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Haemostatic Abnormalities and Renal Damage in Sudanese Hypertensive Patients

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DEDICATION

To my mother soul **.....**

To Sudanese Hypertensive patients

To all cardiac and renal care centers in Sudan

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ABSTRACT

This study was done during the period of October 2003 to February 2007 in Khartoum State Teaching Hospitals (Omdurman, Khartoum, and Soba) to determine the thrombin generation, haemostatic and renal damage markers among Sudanese hypertensive patients.

Two hundred patients (200) and fifty normal controls (50) were studied. Patients were those who fulfilled the clinical diagnosis of hypertension of both sex, on or off treatment. The controls were normal, non-hypertensive individuals of either sex. Both patients and control were above 40 years of age. Patients (male and female) with previous history of venous or arterial thrombosis and diabetes mellitus, who received antiplatelet or anticoagulant drugs in the preceding 15 days, were excluded from the study. A structured questionnaire was prepared which included the general information and laboratory investigations. Blood, plasma, serum and urine samples were collected from all patients and controls for use in laboratory investigations.

The results showed non significant difference between the mean level of patients and controls in the following parameters: prothrombin time (PT) (p=0.626), activated partial thromboplastin time (APTT) (p=0.272), thrombin time(TT) (p=0.863), fibrinogen level(p=0.455), platelets count (p=0.866), protein S level (p=0.123), protein C level (p=0.653), Prothrombin fragment 1+2 (F1+2) (p=0.925), thrombin antithrombin complex (TAT) (p=0.867), serum urea level (p=0.326) and serum creatinine level (p=0.573). The presence of microalbuminuria was correlated with the age of patients (p=0.000) and the duration (p=0.030) of hypertension. The levels of fibrinogen among hypertensive patients in the present study were strongly related to the development of microalbuminuria (p=0.0000). The results demonstrated a significant

difference between patients and controls in the mean level of von Willebrand factor antigen (P=0.000), bleeding time (p=0.042) and plasminogen activator inhibitor-1 (p=0.000). There was no correlation between the age of the patients and serum urea level (p=0.623). However, serum creatinine level was related to the age of the patients (p=0.041). Fibrinogen level (p=0.011), bleeding time (p=0.021), Plasminogen activator inhibitor-1 level (p=0.0001) and Prothrombin fragment 1+2 level (p= 0.012) were significantly correlated to severity of hypertension(stage II), while thrombin antithrombin complex level did not show significant (p=0.124) correlation to the severity of the disease. Both circulating markers of thrombin generation(Prothrombin fragment 1+2 and thrombin antithrombin complex) were significantly (p=0.000) correlated to the duration of hypertension.

The results obtained indicated that measurement of prothrombin time(PT), activated partial thromboplastin time(APTT), Or thrombin time(TT) were unnecessary when evaluating a hypertensive patient in whom there was no clinical evidence of a haemostatic abnormality. An approach would eliminate the need for most of the coagulation tests done in these patients. The results of this study raised the possibility that von Willebrand factor, fibrinogen level and prothrombin fragment 1+2 could be of use in identifying a "high-risk" group of hypertensive patients who were likely to develop thrombotic events. The elevated of PAI-1 would further enhance this prothrombotic tendency. Longitudinal studies would be more informative in this aspect.

The positive correlation between the presence of microalbuminuria and the duration of the disease indicated progressive renal disease with longstanding hypertension. This was inspite of the absence of a significant difference in serum urea and serum creatinine

levels between patients and controls. Microalbuminuria was found to be directly correlated with fibrinogen and von willebrand factor antigen levels, and this was an indication of a relationship between renal damage and the haemostatic disturbance in hypertension.

ملخص الدراسة

أجريت هذه الدراسة خلال الفترة من أكتوبر 2003 إلي فبراير 2007 في مستشفيات ولاية الخرطوم التعليمية (أم درمان , الخرطوم وسوبا الجامعي) بهدف تقدير علامات الثر ومبين , الأرقاء وعلامات الضررِ الكلويِ بين مرضى ارتفاع ضغط الدمِّ السودانيينِ.

شملت الدراسة مائتي (200) مريض بارتفاع ضغط الدم وعدد خمسون(50) من المعادلين الطبيعيين من الجنسين. المرضى أولئك الذين استوفوا التشخيص الطبي من كلا الجنسين بارتفاع ضغط الدم ، تحت أو عدم العلاج آما المرضي الذين لهم تاريخ سابق بأمراض للتخثر الوريدي أو الشرياني , مرضى السكري وأولئك الذين استعملوا الأدوية المضادة للصفائح الدموية ومضادات تجلط الدم في الخمسة عشر يوما السابقة فقد استثنوا من هذه الدراسة. كلا المرضى و المعادلين الطبيعيين فوق سن الأربعين عاما.تم جمع البيانات الخاصة بالمرضى والمعادلين الطبيعيين من خلال استبيان تم إعداده يشتمل علي معلومات عامة وعلي التحاليل المعملية .جمعت عينات البلازما , المصل , الدم والبول من كل المرضى والمعادلين الطبيعيين لإجراء الفحوصات المعملية.

أظهرت النتائج عدم وجود فرق كبير بين المرضي والمعادلين الطبيعيين في متوسط المعايير التالية :زمن البروثرومبين (p=0.626) ، زمن الثرومبين(p=0.272) ,، زمن الثرومبوبلاستين الجزئي (p=0.863) , عدد الصفائح الدموية ، (p=0.455) مستوى الفيبرينوجن (p=0.866) , مستوى البروتين C (p=0.653) , مستوى البروتين S (p=0.123) , جزء البروثرومبين 1+2 ((p=0.925 مركب الثرومبين انتيثرومبين ومستوى الكرياتينين (p=0.326) مستوى اليوريا بالمصل , (p=0.867) متلازم مع عمر microalbuminuria كما أن وجود بالمصل (p=0.573) . والمدة الزمنية لارتفاع ضغط الدم (p=0.000) المريض (p=0.030) . بينما مستويات الفيبرينوجن بين مرضى ارتفاع ضغط الدم في هذه الدراسة كانت ذات علاقة وثيقة بوجود microalbuminuria (p=0.0000) .

أظهرت النتائج وجود فرق كبير بين المرضى و المعادلين الطبيعيين في

زمن , (P=0.000) متوسط مستوى عامل الفون ويلبراند انتيجين plasminogen activator inhibitor-1 (p=0.000) و ، (p=0.042) النزف لا . (p=0.623) يوجد ارتباط بين سن المرضى و مستوى اليوريا بالمصل لكن (p=0.041) مستوى الكرياتينين بالمصل يرتبط بعمر المرضى . (p=0.021) زمن النزف ، (p=0.011) مستوى الفيبرينوجن , plasminogen activator inhibitor-1 (p=0.0001) 2+1 و جزء البروثرومبين مرتبطة بشدة ارتفاع ضغط الدم (المرحلة الثانية) بينما مركب (p= 0.012) بشدة المرض. كل (p=0.124) الثرومبين انتيثرومبين لا تظهر ارتباطا كبير من علامات الثرومبين (جزء بروثرومبين 1+2 ومركب الثرومبين بالمدة الزمنية لارتفاع ضغط (p=0.000) انتيثرومبين) لهما ارتباط كبير الدم.

أشارت النتائج المتحصلة على أن قياس زمن البروثرومبين , زمن الثرومبوبلاستين الجزئي أو زمن الثرومبين غير ضرورية عند تقييم مرضى ارتفاع ضغط الدم عندما لا يوجد اي دليل سريري يشير الي وجود خلل في عملية الارقاء. فمثل هذا النهج من شأنه أن يلغي الحاجة الى اكثر من ذلك في اختبارات تخثر هؤلاء المرضى. اظهرت نتائج هذه الدراسه الى ان عامل فون ويلبراند , مستوى الفيبرينوجن و جزء البروثرومبين 1+2 يمكن ان تكون مفيدة في تحديد مجموعة مرضى ارتفاع ضغط الدم الذين يحتملplasminogen activator "تعرضهم لمخاطر " التخثر. ارتفاع مستوي لدي مرضى ارتفاع ضغط الدم في هذة الدراسة يساعد inhibitor-1 علي التخثر ويؤكد ذلك. دراسات طوليه قد تكون أكثر إفادة في هذا الشأن.

ومدة المرض يشير الى microalbuminuria الارتباط الايجابي بين وجود وجود مرض كلوي متدرج لدى مرضى ارتفاع ضغط الدم القدامى. هذا على الرغم من عدم وجود اختلاف كبير في مستوى اليوريا والكرياتينين بالمصل بين المرضى و المعادلين الطبيعيين. كما ان وجود يرتبط ارتباطا مباشرا بمستوى الفيبرينوجن و عامل microalbuminuria

الفون ويلبراند انتيجيين ، وكان هذا مؤشرا على وجود صلة بين الضرر الكلوي و اضطرابات الارقاء في ارتفاع ضغط الدم .

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ABBREVIATIONS

WHO: world health organization

H. pylori: helicobacter pylori

LVH: left ventricular hypertrophy

JNC: Joint National Committee

ACE: angiotensin-converting enzyme

MRFIT: Multiple Risk Factor Intervention Trial

NHANES: National Health and Nutrition Examination Survey

LDL: low-density lipoprotein

HDL: high-density lipoprotein

PRA: Plasma renin activity

TSH: thyroid-stimulating hormone

PTT: partial thromboplastin time

APTT : activated partial thromboplastin time

vWF: von willebrand factor

vWD: von willebrand disease

PT: prothrombin time

TT: thrombin time

TF: Tissue factor

HMWK: high–molecular-weight kininogen

ACG:Aclelerator globulin

AHF:Antihemophilic factor

AHG:Antihemophilic globulin

PTC: Plasma thromboplastin component

PTA:Plasma thromboplastin antecent

LLF:laki-lorand factor

TPA: Tissue plasminogen activators

DIC: Disseminated intravascular coagulation

HITT: Heparin-induced thrombocytopenia with thrombosis

FDP: fibrin degraduation products

F1+2: prothrombin fragment 1+2

INR: international normalized ratio

APC: activated protien C

VTE: venous thromboembolism

RVVT: Russell's viper venom time

PNH: proxismal nocturnal hematuria

CBC: complete blood count

EDTA: ethylenediamine tetra-acetic acid

TAT: thrombin-antithrombin complex

PAI-1: plasminogen activator inhibitor-1

LCD: liquid crystal display screen

HPF: high power field

TCT: thrombin clotting time

PPP: platelets poor plasma

ELISA: Enzyme-Linked Immunosorbent Assay

OD: optical density

DMSO: dimethyl sulphoxide

TMB: tetramethylbenzidine

SP: Streptavidin-peroxidase

EIA: Energy Information Administration

POD: substrate peroxides

tPA: tissue-type plasminogen activator

uPA: urokinase-type plasminogen activator

HRP: horseradish peroxidase

AHD: anti-hypertensive drug

DCH: diet control and herbal therapy

NA: Absent of microalbuminuria

MA: Present of microalbuminuria

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