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A STUDY OF SERUM ANGIOPOIETIN-1 IN DIABETIC NEPHROPATHY PATIENTS

Thesis

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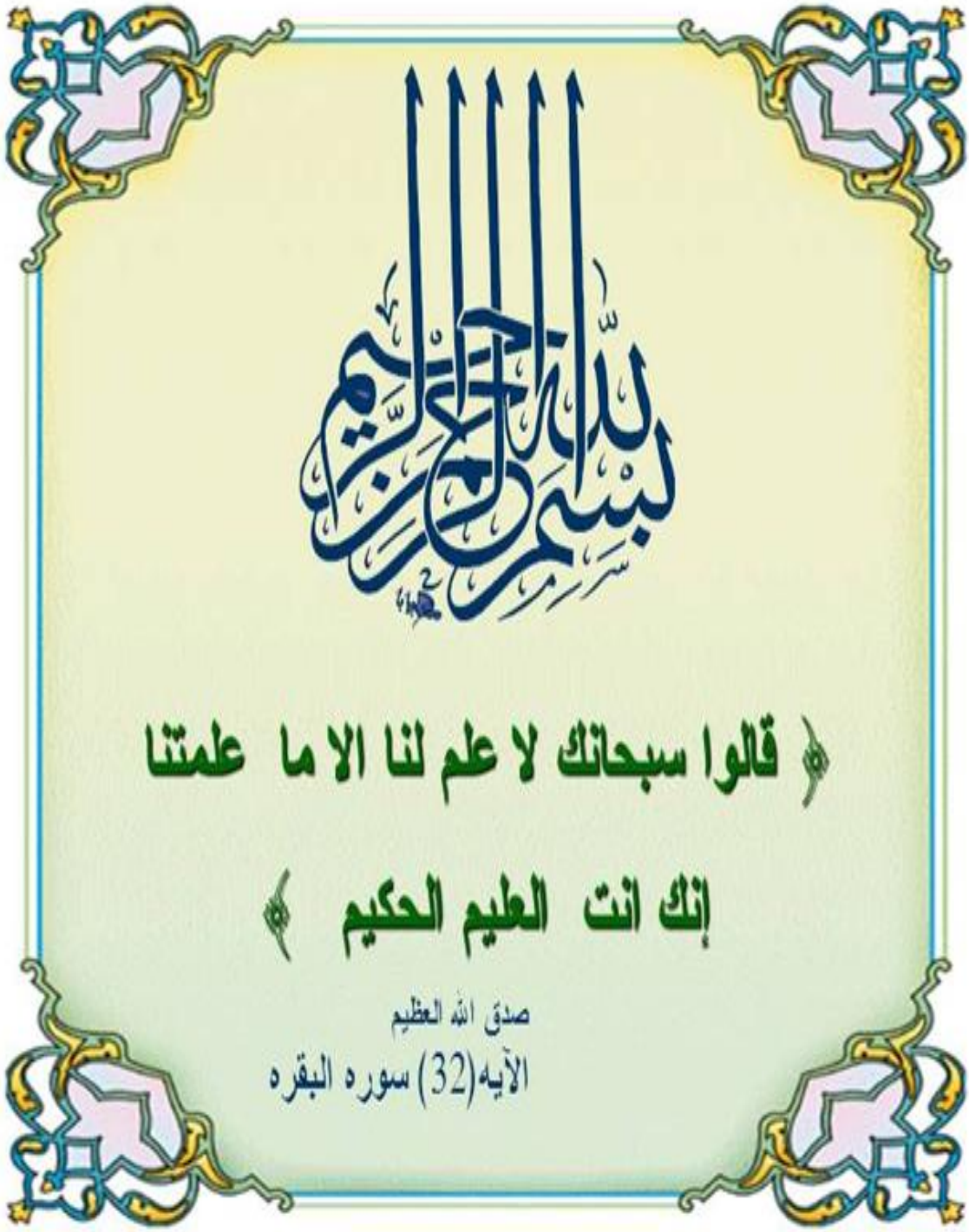
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Ahmed GALAL

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List of Abbreviations

ACE	:	Angiotensin Converting Enzyme
ACR	:	Albumin Creatinin Ratio
ADA	:	American Diabetes Association
AER	:	Albumin Excretion Rate
AGE	:	Advanced Glycosylation End Products
AKI	:	Acute kidney Injury
AKt	:	Protein Kinase-B
Ang	:	Angiopoietin
Ang II	:	Angiotensin 2
Ang-1	:	Angiopoietin-1
Ang-2	:	Angiopoietin-2
Ang-3	:	Angiopoietin-3
Ang-4	:	Angiopoietin-4
AR pathway	:	Aldose Reductase pathway
ARBs	:	Angiotensin Receptors Blockers
BMI	:	Body Mass Index
BP	:	Blood Pressuse
CAD	:	Coronary Artery Disease
CHF	:	Congestive Heart Failure
CKD	:	Chronic Kidney Disease
COMP-**Ang1**	:	Cartilage Oligomeric Matrix Protein-Angiopoietin-1
Cr.Cl	:	Creatinine Clearance
CsA	:	Cyclosporine-A
CSMO	:	Clinically Significant Diabetic Macular Oedema
CV	:	Cardiovascular
CVD	:	Cardiovascular Disease
DCCT	:	Diabetes Control and Complications Trial
DKA	:	Diabetic Keto Acidosis
DM	:	Diabetes mellitus
DN	:	Diabetic Nephropathy
DNA	:	Deoxyribonuclic Acid
DR	:	Diabetic Retinopathy
EC	:	Endothelial Cell
ECAM-1	:	Endothelial cell Adhesion Molecule-1
ECM	:	Extracellular Matrix
EGF	:	Endothelial Growth Factor
eGFR	:	Estimated Glomerular Filtration Rate
ELISA	:	Enzyme Linked Immunosorbent Assay
ESRD	:	End Stage Renal Disease

ESRF	:	End Stage Renal Failure
FDA	:	Food And Drug Administration
FHDM	:	Family History Of Diabetes Mellitus
FKHR	:	Forkhead In Rhabdomyosarcoma
FPG	:	Fasting Plasma Glucose
GBM	:	Glomerular Basement Membrane
GDM	:	Gestational Diabetes Mellitus
GFR	:	Glomerular Filtration Rate
GSH	:	Glutathione
Hb	:	Hemoglobin
HbA1c	:	Glycosylated hemoglobin
HDL	:	High Density Lipoproteins
HNF	:	Hepatocyte nuclear factor
HUVECs	:	Human Umbilical Vein Endothelial Cells
ICAM-1	:	Intercellular Adhesion Molecule-1
IDDM	:	Insulin Dependent Diabetes Mellitus
IFTA	:	Interstitial Fibrosis And Tubular Atrophy
IGT	:	Impaired Glucose Tolerance
IL-18	:	Iterlukin 18
IL-6	:	Interlukin 1
IL-6	:	Interleukin 6
IPF-1	:	Insulin Promoter Factor -1
kDa	:	Kilodalton
KIM-1	:	Kidney InjuryMolecule-1
LDL	:	Low Density Lipoproteins
LDL	:	Low Density Lipoprotein
MCP-1	:	Monocyte Chemoattractant protein-1
MDRD	:	Modification Of Diet And Renal Disease
MI	:	Myocardial Infarction
MMP-9	:	Metaloproteinase-9
MPs	:	Matrix Metaloproteases
MODY	:	Maturity Onset Diabetes Mellitus
mRNA	:	Messenger Ribonucleic Acid
NADH	:	Nicotinamide Adenine Dinucleotide Hydrogen
NADPH	:	Nicotinamide Adenine Dinucleotide Phosphate
NAG	:	N-Acetyl-D-Glucosaminidase
NF-κB	:	Nuclear Factor Kappa B
NGAL	:	Neutrophil Gelatinase-Associaition Lipocalin
NGSP	:	National Glycohemoglobin Standardization Program
NHANES 3	:	Third National Health And Nutrition Examination Survey
NIDDM	:	Non Insulin Dependent Diabetes Mellitus

NKF	:	National Kdney Foundation
NO	:	Nitrous Oxide
NPDR	:	Non- Proliferative Diabetic Retinopathy
OGGT	:	Oral Glucose Tolerance Test
PAD	:	Peripheral Artery Disease
PCO	:	Polycystic Ovary
PDR	:	Proliferative Diabetic Retinopathy
PI3K	:	Phosphatidylinositol 3 Kinase
PKC	:	Protein Kinase C
PPAR α	:	Peroxisome Profileferator-Activated receptor-Alpha
PPAR γ	:	Peroxisome Profileferator-Activated receptor-Gamma
PTF	:	Pentoxyfyllin
RAAS	:	Renin Angiotensin Aldosterone System
RAS	:	Renin Angiotensin System
ROS	:	Reactive Oxygen Species
SDH	:	Sorbitol Dehydrogenase
SLE	:	Systemic Lupus Erythematosus
TG	:	Triglycerides
TGF- β	:	Transforming Growth Factor Beta
TGF-1	:	Transforming Growth Factor-1
Tie	:	Tyrosine Kinase With Immunoglobulin Like And Epidermal Growth Factor Like Domains
TNF- α	:	Tumor Necrosis Factor Alpha
TZDs	:	Thiazolidinedions
UAE	:	Urinary Albumin Excretion
UKPDS	:	United Kingdom Prospective Diabetes Study
UUO	:	Unilateral Ureteral Obstruction
VCAM-1	:	Vascular Adhesion Molecule-1
VEGF	:	Vascular Endothelial Growth Factor
VEGF-A	:	Vascular Endothelial Growth Factor-A
VEGFR	:	Vascular Endothelial Growth Factor Receptor
VSMCs	:	Vascular Smooth Muscle Cells
vWF	:	Von Willebrand Factor
WBC	:	White Blood Cell
WBCs	:	White Blood Cells
WHO	:	World Health Organization
WPB	:	Weibel Palade Body

INTRODUCTION

Diabetic Nephropathy (DN) is the commonest cause of end-stage renal failure (ESRF) in the Western world. Diabetic nephropathy follows a well outline clinical course, starting with microalbuminuria through proteinuria, azotaemia and culminating in ESRF. There is no doubt that there is a positive relationship between hyperglycaemia, which is necessary but not sufficient, and microvascular complications **(Raptis and Viberti, 2001).**

Diabetic nephropathy is typically defined by either macroalbuminuria- that is a urinary albumin excretion of greater than 300 mg in 24 hours urine collection- or by abnormal renal function as represented by abnormality in serum creatinine , calculated creatinine clearance, or glomerular filtration rate (GFR). The common progression from microalbuminuria to overt nephropathy has led many to consider microalbuminuria to define early or incipient nephropathy**(Mongensen et al., 1995).**

Microalbuminuria can be diagnosed from a 24-hour urine collection (between 30–300 mg/24 hours) or, more commonly, from elevated concentrations in a spot sample (30 to 300 mg/L). Both must be measured on at least two of three measurements over a two- to three-month period**(Abid et al., 1984).**

Angiopoietins are protein growth factors that promote angiogenisis, there are four identified angiopoietins: Ang-1, Ang-2, Ang-3 and Ang-4, of them, Ang-1 and Ang-2 are the most studied. These ligands bind to transmembrane receptor Tie2 and possibly Tie1 , members of family of receptor tyrosine kinase expressed primarily in vascular endothelium. Ang-1 has powerful vascular protective effects; it suppresses plasma leakage, inhibits vascular inflammation, and prevents endothelial death. In studies in which Ang-1 is directly administered or overexpressed, it leads to marked improvements of vascular integrity in both growing and adult mice. Ang-1 and vascular endothelial growth factor (VEGF) are thought to have a complementary effecton blood vessel growth**(Brindle et al., 2006).**

Angiopoietin-1/Tie2 signaling is a critical regulator of blood vessel development. In addition, angiopoietin-1 is thought to be required for the stability of mature vessels**(Jeansson et al., 2011).**

Inflammatory processes have been recently seen as underlying the pathogenesis of diabetic nephropathy. Angiopoietin-1 (Ang1) plays essential roles in regulating vascular growth, development, maturation, permeability and inflammation**(Lee et al., 2007).**

Aim of the work

To evaluate the level of plasma angiopoietin-1 in the patients with diabetic nephropathy. And to study the relation between serum angiopoietin-1 and the severity of renal dysfunction in the patients with diabetic nephropathy.

DIABETES MELLITUS

Definition:

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion , insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs especially the eye, kidney, nervs, heart and blood vessels **(Thorn et al., 2009).**

DM is primary disease of carbohydrate metabolism due to deficient/absence of insulin has propensity towards vascular endothelial dysfuncyion resulting into micro and macroangiopathy. In the last two decades our understanding about hyperglycemia and its consequences has increased dramatically. The management of diabetes has changed from glucocentric to organo protective and specially the vascular endothelium, which could lead cardiovascular complications **(Manish et al., 2011).**

Several pathogenic processes are involved in the development of diabetes, these range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency, to abnormalities that result in resistance to insulin action. The basis of abnormalities in carbohydrate, fat and protein metabolism in diabetes is deficient action of insulin on target tissue **(The expert comitte of the diagnosis and classification of diabetes mellitus, 2001).**

Deficient insulin action results from inadequate insulin secretion and/or diminished tissue response to insulin at one or more points in the complex pathway of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patients. It is often unclear which abnormality is the primary cause of the hyperglycemia **(Gelaye et al., 2010).**

Epidemiology

In the middle east and north Africa one in ten adults have diabetes; the area has the highest prevalence of diabetes, at 10.9 %. In Egypt, 42% of people with diabetes (International Diabetes Federation 2013).

Rates of diabetes have increased markedly over the last 50 years in parallel with obesity. As of 2008 there are approximately 285 million people with the disease compared to around 30 million in 1985 **(Fasanmade et al., 2008).**

Diabetes can be found in every country in the world and without effective prevention and management programmes the burden will continue to increased globally. Type-2 diabetes makes up about 85 to 95% of all diabetes in high-income countries and may account for an even higher percentage in low- and middle-income countries. Type 2 diabetes is now a common and serious global health problem, which, for most countries, has developed together with rapid cultural and social changes, ageing population, increasing urbanization, dietary changes, reduced physical activitiy, and other unhealthy behavious **(World health organization, 1994).**

Etiological classification of diabetes mellitus **(World health organization, 2001)**

- Type 1 diabetes:

It is either immune or idiopathic β-cell destruction, usually leading to absolute insulin deficiency.

- Type 2 diabetes:

It ranges from predominant insulin resistance with relative insulin deficiency to predominant insulin secretory defect with or without insulin resistance.

- Other specific types: