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Haemostatic Abnormalities and Renal Damage in Sudanese Hypertensive Patients

by

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**A Thesis Submitted for requirements to the
fulfillment of the degree of Doctor of Philosophy in
Haematology**

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February 2007

DEDICATION

To my mother soul

To Sudanese Hypertensive patients

*To all cardiac and renal care centers in
Sudan*

Acknowledgments

All praise and thanks to Allah the Almighty, who blessed me with courage for preparation and completion of this study.

Completing a PhD is truly a marathon event, and I would not have been able to complete this journey without the aid and support of countless people over the past four years. I must first express my gratitude towards my supervisor, Dr. Maria Mohamed Hamad Satti. Her leadership, support, attention to detailed and hard work are highly appreciated. Dr. Maria Satti was so kind as to read the whole thesis thoroughly and contributed also to the scientific discussion and without her critical advice and support, the completion of this thesis would not have been possible.

I am greatly indebted to Dr. Abdelbagi Elnagi Mohamed for his supervision and helpful advice throughout the process of writing this thesis.

Over the years, I have enjoyed the aid of several fellowships and scholarships from the American Society for Clinical Oncology and the American Society of Hematology which have supported me all throughout my practical work.

I would like to thank Prof. Micheal C. Perry for giving me the opportunity to work with his group at Ellis Fischer Medical Center, Columbia, Missouri, USA. His group contributed essentially to the final outcome of my practical studies, his insights and comments were invaluable over the time, and I look forward to a continuing collaboration with him in the future. I would like also to thank the group at the Missouri Medical Center especially Dr. Kathy Olson and Dr. Raymond Lobins since this research project benefited a lot from their critical discussions. I am, particularly, grateful to the College of Medical Laboratory Science, Soba University Hospital, Fathelrrhman El-bashir

Medical Center and Wadnobawy Medical Center for their support in the collection of samples.

Last, but not least I would like to thank my family and friends who have never lost faith in this long-term research project.

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 إلى فبراير 2007 في مستشفيات ولاية الخرطوم التعليمية (أم درمان ، الخرطوم وسوبا الجامعي) بهدف تقدير علامات الثر ومبين ، الأرقاء وعلامات الضرر الكلوئي بين مرضى ارتفاع ضغط الدم السودانيين .

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

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

أشارت النتائج المتحصلة على أن قياس زمن البروثرومبين , زمن الثرومبولاستين 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 الدراسة الى ان عامل فون ويلبراند , مستوى الفيبرينوجن و جزء البروثرومبين 2+1 يمكن ان تكون مفيدة في تحديد مجموعة مرضى ارتفاع ضغط الدم الذين plasminogen activator يحتمل "تعرضهم لمخاطر " التخرثر. ارتفاع مستوي لدي مرضى ارتفاع ضغط الدم في هذه الدراسة يساعد inhibitor-1 علي التخرثر 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 وبلبراند انتيجيين ، وكان هذا مؤشرا على وجود صلة بين الضرر الكلوي و اضطرابات الارقاء في ارتفاع ضغط الدم .

CONTENTS

Dedication.....	
....I	
Acknowledgements.....	
.....II	
Abstract(English)	
.....III	
Abstract(Arabic)	
.....IV	
Contents.....	
....V	
Abbreviations	
.....VI	
List of Tables.....	
VII	
List of Figures.....	
VIII	

Chapter - 1 **INTRODUCTION AND LITERATURE REVIEW**

1. Introduction and Literature review.....	
.....1	
1.1.Introduction.....	
...1	
1.2. Literature	
review.....8	
1.2.1. Hypertension.....	
....8	
1.2.2. Physiology of Hemostasis.....	
.....26	
1.2.3. Mechanisms of coagulation and fibrinolysis.....	
.....32	

1.2.4. Hemorrhagic Disorders of Coagulation.....	
.....37	
1.2.5 Hypercoagulable /Thrombophilic	
States.....	45

Chapter – 2
RATIONALE AND OBJECTIVES

2. Rationale and Objectives.....	
....63	
2.1.	
Rationale.....	63
2.2. Objectives.....	
.....64	

Chapter – 3
MATERIALS AND METHODS

3. Materials and Methods.....	
....65	
3.1. Type and Place of	
study.....	65
3.2. Study	
population.....	65
3.3. Study technique.....	
...65	
3.4. Research	
tools.....	66
3.5.	
Materials.....	66
3.6.	
Methods.....	67

3.6.1.	
Sampling.....	67
3.6.2. Platelet count	
.....	68
3.6.3. Platelet Aggregation Test.....	
.....	70
3.6.4. Bleeding Time.....	
.....	71
3.6.5. Prothrombin time (PT)	
.....	72
3.6.6. Activated partial thromboplastin time (APTT)	
.....	73
3.6.7. Thrombin time (TT)	
.....	75
3.6.8. Fibrinogen level	
.....	77
3.6.9. Protein S.....	
.....	79
3.6.10. Protein C.....	
.....	82
3.6.11. Von Willebrand Factor (vWF).....	
.....	85
3.6.12. Thrombin anti-thrombin complexes (TAT)	
.....	90
3.6.13. Prothrombin fragment (F 1+2)	
.....	93
3.6.14. Plasminogen Activator Inhibitor-1 (PAI-1)	
.....	96
3.6.15. Microalbuminuria(Immunoturbidimetry Method)	
.....	98
3.6.16. Serum	
Urea.....	100
3.6.17. Serum	
Creatinine.....	101

3.7. Data analysis.....	102
3.8. Difficulties confronted the study.....	102

Chapter – 4 RESULTS

4.Results.....	103
4.1 Characteristics of the study population.....	103
4.2.1 Family History of hypertensive patients.....	103
4.2.2 Duration of hypertension and the treatment.....	104
4.2 Renal function studies.....	110
4.2.1 Status of albumin excretion in the study group.....	110
4.2.2 Serum urea and serum creatinine levels in the study group.....	110
4.3. Haemostatic function studies.....	116
4.3.1 Coagulation system and fibrinogen level.....	116
4.3.2 Platelets count and functions.....	117
4.3.3. Plasma level of von willebrand factor antigen.....	117
4.4. Thrombin generation studies.....	130
4.4.1 Protein C and protein S levels.....	130

4.4.2 Plasminogen activator inhibitor -1(PAI-1)
.....130
4.4.3 Thrombin generation markers.....
131

**Chapter – 5
DISCUSSION**

5. Discussion.....
139

**Chapter – 6
CONCLUSIONS AND RECOMMENDATIONS**

6. Conclusions and
Recommendation.....157
6.1.
Conclusions.....157
6.2. Recommendation.....
.....158

REFERENCES.....
160

APPEDICES.....
190

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:Accelerator 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 degradation products

F1+2: prothrombin fragment 1+2

INR: international normalized ratio

APC: activated protein C

VTE: venous thromboembolism

RVVT: Russell's viper venom time

PNH: proximal 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

LIST OF TABLES

Number	Table	Page
Table 1.1	The physical capabilities of arteries and veins	29
Table 1.2	Coagulation factors with their preferred names and other synonyms	33
Table 4.1	Family history of hypertension among patients in the study group	107
Table 4.2	Family history of hypertension in the control group	107
Table 4.3	Status of albumin excretion and the age of patients in the study group	113
Table 4.4	Correlation of the status of albumin excretion and the duration of hypertension in the study group	113
Table 4.5	Mean of serum urea level in the hypertensive patients and the control group	114
Table 4.6	Mean of serum creatinine level in the hypertensive patients and the control group	114
Table 4.7	Age-related distribution of serum urea levels in the study groups	115
Table 4.8	Age-related distribution of serum creatinine levels in the study groups	115
Table 4.9	Mean values of PT, APTT and TT correlation in hypertensive patients and control groups	119
Table 4.10	Prothrombin time distribution in the study group	119
Table 4.11	Activated partial thromboplastin time distribution in the study group	120
Table 4.12	Thrombin time distribution in the study group	121
Table 4.13	Mean of fibrinogen level in the hypertensive patients and the control groups	121
Table 4.14	Fibrinogen level distribution in the study group	121
Table 4.15	Correlation of the severity of hypertension to the fibrinogen level in the study groups	122
Table 4.16	The correlation of fibrinogen levels distribution and Microalbuminuria	122
Table 4.17	The mean of the platelets count in $\times 10^9/\mu\text{L}$ hypertensive patients and the control group	124
Table 4.18	Platelet aggregation of hypertensive patients and control groups	124
Table 4.19	Mean of bleeding time in the hypertensive patients and the control group	125
Table 4.20	The severity of hypertension related- incidences distribution of bleeding time in the study groups	126
Table 4.21	The mean von willebrand factor antigen level in the hypertensive patients and control group	126
Table 4.22	Plasma level of von willebrand factor antigen distributions in the study groups	126
Table 4.23	The relation between von willebrand factor antigen levels and the urinary albumin excretion in hypertensive patients	126
Table 4.24	The correlation between numbers of platelet and von willebrand factor antigen levels in the study group	129
Table 4.25	The correlation between numbers of platelet and von willebrand	129

	factor levels in the control group	
Table 4.26	The mean level of protein C and protein S in the hypertensive patients and the control group	132
Table 4.27	Mean of plasminogen activator inhibitor-1 level in the hypertensive patients and the control group	132
Table 4.28	The correlation of hypertension severity and the plasminogen activator inhibitor-1 level in the study groups	133
Table 4.29	Mean of prothrombin fragment (F ₁₊₂) level in the hypertensive patients and the control group	135
Table 4.30	Mean of thrombin antithrombin complex(TAT) level in the hypertensive patients and the control group	135
Table 4.31	Correlation of the thrombin generation markers and the duration of hypertension in the study group	135
Table 4.32	The age-related incidences to the increased plasma level of the thrombin generation markers in the study group	136
Table 3.33	Correlation of the thrombin generation markers and the severity of hypertension in the study group	136

LIST OF FIGURES

Number	Figure	Page
Fig. 4.1	Age distribution of hypertensive patients	105
Fig. 4.2	Age distribution of the control group	106
Fig. 4.3	The duration of hypertension in the study group	108
Fig. 4.4	Type of hypertension treatment in the study group	109
Fig. 4.5	Status of albumin excretion among hypertensive patients	112
Fig 4.6	Age-related distribution of fibrinogen level in the study group	123
Fig. 4.7	Patterns of plasma vWF:Ag level among hypertensive Microalbuminuria patients in the study group	127
Fig. 4.8	Patterns of plasma vWF:Ag level among hypertensive normoalbuminuric patients in the study group	128
Fig. 4.9	The Age- related incidences of plasma PAI-1 level distribution in the study group	134
Fig. 4.10	Correlation of antihypertensive drugs and untreated patients in F1+2 levels in the study group	137
Fig. 4.11	Correlation of antihypertensive drugs and untreated patients in TAT levels in the study group	138