EARLY DETECTION OF DIABETIC NEPHROPATHY

An Essay

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BY

Mustafa Fottoh Alshirbeny

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SUPERVISORS

Prof. Dr.

MOHAMMED ABDEL RAHMAN ABDEL HAMED

Professor of Internal Medicine
Faculty of Medicine
Cairo University

Prof. Dr.

MOHAMED AHMED EISSA

Professor of Internal Medicine
Faculty of Medicine
Cairo University

FACULTY OF MEDICINE
Cairo UNIVERSITY
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ABSTRACT

Diabetic nephropathy is one of the major "microvascular" complications of diabetes and the most common single cause of end-stage renal disease (ESRD).

Hyperglycemia, increased blood pressure level and genetic predisposition are the main risk factors for the development of diabetic nephropathy. Elevated serum lipids, smoking habits, amout and origin of dietary protein also seem to play a role as a risk factors.

Diabetic nephropathy is characterized by a prolonged clinical latency period that lasts for years, a major barrier in DNP research is the absence of targeted investigation of molecular and cellular changes that occur in kidneys of individuals with new onset of diabetes.

Key Words:
Diabetes Mellitus, Complications of Diabetes, Diabetic Nephropathy (Dnp), Recent Methods for Early Detection of Diabetic Nephropathy

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List of Abbreviations

ACE	:	Angiotensin-converting-enzyme
ADMA	:	Asymmetric form of dimethylarginine
ADRP	:	Adipocyte differentiation-regulated protein
AER	:	Albumin excretion rate
AGEs	:	Advanced glycation end products
AKR1B1	:	Aldose reductase gene
APOE	:	Apolipoprotein E gene
ARB	:	Angiotensin receptor blocker
Betaig-h3	:	Beta-induced protein h3
CE-MS	:	Capillary electrophoresis coupled to mass spectrometry
CNDP1	:	Carnosinase gene
CKD	:	Chronic kidney disease
DNP	:	Diabetic nephropathy
ECM	:	Extracellular matrix
ELISA	:	Enzyme-Linked Immunosorbent Assay
ELMO1	:	Engulfment and cell motility 1
EPO	:	Erythropoietin gene
ESRD	:	End stage renal disease
FABP2	:	Fatty acid-binding protein
FIND	:	Family Investigation of Nephropathy and Diabetes
FPG	:	Fasting plasma glucose
GAD	:	Flutamic acid decarboxylase
GDM	:	Gestational diabetes mellitus
GFR	:	Glomerular filtration rate
Gpx3	:	Glutathione peroxidase 3
HbA1c	:	Glycosylated hemoglobin
HDL	:	High-density lipoproteins
HLA	:	Human leukocyte antigen
IDOenzyme	:	Indoleamine 2, 3-dioxygenase
IFG	:	Impaired fasting glucose
IGF	:	Insulin like growth factor
Jak-2	:	Janus kinases-2
LDL	:	Low-density lipoproteins
LMW-AGEs	:	Low molecular weight Advanced glycation end products

LOD	:	Likelihood of dysequilibrium
MCP-1	:	Chemokine monocyte chemoattractant protein-1
MHC	:	Major histocompatibility complex
MI	:	Myo-inositol
MIOX	:	Myo-inositol oxygenase
NKF	:	National kidney foundation
NO	:	Nitric oxide
NOS_3	:	Endothelial nitric oxide synthase
OGTT	:	Oral glucose tolerance test
PKC	:	Protein kinase C
PPARG2	:	Peroxisome proliferator-activated receptor gamma 2
PRMTs	:	Protein arginine methyltransferases
RAS	:	Renin-angiotensin system
ROS	:	Reactive oxygen species
SDMA	:	Symmetric form of dimethylarginine
SLC2A1	:	Glucose Transporter 1 gene
SNP	:	Single nucleotide polymorphism
STAT	:	Signal transducers and activators of transcription
TGF-β1	:	Transforming growth factor β1
UAE	:	Urinary albumin excretion
UbA52	:	Ubiquitin protein
UKPDS	:	United Kingdom Perspective Study
VEGF	:	Vascular endothelium growth factors
WHO	:	World health organisation
1H NMR	:	Proton nuclear magnetic resonance
2hrPPG	:	Two hours post-prandial glucose

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INTRODUCTION

Diabetes mellitus is a chronic illness that requires continuing medical care and patient self-management to prevent acute complications and to reduce the risk of long-term complications of retinopathy, nephropathy and/or neuropathy (***Collins et al.,2005***).

Diabetic nephropathy (DNP) is by far the most common cause of end stage renal disease (ESRD). Approximately one third of individuals with diabetes develop DNP with a high likelihood of progression to ESRD. In addition, DNP is associated with considerably increased cardiovascular disease risk and mortality. Thus, the public health burden from DNP is enormous. Current evidence suggests that both genetic and environmental factors determine susceptibility to develop DNP and the risk for and rate of progression of DNP(***Jones et al .,2005***).

Epidemiologic studies have shown that DNP is strongly clustered in families and that race has a major effect on DNP susceptibility and rate of progression, firmly establishing the importance of genetic risk factors in the development of DNP (***Ng DP et al.,2005***).

Currently available therapeutic approaches are focused on blockade of the renin-angiotensin system (RAS). Thus, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are able to slow the rate of progression but do not arrest or reverse the disease (***Brenner et al.,2001***).

Moreover, RAS blockade is usually initiated only after DNP manifests itself clinically with persistent proteinuria in both type 1 and type 2 diabetes. However, the initiating pathomechanisms of DNP precede the clinical onset considerably. Indeed, it is possible that molecular and cellular changes that eventually lead to clinical DNP are present in kidneys of

individuals who already are at risk shortly after the onset of diabetes. For example, several studies suggest that reduction of podocyte numbers per glomerulus is detectable early in the course of both type 1 and type 2 diabetes and is a strong predictor of subsequent proteinuria (***Steffes et al.,2001***).

In recent years, biomarker discovery has been booming, mainly due to there has been a considerable shift in clinical medicine from trying to treat chronic debilitating conditions (including diabetes, cancer, and renal disease), which has not been very successful, to early diagnosis and prevention, which has been far more successful in the area of various cancer types and cardiovascular disease.Thus genetics, genomics, proteomics, and metabolomics are preferentially used in biomarker discovery (***Gershon et al.,2002***).

The hope is that these new biomarkers will predict the development of the disease earlier than the currently used disease marker, albuminuria. Low-grade albuminuria (microalbuminuria) is a poor predictor of diabetic nephropathy. high-grade albuminuria, which is a strong predictor of disease progression, only develops at advanced diabetic nephropathy, a stage when less can be done to prevent the development of end-stage kidney failure (***Perkins et al.,2007***).

Large genetics trials have been conducted to find genetic polymorphisms associated with diabetic nephropathy (***Schelling et al.,2008).***

Proteomic analyses probably hold the greatest promise to identify a new diabetic nephropathy biomarker that can be rapidly translated to clinical medicine ***(Sharma et al.,2005).***

Metabolomics is also receiving increasing attention as recent estimates suggest that the human metabolome comprises of 3,000 small molecules, which may carry details about severity and pathogenesis of diabetic nephropathy ***(Mueller et al.,2006).***

Recent advances in proteomics, Metabolomics and genomic enable screening of a vast array of methods simultaneously, aiding assessment of their potential role in the development and progression of diabetic nephropathy (***Fliser et al.,2007***).

AIM OF THE WORK

To evaluate the early detection of diabetic nephropathy to improve designs of preventive clinical trials and for clinical management for individuals affected by diabetes and saving them form reach and stage renal disease.

DIABETES MELLITUS

Definitions:

The term diabetes mellitus describes a metabolic disorders of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrates, fat and protein metabolism resulting from defect in insulin secretion, insulin action or both ***(Valdez et al.,2007).***

Symptoms usually are not severe, or may be absent, and consequently hyperglycemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made.The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease (***Lesli et al.,2006***).

Classification:

The classification of diabetes includes four clinical classes:

- Type 1 diabetes (results from β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g.,
  - Genetic defects of beta-cell function
  - Genetic defects in insulin action
  - Diseases of the exocrine pancreas

- Endocrinopathies
- Drug- or chemical-induced
- Infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes sometimes associated with DM

↳ Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy) ***(Shaw et al.,2001).***

Type 1 diabetes mellitus is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency. The onset is usually acute, developing over a period of a few days to weeks.Over 95 percent of persons with type 1 diabetes mellitus develop the disease before the age of 25, with an equal incidence in both sexes and an increased prevalence in the white population ***(Harrison et al.,2003).***

Type 2 diabetes mellitus is characterized by insulin resistance in peripheral tissue and an insulin secretory defect of the beta cell. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. It is more common in women, especially women with a history of gestational diabetes, and in blacks, Hispanics and Native Americans. Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance.Defective beta cells become exhausted, further fueling the cycle of glucose intolerance and hyperglycemia ***(Esposito et al., 2009).***

Types of diabetes mellitus of various known etiologies are grouped together to form the classification called "other specific types." This group includes persons with genetic defects of beta-cell function or with defects of insulin action, persons with diseases of the exocrine pancreas such as

pancreatitis or cystic fibrosis, persons with dysfunction associated with other endocrinopathies (e.g., acromegaly), and persons with pancreatic dysfunction caused by drugs, chemicals or infections ***(Valdez et al.,2007).***

Diagnosis:

The fasting plasma glucose (FPG) is the preferred test to diagnose diabetes in children and non pregnant adult (***Nathan et al.,2007***).

Table 1: Criteria for the Diagnosis of Diabetes Mellitus and Impaired Glucose Homeostasis.

Diabetes mellitus--positive findings from any two of the following tests on different days: Symptoms of diabetes mellitus plus casual plasma glucose concentration >=200 mg per dL (11.1 mmol per L) *or* FPG >=126 mg per dL (7.0 mmol per L) *or* two hours post-prandial glucose(2hrPPG) >=200 mg per dL (11.1 mmol per L) after a 75-g glucose load
Impaired glucose homeostasis Impaired fasting glucose(IFG): FPG from 110 to <126 (6.1 to 7.0 mmol per L) Impaired glucose tolerance: 2hrPPG from 140 to <200 (7.75 to <11.1 mmol per L)
Normal FPG <110 mg per dL (6.1 mmol per L) 2hrPPG <140 mg per dL (7.75 mmol per L)

(Hamman et al.,2006).