بِسْمِ اللّهِ الرَّحْمَنِ الرَّحِيمِ

قال الله تعالى

لا يُكَلِّفُ اللَّهُ نَفْساً إِلَّا وُسْعَهَا لَهَا مَا كَسَبَتْ وَعَلَيْهَا مَا اكْتَسَبَتْ رَبَّنَا لا تُؤَاخِذْنَا إِنْ نَسِينَا أَوْ أَخْطَأْنَا رَبَّنَا وَلا تَحْمِلْ عَلَيْنَا إِصْراً كَمَا حَمَلْتَهُ عَلَى الَّذِينَ مِنْ قَبْلِنَا رَبَّنَا وَلا تُحَمِّلْنَا مَا لا طَاقَةَ لَنَا بِهِ وَاعْفُ عَنَّا وَاغْفِرْ لَنَا وَارْحَمْنَا أَنْتَ مَوْلانَا فَانْصُرْنَا عَلَى الْقَوْمِ الْكَافِرِينَ

صدق الله العظيم

سورة البقرة الآية: 286

Dedication

To my country Sudan,

To my family,

To my colleagues

and

To all whom I love

Acknowledgment

Thanks at first and last to (ALLAH) who enabled us to be muslims and to conduct this study.

I like to express my immense thanks and respect to my supervisor Dr. khalda M. Hamza for her close supervision, effort, patience, invaluable advices and kind guidance.

My special thanks and respect also to my colleagues in Jaber Abu.Eleaz specialized center and Turkish Teaching Hospital for their valuable helps in providing facilities and solving problems encountered throughout the study.

My thanks expend to involve all who stand beside me, encouraged and supported me till this study emerged to light.

Abstract

This is an analytical case control study conducted during the period from November 2009 to March 2010, in Jaber Abu Eleaz Specialized Center and Turkish Teaching Hospital. The study population were diabetic patients, the investigation included PT, APTT and INR to evaluate coagulation mechanism among diabetic patients.

One hundred samples were collected from diabetic patients of both type1 and type2 with age range 5 to 75 years and disease duration range 1 to 30 years. Twenty control samples were collected from healthy- non diabetic volunteers within the same age groups of the study population.PT and APTT were estimated using Coagulometer.

Variable results for PT value were found when compared with mean PT of controls according to age groups and duration of the disease without statistical significant difference and showed slight increased in both type1 and type2 D.M. but also without statistical significant ,and there was positive weakly statistically insignificant correlation between PT and age of the patient(P-value =0.177) and duration of the disease(P-value =0.783) .APTT showed increased values within age where the significant elevation occurred in age above 65 years (66-75 years old) (P-value=0.006) according to the duration of the disease APTT showed elevation

directly proportional to the increased duration of the disease where the significance elevation was found to be among duration of more than 25 years (26-30 years duration group) (P-value=0.032), according to type of D.M. APTT increased in both types but in type1 there was a significant elevation (P-value=0.004) ,there were weakly positive statistically insignificant correlation between APTT and age of the patient(P-value =0.545) and there were weakly positive statistically significant correlation between APTT and duration of the disease (P–value=0.023). INR according to age group and duration of the disease showed variable results without significant differences but according to type of D.M. showed slightly increase when compared to mean INR of normal controls in both type1 and type2 D.M. but without statistical significance, there were weakly positive statistically insignificant correlation between INR and age of the patient(P-value=0.504) and duration of the disease(P-value=0.705) .

دراسة وصفية تحليلية أجريت في الفترة من نوفمبر 2009 إلى مارس 2010 فى مركز جابر أبو العز التخصصي لإمراض السكرى والمستشفى التركى التعليمى وكانت تستهدف مرضى السكرى حيث تم إجراء الفحوصات الآتية 1) زمن تجلط البروثرومين 2) زمن تجلط الثروميوبلاستين الجزئي 3)المعدل الطبيعى العالمى. وذلك للوقوف على مستوى أداء وكفاءة عوامل التجلط عند مرضى السكرى .

تم جمع مائة عينة دم من مرضى السكرى بنوعية النوع الأول والنوع الثاني من اعمار تتراوح ما بين 5-75 سنة وفترة استمرارية للمرض مابين سنة واحدة الى ثلاثين سنة . وللمقارنة تم جمع عشرين عينة من متبرعين أصحاء غير مصابين بمرض السكرى من اعمار تقارب اعمار المرضى. . تم إجراء الفحوصات باستخدام جهاز زمن التجلط الالى .

وجد من التجربة أن نتائج زمن تجلط البروثرومبين لمرضى السكرى عند مقارنتها بمتوسط نتائج المشاركين الأصحاء اعتماداً على العمر وفترة استمرارية المرض ذات نتائج متفاوتة ولكن دون قيمة معنوية وعند مقارنتها اعتماداً على نوع السكرى وجد أنها تزيد زيادة فى كلا النوعين ولكن من غير قيمة معنوية وجد أيضا أن هنالك علاقة طردية ضعيفة دون قيمة إحصائية معنوية بين زمن تجلط البروثرومبين وعمر المريض (قيمة المعنوية=0.177) وفترة استمرارية المرض(قيمة المعنوية=0.783) . وجد من نتائج زمن تجلط الثروميوبلاستين الجزئي النشط عند مرضى السكرى عند مقارنتها بمتوسط نتائج المشاركين الأصحاء اعتماداً على العمر ان زمن التجلط يزيد زيادة معنوية فى الأعمار فوق 65 سنة (66-75 سنة) (قيمة المعنوية 0.006) وعند مقارنتها اعتماداً على فترة استمرارية المرض وجد أنها تزيد تزايد طردي كلما ازدادت مدة المرض حيث إن أعلى زيادة فى المرض الأكثر من 25 سنة (26-30 سنة) (قيمة المعنوية 0.032) وعند المقارنة اعتماداً على نوع السكرى وجد انه يزيد فى النوعين ولكن فى النوع الأول هنالك زيادة ملحوظة ذات قيمة

معنوية (قيمة المعنوية=0.004) وجد أيضا أن هنالك علا قة طردية ضعيفة دون قيمة معنوية بين زمن تجلط الثرومبوبلاستين الجزئي النشط وعمر المريض(قيمة المعنوية =0.545) وهنالك علا قة طردية ضعيفة ذات قيمة إحصائية معنوية بين زمن تجلط الثرومبوبلاستين الجزئي النشط وفترة استمرارية المرض(قيمة المعنوية =0.023). كما وجد من الدراسة ان نتائج المعدل الطبيعى العالمى للتجلط لمرضى السكرى عند مقارنتها بمتوسط نتائج المشاركين الأصحاء اعتماداً على العمر وفترة استمرارية المرض ذات نتائج متفاوتة ما بين الزيادة والنقصان ولكن من دون فروقات ذات قيمة معنوية وعند مقارنتها اعتماداً على نوع السكرى هنالك زيادة طفيفة فى كلا النوعين ولكن من دون قيمة معنوية وان هنالك علا قة طرديه ضعيفة دون قيمة معنوية بين المعدل الطبيعى العالمى للتجلط وعمر المريض(قيمة المعنوية =0.504) وفترة استمرارية المرض (قيمة المعنوية = 0.705) .

List of abbreviations

ADP	Adenosine diphosphate
AGE	Advanced glucation end-product
APTT	Activated partial thromboplastin time
ATP	Adenosine triphosphate
CAD	Coronary artery disease
cAMP	Cyclic adenosine mono phosphate
cGMP	Cyclic guanosine monophosphate
CHD	Coronary heart disease
CVD	Cardio vascular disease
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
ECs	Endothelial cells
EDRF	Endothelial derived relaxing factor
FDP	Fibrin degradation products
GDM	Gestational diabetes mellitus
GLUT4	Glucose Transporter 4

GP	Glycoprotein
GTT	Glucose Tolerance Test
HC-II	Heparin co-factor II
HMWK	High molecular weight kininogen
IDDM	Insulin dependent diabetes mellitus
IL	Interleukin
INR	International normalized ratio
IP3	Inositol triphosphate
IR	Insulin resistance
Lp-A	Lipo protein –A
α2-MG	α2- macro globulin
MI	Myocardial infarction
mRNA	Messenger ribonucleic acid
NADP	Nicotinamide adenine dinucleotide phosphate
NIDDM	Non- Insulin dependent diabetes mellitus
NO	Nitric oxide
OCS	Open canalicular system
PAI-1	Plasminogen activator inhibitor-1
PGI_2	Prostaglandin-I_2
PT	Prothrombin time
TATc	Thrombin-antithrombin complex

TF	Tissue factor
TNF	Tissue necrosis factor
t.PA	Tissue plasminogen activator
TXA2	Thromboxan A2
u.PA	Urinary plasminogen activator
VCAM-1	Vascular cell adhesion molecule-1
VWF	Von Willebrand factor

List of Figures

Title Page

1-1: The hemostatic mechanism……..……..……..……3

1-2: The anatomy of blood vessel……..……..5

1-3: Platelet ultrastructure…….……..9

1-4: The coagulation cascade reaction …….……..……..……..15

1-5:Reactions of Prothrombin Time PT and Activated Partial Thromboplastin Time (APTT)……..…….22

3-1:Mean levels of PT of the study group compared to the mean of the normal control….....60

3-2: Mean levels of APTT of the study group compared to the mean of the normal control……60

3-3: Mean levels of INR of the study group compared to the mean of the normal control……...60

3-4:PTmean levels in age groups of the study population compared to mean of normal control.62

3-5: APTT mean levels in age groups of the study population compared to mean of normal control……62

3-6:INR mean levels in age groups of study population compared to mean of normal control…62

3-7: Mean levels of PT in the study group according to the duration of the disease compared with mean of normal controls……...….65

3-8:Mean levels of APTT in the study group according to duration of the disease compared with mean of normal controls……....65

3-9: Mean levels of INR in the study group according to duration of the disease compared with mean of normal controls……65

3-10: Mean levels of PT in the target population according to type of diabetes compared with mean of normal control……..……....68

3-11: Mean levels of APTT in the target population according to type of diabetes compared with mean of normal control……..……68

3-12: Mean levels of INR in the target population according to type of diabetes compared with mean of normal control……..……....68

List of Tables

Title Page

1-1:Contents of platelet granules…..……...….9

1-2: Properties of coagulation factors …….……...……...14

1-3:WHO diagnostic criteria……...……...……31

1-4:Risk factors for atherothrombosis……...……35

1-5:Endothelial variable in diabetes mellitus…….……38

1-6:Natural anticoagulant variable in diabetes mellitus……..……..42

3-1:Distribution of study population according to the age……..…….58

3-2:Distribution of study population according to the duration of the disease…….…..……..58

3-3:Distribution of study population according to the sex…….……..……59

3-4:Distribution of study population according to the type of diabetes mellitus…….……59

3-5:Mean levels of PT, APTT and INR of the study group compared to the mean of normal control……...….59

3-6: PT , APTT and INR mean levels in age groups of the study population compared to mean of normal control……...……61

3-7: PT, APTT and INR results compared between the study population according to the age group…….63.

3-8: PT , APTT and INR correlation with the age of patients…….……..……63

3-9:Mean levels of PT, APTT and INR in the target group according to duration of the disease compared with mean of normal controls……...…64

3-10:PT , APTT and INR results compared between target population according to the duration of the disease…….…….66

3-11: PT , APTT and INR correlation with the duration of the disease……66

3-12: Mean levels of PT, APTT and INR in the target population according to the type of diabetes compared with mean of normal control ……..……67

CONTENTS

Title	Page
الآية……	I
Dedication …..……..	II
Acknowledgement……..……..……	III
Abstract……	IV
مستخلص البحث.……..…….….....	VI
List of Abbreviations……	VIII
List of figures……	XI
List of tables……	XIII
CHAPTER I	
1.1 Hemostasis……	1
1.1.1 General overview……..……	1
1.1.2 Blood vessels……	4
1-1-3 The endothelium……..……	5
1-1-4 Platelets……	7
1-1-4-1 Platelet structure……	7
1-1-4-2 Platelets function……	9
1-1-4-3 Platelet procoagulant activity……..……	11
1-1-4-4 Stimulatory agonists of platelets……..……	11
1-1-4-5 Inhibitory agonists of platelets……	12
1-1-5 Coagulation Factors…….	12

1-1-5-2 Natural occurring inhibitors of blood coagulation…… 15

1-1-6 Fibrinolysis…… 17

1-1-6-1 Activation of plasminogen……..…… 18

1-1-6-2 Inhibitors of fibrinolysis…… 19

1-1-7 Prothrombin Time (PT) …… 20

1.1.8 Activated Partial Thromboplastin Time (APTT) ……... 21

1-2 Metabolism of Carbohydrates…… 23

1.2.1 Regulation of blood Glucose Concentration…….. 23

1-2-2 Insulin…… 24

1-2-3 Diabetes Mellitus (D.M) …….. 26

1-2-3-1 Definition…….. 26

1-2-3-2 Classification of D.M……. 26

1-2-3-3 Causes of Diabetes Mellitus…….. 28

1-2-3-4 Clinical features of Diabetes Mellitus…… 29

1-2-3-5 Complications of Diabetes Mellitus……. 29

1-2-3-6 Diagnosis of Diabetes Mellitus…… 31

1.3 Thrombosis…… 32

1.3.1 Type of thrombosis……. 32

1.3.2 Atherothrombosis…… 33

1.3.3 Pathophysiology…… 33
…….

1.3.4 Risk factors for atherothrombosis…….. 34

1.3.5 Insulin resistance and diabetes…… 35

1.4 Hemostatic abnormalities in diabetes mellitus……..…….. 38

1.4.1 Abnormalities of endothelial cells…….. 38

1.4.2 Abnormalities of platelets……. 39

1-4-3 Abnormalities of coagulation…… 41

1-4-4 Abnormalities of fibrinolysis…… 42

1-4-5 The effect of hyperglycemia and hyperinsulinemia…….. 43

1.5 Rationale……..… 50

1-6 General objective……..……..…….. 51

1-7 Specific objective…….…… 51

CHAPTER II

Materials and method…… 52

2-1 Study design……..……. 52

2-2 Study area……..…… 52

2-3 Study population…….…….. 52

2-4 Exclusion criteria…… 52

2-5 Study duration……..…….. 53

2-6 Sample size……..…..…….. 53

2-7 Data collection…….……... 53

2-8 Data analysis…….…….. 53

2-9 Ethical consideration…….…….. 53

2 -10 Methodology…… 54

2-10-1 Sample collection…… 54

2-10-2 The anticoagulant…… 54

2-10-3 Preparation of platelet poor plasma……. 54

10-4 Equipments……. 54

2-10-5 Reagents…… 55

2-10-6 Principles…… 55

2-10-7 Procedures…… 56

2-10-8 Normal values…….. 57

2-10-9 Quality Control……..……... 57

CHAPTER III

Results……..……. 58

CAPTER IV

4-1 Discussion…… 69

4-2 Conclusion…… 73

4-3 Recommendation……. 74

CHAPTER V

References……. 75

Appendixes

1- Questionnaire…… 79

2-ethical clearance……. 80

3-results of the study population…… 81

4-result of normal controls……..…….. 84

5-results of internal quality control(normal and abnormal plasma controls)…… 85

6-Levey-Jenning control charts of PT and APTT……. 86