URINARY TRANSFORMING GROWTH FACTOR-BETA 1 AND ALPHA 1-MICROGLOBUIN IN CHILDREN AND ADOLESCENTS WITH TYPE-1 DIABTES

Thesis
Submitted for Partial Fulfillment of
Master Degree in pediatrics medicine

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2007

عامل النمو المحول البولى بيتا 1 والمايكروجلوبيولين الفا1 فى الاطفال والمراهقين المصابين بداء السكرى

رسالة عملية توطئة للحصول على درجة الماجستير فى طب الاطفال

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بكالوريوس الطب والجراحة جامعة مصر للعلوم والتكنولوجيا يوليو **2002**

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2007

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ACR	Albumin Creatinine Ratio
ARBs	angiotensin II type 1-receptor blockers
BMP	Bone morphogenetic protein
CD	Cluster of differentiation
COOPERATE	Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Nondiabetic Renal Disease
CTLA	cytotoxic T lymphocyte antigen
DCCT	The Diabetes control and Complications Trial
DIDMOAD syndrome	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness
DM	Diabetes Mellitus
DPT-1	The Diabetes Prevention Trial – type 1
ELISA	Enzyme Linked Immunosorbent Assay
ENDIT	The European Nicotinamide Diabetes Intervention Trial
EURODIAB	European Diabetes
FPG	Fasting plasma glucose
GAD	glutamic acid decarboxylase
GFR	Glomerular Filteration Rate
Hb	Hemoglobin
HBV	Hepatits B Virus
HCV	Hepatits C Virus
HIV	Human Immuno-diffieciency Virus
HLA	Human leukocyte antigen
HOT	Hypertension Optimal Treatment
IDDM	Insulin dependent Diabetes Mellitus
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LAP	latency-associated peptide

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LDL	Low density lipoprotein
LLC	large latent complex
LTBP	latent TGF-ß binding protein
LTBP	latent TGF- β1 binding protein
MDRD	Modification of Diet in Renal Disease Trial
MICRO-HOPE	Heart Outcomes Prevention Evaluation
MIS	Mullerian inhibitory substance
mRNA	Messenger ribonucleic acid
NIDDM	Non insulin dependent Diabetes Mellitus
OGTT	Oral glucose tolerance test
RAS	Renin angiotensin system
RBP	Retinol binding protein
SP	signal peptide
TGF	Transforming growth factor
UAE	Urinary albumin excretion
UKPDS	United Kingdom prospective diabetes study

Introduction

Introduction

Diabetic nephropathy is the leading cause of kidney disease in patients starting renal replacement therapy and affects ~40% of type 1 and type 2 diabetic patients. It increases the risk of death, mainly from cardiovascular causes, and is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases. Diabetic nephropathy is categorized into stages: microalbuminuria (UAE >20 µg/min and ≤199 µg/min) and macroalbuminuria (UAE ≥200 µg/min). Hyperglycemia, increased blood pressure levels, and genetic predisposition are the main risk factors for the development of diabetic nephropathy. Elevated serum lipids, smoking habits, and the amount and origin of dietary protein also seem to play a role as risk factors. ***(Jorge L. et al., 2005)***.

Screening for microalbuminuria should be performed yearly, starting 5 years after diagnosis in type 1 diabetes or earlier in the presence of puberty or poor metabolic control. In patients with type 2 diabetes, screening should be performed at diagnosis and yearly thereafter. Patients with micro- and macroalbuminuria should undergo an evaluation regarding the presence of comorbid associations, especially retinopathy and macrovascular disease. Achieving the best metabolic control (A1c <7%), treating hypertension (<130/80 mmHg or <125/75 mmHg if proteinuria >1.0 g/24 h and increased serum creatinine), using drugs with blockade effect on the renin-angiotensin-aldosterone system, and treating dyslipidemia (LDL cholesterol <100 mg/dl) are effective strategies for preventing the development of microalbuminuria, in delaying

the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with type 1 and type 2 diabetes ***(Jorge L. et al., 2005)***.

Improvements in glycemic control and the greater use of antihypertensive therapy should eventually have a beneficial impact on the incidence of severe nephropathy in type 1 diabetes. However, early disease, such as microalbuminuria and macroalbuminuria, will continue to occur because glycemic control cannot wholly prevent the progression of albuminuria, and there is currently little evidence that antihypertensive use in normotensive normoalbuminuric patients is of clinical value. Both microalbuminuria and macroalbuminuria significantly increase the risk of morbidity and mortality from coronary heart disease and are strong predictors of subsequent severe renal disease. Prevention of the early stages of diabetic renal disease and reduction in progression should now be priorities, but these steps require a more complete understanding of the etiology to identify suitable targets for intervention ***(Nish C. et al., 2002)***

Diabetic nephropathy is characterized by hypertrophy of the glomerular and tubuloepithelial structures and thickening of the glomerular and tubular basement membrane, due largely to the effects of hyperglycemia . The cytokine transforming growth factor (TGF)-ß1 appears to be a key mediator for these changes . TGF-ß1 expression is enhanced in the presence of diabetes, either as a direct consequence of hyperglycemia or indirectly via the formation of early or advanced glycation end products . Hyperglycemia stimulates condensation reactions

between glucose and proteins, and an early product of this reaction is an Amadori protein ***(Nish C. et al., 2002).***

Transforming growth factor-β1 (TGF-β1) is a potent multifunctional polypeptide that is involved in normal renal function and in the development of glomerular sclerosis. It is also an important mediator of the immune and anti-inflammatory responses ***(Pierina De Muro., 2004)***.

TGF-β represents a group of 25-kD proteins that are actively involved in the development and differentiation of various tissues and in the healing process after a tissue injury . Three isoforms of TGF-β have been identified in mammalian species and TGF-β1 is the most commonly found in humans. Normally, TGF-β1 release ceases by feedback mechanisms when the healing process has been completed . However, if TGF-β1 release is not switched off, extracellular matrix components (ECM) are accumulated and tissue fibrosis occurs . TGF-β1 is involved in the development of scarring in crescentic nephritis via activation of myofibroblasts from glomerular parietal epithelial cells . Interstitial myofibroblasts also contribute to the development of fibrous crescents through their migration into the Bowman's space of glomeruli with disrupted capsules . The implication of TGF-β1is further supported by the observation of amelioration of histologic damage in experimentally induced anti-GBM nephritis with the blockade of TGF-β1 action ***(Dimitrios S Goumenos et al., 2005).***

Since the discovery of the central role of transforming growth factor (TGF)-β in fibrotic kidney disease , urinary TGF-

β activity has been studied in experimental models of kidney disease together with renal TGF-β mRNA and protein expression, and indexes of fibrosis . A simultaneous increase in urinary TGF-and glomerular TGF-β mRNA and protein was observed in a rabbit model of an antibody- mediated crescentic nephritis. In people with various glomerular diseases, urinary TGF-_ correlated with the grade of interstitial fibrosis. In patients with membranous glomerulonephritis, urinary TGF-β1 at baseline was lower in those patients who later reached remission than in patients whose disease had a more progressive course. In type 2 diabetic patients, urinary TGF-_1 is elevated and associated with histologically proven severe mesangial expansion ***(Korpinen E. et al., 2000)***.

Aim of the Work

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The aim of our work is study the urinary TGF-β1 excretion in children and adolescents with type-1 diabetes and its relation with the 2 conventional markers of glomerular and tubular injury; urinary albumin and α1-microglobulin.Also to assess the relation between urinary TGF- β1 excretion with parameters of glycemic control as HbA1c.