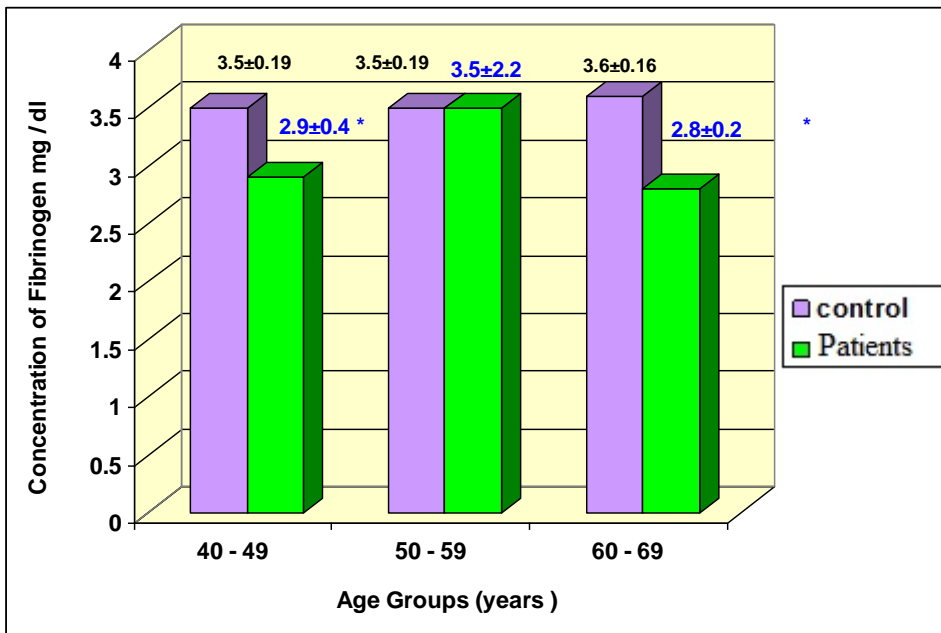
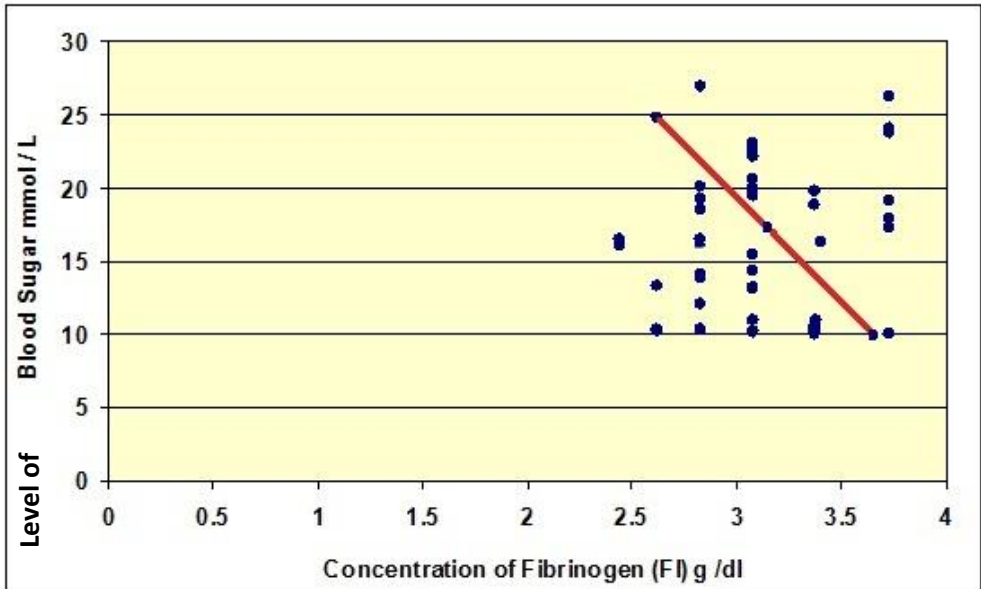


Figure (4) The mean of fibrinogen concentration (F1 mg / dl) in female of diabetic patients.

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably different ($p < 0.05$)

Correlation Coefficients of F1 Concentration and Blood Sugar of Diabetic Patients .

The results indicate marked negative correlation ($r = - 0.06$) for fibrinogen level with blood sugar (Figure 5).



$r = - 0.06$

Figure(5) Correlation coefficients between F1 level and blood sugar in diabetic patients.

The Concentration of Stable Factor (FVII) in Male Diabetic Patients (type2)

The results obtained and illustrated from the present study in figure (6) showed a significant heightening ($p < 0.05$) in first group in male of diabetic patients in matching with those of control group and non – significant increase ($p > 0.05$) in second age group and non -significant decrease in third age group when matched with their counterparts of healthy control group .

There are non – significant differences ($p > 0.05$) among (second group, third group) and there is a significant difference (80.5) in the first group

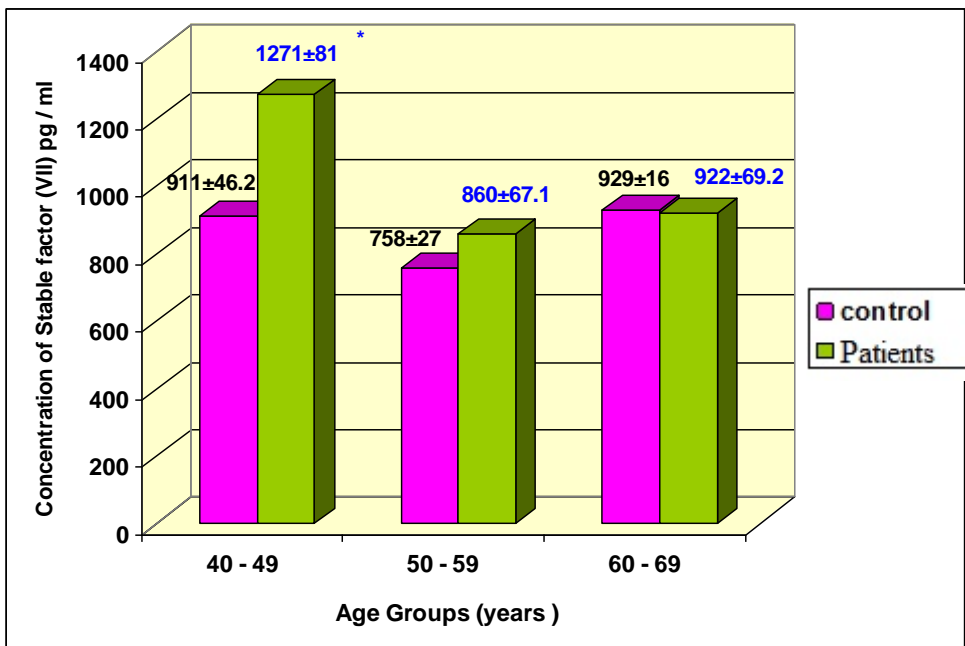


Figure (6) The results of FVII (pg / ml) for males of diabetic patients.

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably diferent ($p < 0.05$)

The Levels of FVII in Female Diabetic Patients

The data obtained and showed from the present study in figure (7) confirmed a significant elevation ($p<0.05$) in two age group (second group , third group) in female of diabetic patients in matching with control group and non – significant drop ($p>0.05$) in the first group of female diabetic patient in a comparison with control.

It is indicated non – significant difference ($p>0.05$) among (second group , third group) and there is a significant difference ($p<0.05$) (95.4) in the third group

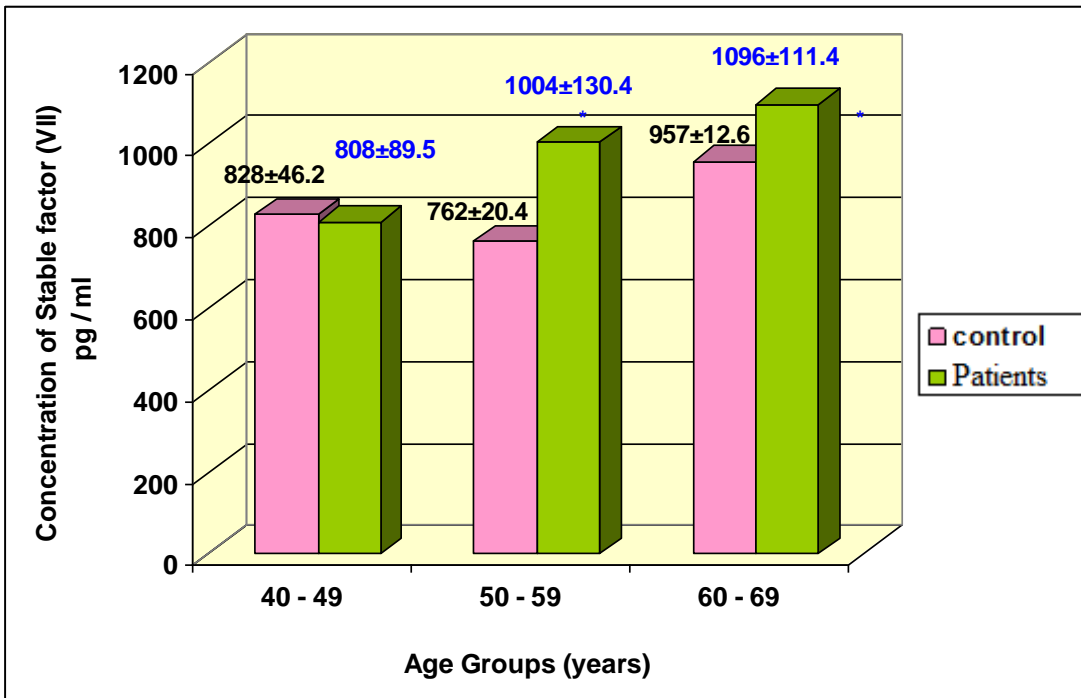
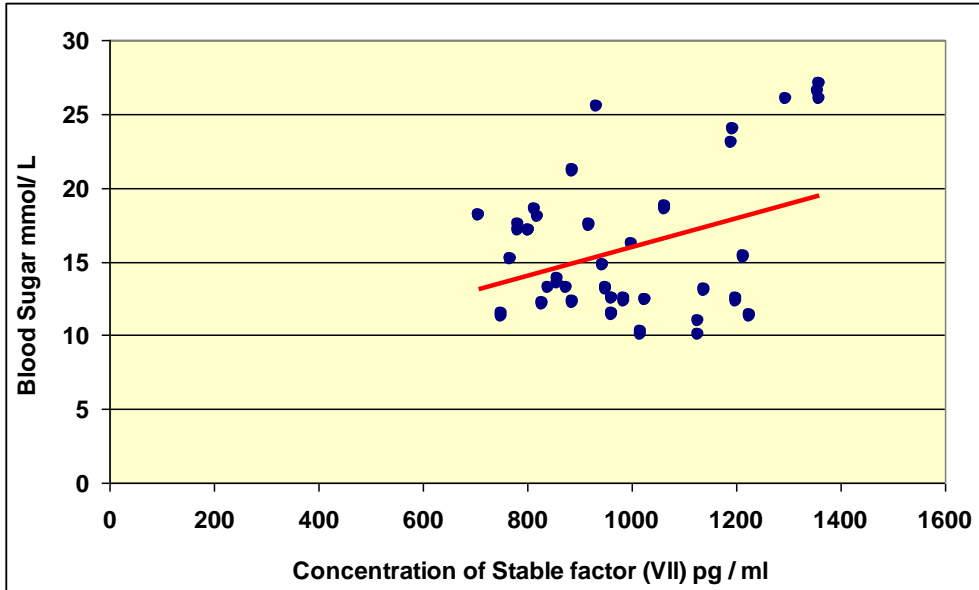


Figure (7) The results illustrate stable factor (FVIIpg / ml) for females of diabetic patients.

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably different ($p<0.05$)

Correlation Coefficients of FVII Concentration with Bblood Sugar in Diabetic Patients.

The correlation data which are presented below (Figure 8) indicated high positive correlation ($r = 0.36$) of FVII level and blood sugar in diabetic patient .



$r = 0.36$

Figure (8) Correlation coefficients between FVII level and blood sugar in diabetic patients .

The Concentration of Antihemophilic Factor (FVIII)

The values obtained and depicted below(figure 9) showed a remarkable increase ($p < 0.05$) for FVIII of the first group in males of diabetic patients in of a compression with healthy control and recorded non – significant drop ($p > 0.05$) in the (second group , third group) of male diabetic patients in a comparison with controls .

It was found that are non – significant difference ($p > 0.05$) among age group (second group , third group) and there is a significant difference ($p < 0.05$) (3.3) in the first group.

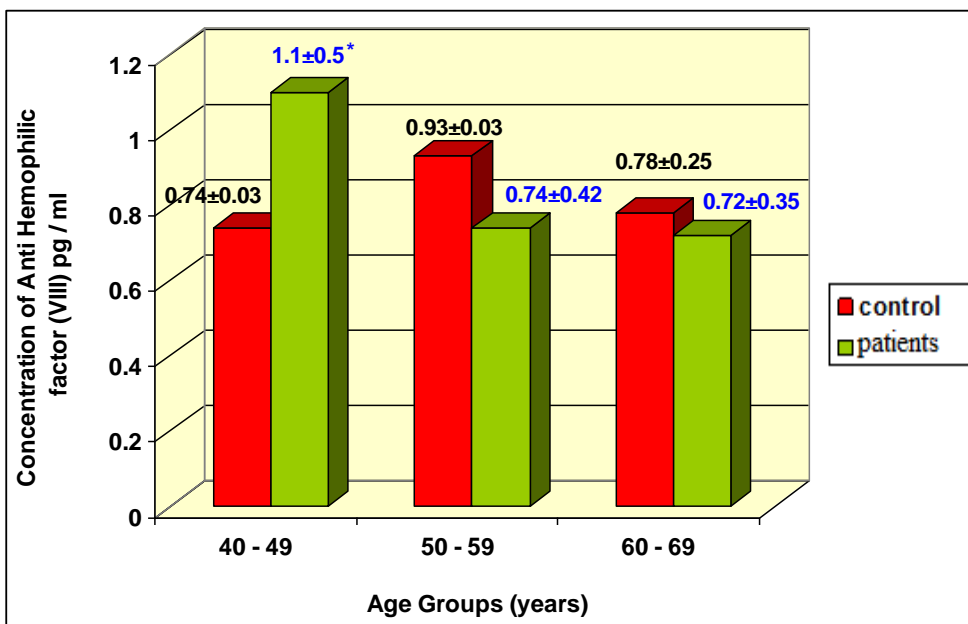


Figure (9) The mean of antihemopphlic factor (FVIIIpg / ml) in male of diabetic patients.

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably diferent ($p < 0.05$)

The Levels of Antihemophilic Factor(FVIII)

The data obtained and elaborated from the present study(figure 10) indicated a marked decrease ($p < 0.05$) of two age group (second group , third group) in female of diabetic patients in a comparison with control group and non – significant decrease ($p > 0.05$) in the first group of diabetic patient in a comparison with those control .

There are non – significant difference ($p > 0.05$) among group of age (first group , third group) and there is a significant (0.15) in the second group .

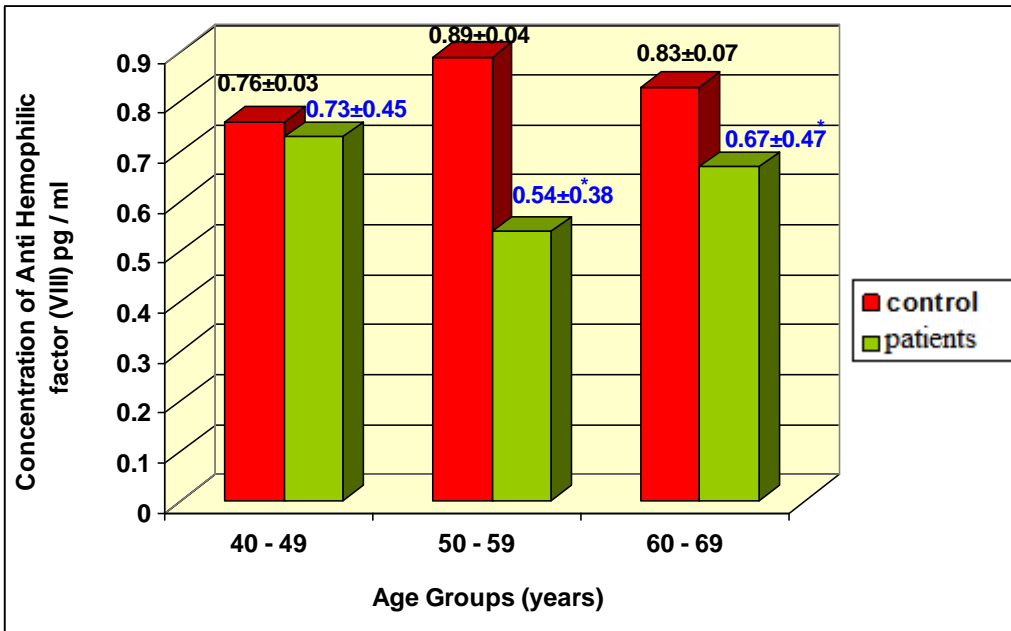
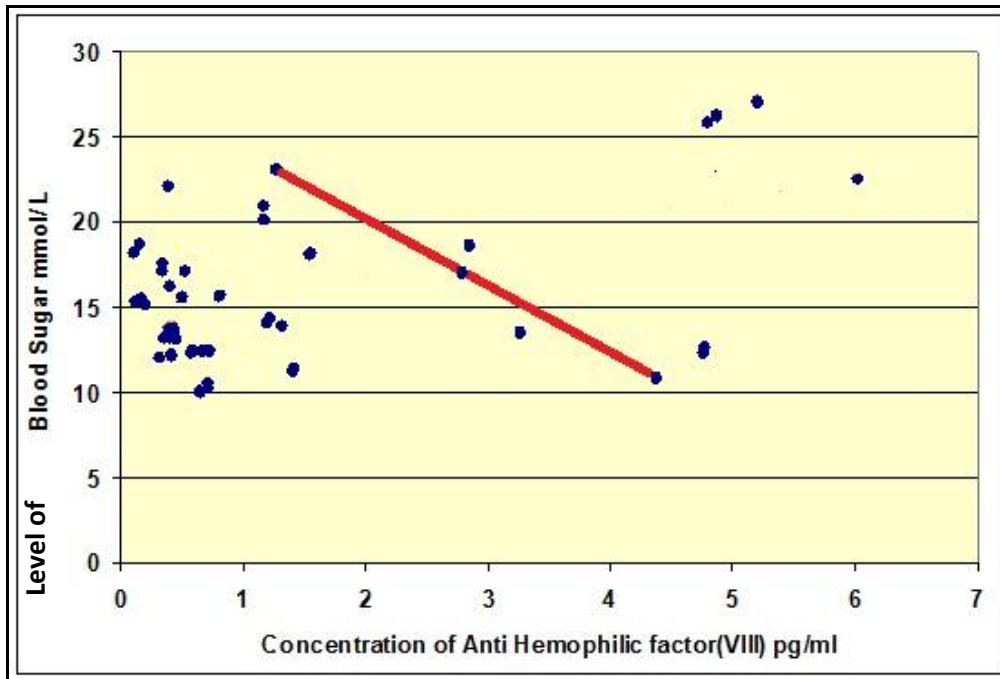


Figure (10) The result of antihemophilic factor FVIII(pg / ml) of females of diabetic patients.

- Results indicated means ± standard deviation .
- Results that have (*) are remarkably different ($p < 0.05$)

Correlation Coefficients of FVIII Level with Blood Sugar of Diabetic Patients .

Result showed negative correlation coefficient ($r = - 0.57$) of antihemophilic factor level with blood sugar in diabetic patient (Figure 11).



$r = 0.57$

Figure (11) Correlation coefficients between FVIII level and blood sugar in diabetic patients .

Discussion

Fibrinogen

Data which are obtained from the present study revealed a marked drop ($p < 0.05$) in the fibrinogen concentration in both tested group (males and females) and these results explained a low correlation ($r= 0.06$) with blood sugar .Previously , it was found that fibrinogen level confirms a minimum correlation when compared with fasting glucose level and low density lipoprotein .In addition , fibrinogen (F1) can be elevated in subject suffering from NIDDM in early stage of influence⁸. Previous study of Meade *et al* . , (1993) indicated that there is marked correlation (positively) between fibrinogen (F1) and stable factor (FVII) in subjects affected with cardiac disease⁹. Also fibrinogen is the most clotting factor that has been implicated to incidence of caroted atherosclerosis events¹⁰.

With age , level of fibrinogen progress with advance age, obesity , smoking , leukocytes , menopause , contra- captive drugs¹¹. Previous report of Kohler, (2002) found many cluster factors that become abnormal in diabetic patients including elevation of fibrinogen concentration, elevated blood pressure , and dyslipemia. Also confirms that a high level of fibrinogen could be consider a triggering point of incidence of thrombosis¹² . Aging and administration of contraceptive drug exerts apposite effects on fibrinogen concentration, it was found that aging elevate fibrinogen while contraception therapy depresses it^{13,14} . Our data were inconsistent with study of Barazzoni *et al* .,(2003) his results confirmed that with age there is an elevation of fibrinogen concentration particularly in patients affected with type 2 – diabetes and concluded that excess fibrinogen is implicated in incidence of cardiovascular events of those patients ¹⁵. A previous research was established by Venkataramana, (2013) hypothesized that diabetic patients were suffering from chronic inflammatory reactions and attributed these abnormalities to higher level of inflammatory marker such as white blood cell , fibrinogen over load or drop of albumin¹⁶ . However, it should be stressed that the factors which are implicated in elevation of fibrinogen still unknown¹⁷.

Stable factor

Results of the present study revealed that factor VII levels were remarkably elevated ($p < 0.05$) in groups of diabetic patients and these results have low correlation ($r = 0.36$) with blood sugar .

Excessive levels of FVII are accompanied with increased incidence of many cardiovascular risk⁹. Resent study of Bustamante *et al.*, (2016) involves when drop of factor VII lead to activate protease (FSAP) antigen that increase the susceptibility of vascular to return to normal (recanalization) that occurs after administration of plasminogen activator therapy¹⁸. Both factor VII and tissue factor pathway inhibitor represented regulating components of blood clotting, in specific, in extrinsic pathway, since , secretion of tissue factor in to blood circulation binds to FVII causing pathway¹⁹. Our results appear consistent with previous study that achieved by Alzahrani and Ajjan , (2010) which confirm increase concentration of FVII in type 2 diabetic patients and metabolic syndrome. Also, FVII appears a hallmark factor in incidence of cardio vascular disease of patients affected with type 2 diabetes²⁰.

A lot of studies indicated that activity and concentration of stable factor are affected by polymorphism in gene that encoded factor VII, in addition, environmental fluctuations such as foods, body wasting, physical activities^{21,22}. Moreover, in other previous study of Kohler, (2002) indicated up regulation of FVII concentration in patients suffering from non – insulin dependent diabetes mellitus and found that there is some association between insulin resistance and high concentration of FVII¹².

It should be known that diabetes disease seems to be a procoagulant condition because increase concentration of TF or factor III and disappear of TFPI – 1. These changes are associated with elevated level of factor VII and vWF with concurrent decrease in fibrinolytic activity resulted from increase of tPAI²³.

The formation of TF – VII complex is a necessary action in the susceptibility to coagulation. Together, vWF and TF – VII complex are recognized to become increase in type 2 diabetic patients²⁴. In study of Altinobas *et al.*, (1999) who concluded that the activity and concentration of FVII are elevated simultaneously with vWF in type 2 diabetic patients²⁵. However, it is well documented that up regulation of factor VII in plasma is developed in combination with dyslipidemia and clearly evidence showed that vitamin k – dependent clotting factors are associated with increase triglycerides²⁶.

The complete know indicates that factor III (tissue factor) is largely expressed in tunica adventitia of blood vessels and can be to initiate blood clotting via extrinsic pathway . In addition , express on there are many amount of TF in circulation and other organ²⁷, There for , diabetic patient undergo from catabolic and damage to many of organ which can be to liberated considerable amount of T.F .

Antihemophilic Factor

Data which were explained in figure 9 and figure 10 recorded a marked decrease in most age groups of both sexes affected with diabetes type 2 and these data were correlated with blood sugar.

Our results were conflicted with study of Zipser *et al.*, (2005) who showed that factor VII ,VIII , and vWF are elevated in diabetic patients²⁸. Also it was found that activity of FVIII activity appear to be maximum in patients affected with diabetes type 2²⁷. Antihemophilic activity was found to be greater in both patients who are affected with type 1 and type 2 diabetes and there are no different in both types of disease²⁹. Barillari *et al.*, (2009) showed that accumulation of glucose derivatives in blood and tissues of diabetic patients can lead to produce oxidative stress (or free radicals). These free radicals resulted in damage to many cellular compartment and explained that type 2 – diabetes is associated with increase activities and concentrations of FVIII , FIX , FXII³⁰.

The coagulability was found to increase while fibrinolytic mechanism appear to down regulate in diabetic patients due to of higher of rate clot formation that are more resistance to destroyed by plasmin and increase level of plasminogen activator inhibitor type - 1³¹. Study of Passaro *et al.*, (2008) indicated that the activities of FVII and FVIII appear to become lower in apposite of fibrinogen level that remain without alteration³². This more coaguable Condition is produced as a result from imbalance among many clotting factors in blood and endothelial cell surfaces of blood vessels³³. Concerning fibrinolytic mechanism , the previous reports are conflicted , some of those suggest that fibrinolysis is increased and other proposed to be down regulate or remain normal. Lowering fibrinolysis mechanism can be returned to depressed production of tissue plasminogen activator (t – PA) that enhance stimulation plasminogen³⁴. There is clearly evidence confirm that subjects with diabetes can develop susceptibility to thrombosis and attribute these conditions because of elevated many procoagulant concentration associated with down regulation of fibrinolytic ability³⁵. Clearly ,

glucose overload and excess insulin have many and specific consequences on regulation of most hemostatis in subjects without diabetes. In chronic condition of diabetes, there are many effect of glucose overload on amount of clotting factor , in the same manner, hyperinsulinemia can to suppress fibrinolytic mechanism away from level of blood glucose³⁶⁻³⁷.

We can conclude that decrease of FVIII either can be return to damage of hepatocytes resulted from hyperglycemia which lead to product ion of free radicals or there is negative feedback mechanism involve higher activation to extrinsic pathway including TF-VII and inhibition of intrinsic pathway of blood coagulation .

Conclusion

From the present data, it is appear clearly to concluded that increase concentration of F VIII gives clear evidence to the increase of activities of extrinsic pathway of clotting mechanism in diabetic patients of type-2 diabetes. And decrease concentration of fibrinogen can confer an indicator about catabolic activities of proteins because of absence glucose utilization and damage of hepatic tissues. Also it was found that decrease FVIII concentration refer, that intrinsic pathway can be inhibited as a result of increase extrinsic pathway , factor VIII increase associated with increase liberation of tissue factor (III) can be lead to increased incidence of thrombotic event as a result of degradation and catabolic effects of diabetes disease on different part of the body.

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