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Fibrinolytic Alteration among Sudanese Patients with Hypertensive Type 2 Diabetic Mellitus patients

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Abstract:

Background: *Diabetes mellitus and hypertension are complexes diseases result from inter reaction of different of predisposing factors.*

Aim*: to assess levels of Fibrinogen, D-Dimer and Fibrin Degradation Products in Sudanese with Hypertensive type 2 Diabetic mellitus patients.*

Methods: *Case control study, a total of 400 subjects classified to 300 Sudanese with hypertensive type 2 diabetic mellitus as patients and 100 healthy individual as control group, age range between 30 and 90 years. Fibrinogen was assessed by coagulometer, D-Dimer and Fibrin Degradation Products measured by ELISA.*

Results: *Significant increase between Fibrinogen, D-dimer and fibrin degradation Products levels according to study compared to control groups (p-value = 0.000). There were Significant decrease between Fibrinogen, D-dimer and fibrin degradation Products levels according to neuropathy in population study (p-value =0.012, 0.008 and 0.0.005) respectively. Significant increase in Fibrinogen and D-dimer of nephropathy in case study (p-value=0.021). There were significant decrease Fibrinogen and D-dimer in retinopathy in case*

group (p-value=0.049 and 0.004) respectively. Fibrinogen, D-dimer were significantly increase between age groups (p-value =0.00 and 0.010) respectively.

Conclusions: *There are most increase in parameters of fibrinogen, D-dimer and FDPs of patients and others demographic data and thus recommended used to monitor a complications.*

Key words: Type 2 diabetic hypertensive patients, Fibrinogen, D-dimer Fibrin Degradation Products**.**

INTRODUCTION:-

Diabetes mellitus (DM) is metabolic disorders characterized by chronic hyperglycemia due to disturbance of carbohydrates, fats and protein metabolism associated with absolute or relative deficiencies in insulin or insulin action or both [(1)].Over 170 million people worldwide and about 1.9-7.0% of African population were affected [(2)].

Diabetes has three main types, type 1 diabetes mellitus, which is called (Insulin Dependent Diabetes Mellitus).Type 2 diabetes mellitus, which is called (Non Insulin Dependent Diabetes Mellitus) and gestational diabetes which is classified as type two diabetes mellitus [(3)].The long term affects and complications of diabetes include progressive development of retinopathy, nephropathy and neuropathy with micro vascular and macro vascular diseases. Macro vascular disorder such as atherosclerosis are recognized as major causes of mortality in the diabetic population ,and are implicated in circulatory disturbances that are seen in diabetes. The circulatory disturbance in platelets count, activity, coagulopathy, fibrinolytic aberration, haemorrlogical factors and change in endothelial metabolism. Many studies have shown that DM cause hypercoagulable state [(4)]. The prevalence of DM in the Sudan, as in many other low-income countries, is increasing to

epidemic proportions, leading to the emergence of a public health problem of major socio-economic impact. Type 2 DM in Sudan is common among the adult population of northern Sudan and prevalence of type 1 DM was estimated at 0.1 % among school children 7-14 years of age [(5)]. Hypertension is sustained high blood pressure (≥140/90mmHg) [(6)].When hypertension coexists with overt diabetes, which is commonly does, the risk for cardiovascular disease, including nephropathy, is raised two fold. Improved control of blood pressure in diabetic patients has been shown to be effective in reducing the risk of cardiovascular complications [(7).] Fibrinogen is a glycoprotein circulates in plasma at a concentration of approximately 9 micrometer. Fibrinogen molecules are elongated, 45-nanometer long structures with 2 outer D domains that are connected by a coiled-coil segment to a central E-domain. They consist of 2 symmetric half molecules, each containing a set of 3 different polypeptide chains termed A, B and G. The 3 chains are encoded by 3 separate genes, fibrinogen alpha, fibrinogen beta, and fibrinogen gamma, clustered in a region of approximately 50 kilo base on chromosome 4q31.3, fibrinogen beta contains 8 exon [(8)].Fibrinogen production in the liver is regulated by cytokines, mainly by interleukin-6, and is greatly enhanced by the acute phase response to inflammatory processes hence; fibrinogen elevation might simply reflect the low-grade inflammation associated with vascular disease. On the other hand, increased fibrinogen levels (due to inflammation or other mechanisms) may still participate in the pathogenesis of vascular lesions, i.e. be a true modifier of the atherosclerotic disease and contribute to its progression. Moreover, fibrinogen and fibrin degradation products might in turn enhance the inflammatory aspect of vascular lesions by regulating cytokine production and leukocyte-endothelial interactions [(9)]. D-dimer is the primary degradation product of cross-linked fibrin and therefore serves as a direct marker of

ongoing coagulation with fibrinolysis. D-dimer, a fragment cleaved from cross linked fibrin as part of fibrin clot degradation, reflects thrombin production and fibrinolysis. A meta-analysis has suggested an independent 1.7-fold increased risk of coronary heart disease (CHD) for the highest versus lowest tertile of D-dimer[10]. The specificity of the relation of these hemostatic factors with cardiovascular disease nevertheless may be questioned, because they often are related positively to risk of other chronic conditions, such as cancer or total mortality or show a moderate degree of correlation with markers of inflammation [11]. Fibrin degradation product is two basic steps that lead to fibrin degradation, the initial step is the activation of plasminogen to plasmin by several important protein/enzymes as tissue Plasminogen Activator (t-PA) and urokinase Plasminogen Activator (u-PA). In the second and final step, the active plasmin that is able to complex, with fibrin, specifically degrades the complexes fibrin into soluble fibrin degradation products [11].Elevated plasma fibrinogen concentrations have been associated with increased plasma viscosity and platelet aggregability and, thus, may contribute to vascular disease [8]. The risk of venous thromboembolism appears to be elevated in both type 1 and type 2 diabetic patients [12]. Increased thrombin generation and higher concentration of procoagulant cell-derived circulating micro particles in patients with type 2 diabetes suggest that hyper coagulability may play an important pathogenic role in the increased frequency of venous thromboembolism [11]. Diabetic foot gangrene results from peripheral arterial disease with or without foot sepsis. It is associated with excess mortality, although venous thrombosis has been reported in association with gangrene [13]. Evidence also links haemostatic variables to the future risk of myocardial infarction and stroke. So far, a variety of markers of a procoagulatory tendency e.g. elevated fibrinogen, coagulation factor VII,von Willebrand factor,

platelet hyper aggregation, and plasma levels of D-dimer [14]. This study to assessed fibrinogen, D-Dimer and fibrin degradation products level in Sudanese with type 2 diabetic hypertensive patients**.**

MATERIALS AND METHODS:

Subjects:

This was a descriptive study conducted on Sudanese with type 2 diabetic hypertensive patients and were done in Khartoum teaching hospital in Khartoum state during the time period from January 2014 to October 2016**.** The Demographic data (Number, age, gender, duration of disease, type of treatment, dosage of therapy and presence or absence of other diseases) were collected through questionnaire. The study was included (300) of Sudanese type 2 diabetic hypertensive patients and (100) non diabetic non hypertensive individual as controls. Diabetic patients without hypertension or with type 1 Diabetes Mellitus were e excluded. The objectives of the study were explained at the beginning to all individual under study. Written consent was obtained from each participant in the study. An interview with subjects was conducted to obtain the clinical data, questionnaire including informative data (Number, age, gender, duration of disease, type of treatment, and presence or absence of other diseases).

The data of this study will be analyzed by SPSS computer program version 16.0 software to calculate means, standard deviation and probability value (*P*.value) of parameters of fibrinogen level, D-dimer and fibrin degradation product for case and control and numbers. Independent T.test will be used to analysed data and then results. Age, duration of disease, and dosage of therapy will be classified into three groups by One Way ANOVA. Qui square I will be used to place frequencies of each alleles to each group.

Biochemical measurements:

Blood was collected in Sodium citrate then plasma was separated and stored at -20^{o}C.

Fibrinogen Assay:-

The plasma fibrinogen level was measured by von Clauss method; the functional assays based upon the time of fibrin clot formation and was used automated coagulation analyzer (model Kselemed Coagulometer K-3002 Auto) (Clauss, 1957).Samples were collected, into the plastic or siliconzed glass tube, 9 parts of freshly venous blood was drawn and 1 part of trisodium citrate 3.8%. The plasma was separated after centrifugation of the mixture for 10minutes 'at 1500 rpm. Stability: 4 hours at 15-25°C or 24 hours at -20°C. Do not use EDTA or heparin. Reagents was Bovine thrombin: Buffered lyophilized bovine thrombin, preservatives Plasma Calibration "Cal-Fib": Lyophilized human plasma, stabilizers and preservatives. ControlPlasma "Pat-Fib": Lyophilized human plasma, stabilizers and preservatives.Material required were test tubes for analysis, coagulometer cuvette, sterirre, auomicropipettes 0.1, 1 ml and gloves, tipsand automated coagulation analyzer. Procedure for Fibrinogen determination was performed using citrated plasma by means of a standard kit made especially for coagulometer. The standard kit for the quantitative determination of fibrinogen was based on the addition of a relatively large amount of thrombin to diluted citrated plasma, ensuring that the clotting time depended on only the fibrinogen contained in the sample. The assay procedure consisted of placing 200µl of diluted plasma (diluted 1:10 by the combination of 100µl of plasma +900 µlof buffer) in a test tube preheated to 37 C^{0} incubating for an additional 2 min at 37 C^{0}, and then adding 100µl of the fibrinogen reagent. Upon the addition of fibrinogen reagent, a stopwatch was started, and the clotting time was measured. The time (seconds) until clot

formation was read converted into mg/dl by calibration graph. Expected value was each laboratory must provide the definition of reference values for the population under investigation. Bibliographical lists which reference interval: Fibrinogen 200 - 400 mg/dl (2 - 4 g/L).

D-dimer and Fibrin degradation Products assay:-

The D-dimer and FDPs assay depends on the binding of a monoclonal antibody to a particular epitope on the D-dimer and FDPs fragment, the area to which the antibody binds is known. The binding of the antibody is then measured quantitatively by enzyme-linked immunosorbent assays (model Automated ELISA liquid handing wit).D-dimer reference range (200-400 µg/ml.) and FDPs reference range (100-200µg/ml).

Principle of the Test were the Simple Step ELISA employs an affinity tag labeled capture antibody and a reporter conjugated detector antibody which immune capture the sample analyte in solution. This entire complex (capture antibody/analyte/detector antibody) is in turn immobilized via immune affinity of an anti-tag antibody coating the well. To perform the assay, samples or standards are added to the wells, followed by the antibody mix. After incubation, the wells are washed to remove unbound material. TMB substrate is added and during incubation is catalyzed by HRP, generating blue coloration. This reaction is then stopped by addition of Stop Solution completing any color change from blue to yellow. Signal is generated proportionally to the amount of bound analyte and the intensity is measured at 450 nm. Optionally, instead of the endpoint reading, development of TMB can be recorded kinetically at 600 nm.

Patients' characteristics

A total of 400 participants were included; the number of female patients was significantly higher than male patients. However,

female sex predominated in tow groups. The mean age was 55 years. Age of patients was significantly higher compared with the other control groups. All risk factors for patients were significantly when compared with controls.

RESULTS:-

Table (1) shows increase in proteins parameters of study population compared to control group.

There are some different of proteins parameters of gender in table (2). Table (3) shows proportional increase between proteins and duration of time. Increase proteins parameters in study group of neuropathic complication shows in table (4). In nephropathy complication only fibrinogen higher, in table (5). Table (6) shows high level in D-dimer of retinopathy in case group. Proportional high proteins level with age group shows in table (7). Table (8) and (9) shows different proteins parameters according to the others disease and hypertension stage in case group.

Table 1:
Comparison between Fibrinogen, D dimer and FDPs levels according to study and control group.

Parameters	Case Mean±SD	Control Mean±SD	*p*-value
Fibrinogen/ (mg/dl)	545±155	323±155	0.000
Ddimer/ (ng/m)l	672±400	330±71.1	0.000
FDPs/ (ng/ml)	293±110	159±28.4	0.000

Table 2:
Comparison between Fibrinogen, D dimer and FDPs levels according to gender in case group.

Parameters	Male Mean±SD	Female Mean±SD	*p*-value
Fibrinogen/ (mg/dl)	565±165	236±150	0.131
Ddimer/ (ng/m)l	729±463	646±367	0.096
FDPs/ (ng/ml)	302±121	289±105	0.340

Table 3:
Comparison between Fibrinogen, D dimer and FDPs levels according to duration time of diseases in patient s group.

Parameters	Less than 5years Mean±SD	More than 5 years Mean±SD	*p*-value
Fibrinogen/ (mg/dl)	487±113	610±171	0.006
Ddimer/ (ng/m)l	518±197	849±491	0.003
FDPs/ (ng/ml)	264±94.7	326±117	0.009

Table 4:
Comparison between Fibrinogen, D dimer and FDPs levels according to neuropathy of study group.

Parameters	Present neuro Mean±SD	Abcsent neuro Mean±SD	*p*-value
Fibrinogen/ (mg/dl)	615±178	635±149	0.012
Ddimer/ (ng/m)l	884±506	642±376	0.008
FDPs/ (ng/ml)	356±145	356±145	0.005

Table 5:
Comparison between Fibrinogen, D dimer and FDPs levels according to nephropathy of study group.

Parameters	Present nephropathy Mean±SD	Absent nephropathy Mean±SD	*p*-value
Fibrinogen/ (mg/dl)	662±165	441±154	0.021
D-dimer/ (ng/m)l	102±659	661±386	0.138
FDPs/ (ng/ml)	346±111	291±110	0.144

Table 6:
Comparison between Fibrinogen, D dimer and FDPs levels according to retinopathy of study group.

Parameters	Present Mean±SD	Abcsent Mean±SD	*p*-value
Fibrinogen/ (mg/dl)	563±172	531±140	0.094
D-dimer/ (ng/m)l	765±478	613±335	0.004
FDPs/ (ng/ml)	304±121	285±101	0.151

Table 7:
Comparison between Fibrinogen, D dimer and FDPs levels according to age groups.

Parameters	38-55 years Mean±SD	56-72years Mean±SD	73-90 years Mean±SD	*P* value
Fibrinogen/ (Mg/dl)	513±139	536±161	545±133	0.000
D-dimer/ (Ng/m)l	594±289	725±460	484±461	0.010
FDPs/ (Ng/ml)	278±100	301±117	349±110	0.075

Table 8:
Comparison between Fibrinogen, D dimer and FDPs levels according to others diseases

Parameters	Atheroscorlo **Mean±StdDeviation**	Thyroid **Mean±StdDeviation**	Absent **Mean±StdDeviation**	***P*** **value**
Fibrinogen/ (Mg/dl)	541±236	478±70.0	564±155	0.685
D-dimer/ (Ng/m)l	925±554	461±70.3	672±400	0.261
FDPs/ (Ng/ml)	369±151	257±27.9	292±110	0.316

Table 9:
Comparison between Fibrinogen, D dimer and FDPs levels according to hypertension stag

Parameters	**Essential HTN Mean±Std Deviation**	**Secondary HTN Mean±Std Deviation**	***P*** **value**
Fibrinogen/ (Mg/dl)	545±158	514±120	0.687
D-dimer/ (Ng/m)l	675±402	486±171	0.350
FDPs/ (Ng/ml)	293±110	269±102	0.663

DISCUSSION:-

Present study caluss method to evaluate fibrinogen level and enzyme immune surrbdend assay to measured D- dimer and fibrin degradation products in the occurrence of type 2 diabetic hypertensive Sudanese patients referred to Khartoum Teaching hospital in Khartoum State were compared with controls.

As expected, the classic risk factors for type 2diabetic hypertensive were significantly more common in the study group. Similar to other studied populations, they were significant increase between Fibrinogen, D-dimer and fibrin

degradation Products levels according to study and control group (*P.* value <0.05).This is in agreement with the study by Khan *et al.* [15], who did found that significant increased of fibrinogen between patients and control individuals. Van Wersch, *et a l*[16] Palanisamy *et al* [17]and Leonardo *etal* [18] who were agreement with related study who did found that significant of D-dimer between study population and control individuals.

Insignificant different between Fibrinogen, D-dimer and fibrin degradation Products levels according to male and female (*P* value >0.05). This is in agreement with the study Erem C *et al.*[19], who did found insignificant difference of gender variable.

They were significant increase between Fibrinogen, D-dimer and fibrin degradation Products levels according to onset of diseases (*P* value <0.05).This is in agreement with the study by Abdulrahaman Y and Dallatu M.K. [20],who were found that significant Fibrinogen, D-dimer and fibrin degradation Products level in duration time of diseases.

Significant decrease between Fibrinogen, D-dimer and fibrin degradation Products levels according to neuropathy. (*P.* value <0.05). This agreement with related study done by Bolman *etal* [21] who were found significant in neuropathy in fibrinogen and D-dimer of study group (P value<0.005).

Significant increase in Fibrinogen and D-dimer of nephropathy in case study *(P.*value<0.05).

This agreement with related study done by Bolman *et al* [21] who were found significant in nephropathy of fibrinogen and D-dimer in study group (P value<0.005).

Fibrin degradation Products levels insignificant in study population*(P.* value>0.05).

There were significant decrease Fibrinogen and D-dimer in retinopathy in case group (*P.*value<0.05).This is agreement with the related study by Fujisawa*et al.* [22], who did found that

significant in Japanese diabetic type 2 hypertensive populations. Insignificant of Fibrin degradation Products levels of retinopathy *(P.* value >0.05).

Fibrinogen, D-dimer were significant increase between age groups *(P.value*<0.05). This is in agreement with the study done by Leonardo *etal.* [18], who did found that significant between age groups in case study. Insignificant in Fibrin degradation Products levels of age groups (*P* value <0.05).

They were insignificant differences between Fibrinogen, D-dimer and fibrin degradation Products levels according to essential and secondary of hypertension (*P* value >0.05).

Insignificant different between Fibrinogen, D-dimer and fibrin degradation Products levels according to others diseases were found with diabetic type 2hypertesive patients (*P* value >0.05).

CONCLUSION:

Significant increase between Fibrinogen, D-dimer and fibrin degradation Products levels according to study and control group (*p*-value = 0.00). Insignificant different between Fibrinogen, D-dimer and fibrin degradation Products levels according to male and female (*P*.value=0.13, 0.12 and 0.31), respectively. Significant decrease between Fibrinogen, D-dimer and fibrin degradation Products levels according to neuropathy in case study (*p*-value 0.01). Significant increase in Fibrinogen and D-dimer of nephropathy in case study (*P*.value=0.02 and 0.01), and FDPs insignificant (p-value=0.14). There were significant decrease of Fibrinogen and D-dimer in retinopathy in case group (*p*-value=0.03 and 0.00). Insignificant of Fibrin degradation Products levels of retinopathy (*P.* value =0.17). Fibrinogen, D-dimer were significant increase between age groups (*p*-value =0.00 and 0.01), FDPs were insignificant different (*p*-value=0.07).They were insignificant differences

between Fibrinogen, D-dimer and fibrin degradation Products levels according to essential and secondary of hypertension (*P*.value=0.06, 0.35 and 0.11) respectively. Insignificant different between Fibrinogen, D-dimer and fibrin degradation Products levels according to atheroscorlosis and thyroid and others diseases were found with diabetic type 2hypertesive patients (*P* .value =0.68, 0.26 and 0.31) respectively.

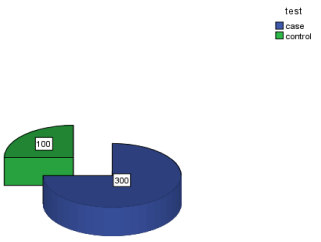

Figure (1)

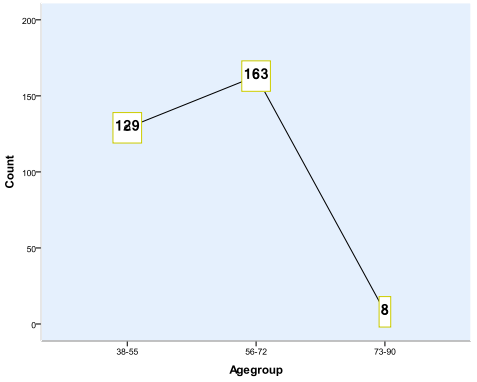

Figure (2)

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