Risk factors for diabetic nephropathy in diabetic patients with proliferative retinopathy

Thesis
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قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
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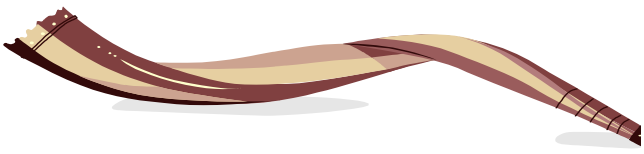

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List of Abbreviations

AAO	: American academy of ophthalmology
ACE	: Angiotensin converting enzyme
ACR	: Albumin /creatinine ratio
ADA	: American diabetic association
AGEs	: Advanced glycation end products
ARB	: Angiotensin receptor blocker
CKD	: Chronic kidney disease
CSME	: Clinically significant macular oedema
CWS	: Cotton wool spots
DCCT	: Diabetes control and complicatins trial
DM	: Diabetes mellitus
DME	: Diabetic macular oedema
DN	: Diabetic nephropathy
DR	: Diabetic retinopathy
ECM	: Extracellular matrix
ESRD	: End stage renal diease
ET-1	: Endothelin 1
ETDRS	: Early treatment diabetic retinopathy study
GFR	: Glomerular filtration rate
HDL	: High density lipoprotein
Hex	: Hard exudates
IRMA	: Intraretinal microvascular abnormalities
KDOQI	: Kidney disease outcome quality initiative
LDL	: Low density lipoprotein
Ma	: Micro aneurysms
NADPH	: Nicotinamide adenine dinuclutide phosphate
NF-KB	: Nuclear factor kappa-high chain enhancer of activated B cells
NO	: Nitric oxide
NPDR	: Non proliferative diabetic retinopathy
NVD	: New vessles on the disk
NVE	: New vessles elsewhere
PKC	: Protein kinase C
RAGES	: Receptor for Advanced glycation end products

List of Abbreviations

RAS	: Renin angiotensin system
RENAAL	: Reduction of end points in NIDDM with angiotensin 2 antagonist losartan
ROS	: Reactive oygen species
TC	: Total cholesterol
TG	: Triglycerides
TGFB	: Transforming growth factor B
UKPDS	: UK prospective diabetes study
UT	: Urotensin
VEGF	: Vascular endothelial growth factor
WESDR	: Wiscosin epidemiological study of diabetic retinopathy

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Introduction

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 DM is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels ***(Genuth et al., 2003).***

All forms of DM increase the risk of long-term complications. These typically develop after many years, but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications are related to the damage of the blood vessels. DM doubles the risk of the "macrovascular" diseases related to atherosclerosis of larger arteries including ischemic heart disease ,stroke and peripheral vascular disease***(Sarwar et al., 2010).***

Diabetes also causes "microvascular" complications, Diabetic retinopathy, which affects the blood vessels of retina, can lead to visual symptoms, reduced vision, and potentially blindness. Diabetic nephropathy can lead to loss of small or progressively larger amounts of albumin in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy is the impact of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation***(Boussageon, 2011).***

The major microvascular complications of DM, i.e, retinopathy and nephropathy, are the most important causes of blindness and end-stage renal disease worldwide. Diabetic nephropathy is the most common cause of endstage renal disease in many countries, and it follows a well-defined clinical course, starting with microalbuminuria through proteinuria and azotaemia, and culminating in end-stage renal failure (ESRF). However, not all subjects with diabetic nephropathy progress through these stages. Risk factors such as duration of diabetes mellitus, tightness of glycaemic control and blood pressure are implicated in the pathogenesis of diabetic nephropathy. Other less important risk factors are smoking, dyslipidaemia, and dietary factors ***(Gross et al., 2005).***

Nearly all patients with Type I DM and more than 60% of patients with Type II DM have some degree of retinopathy after 20 years of diabetes. In contrast to retinopathy, Diabetic nephropathy does not develop in about 50% of patients with DM, even when high glucose levels are maintained for long periods of time. This suggests that only a subset of diabetic patients is at risk of developing renal disease ***(Magri et al., 2012).***

Aim of Work

The aim of this study is to compare the clinical and the laboratory findings in diabetic patients with both diabetic retinopathy and nephropathy with those of patients with retinopathy but no nephropathy. Hence, we could study which factors are truly associated with diabetic nephropathy, rather than with microvascular disease in general.

Diabetic Nephropathy

Diabetic kidney disease is a glomerulopathy defined by characteristic structural and functional changes. The predominant structural changes include mesangial expansion, glomerular basement membrane thickening, and glomerular sclerosis. The major clinical manifestations of diabetic nephropathy are albuminuria and, in many patients, progressive chronic kidney disease ***(De Boer et al., 2011).***

Diabetic nephropathy is the most common cause of endstage renal disease, it follows a well-defined clinical course as shown in table (1), starting with microalbuminuria through proteinuria and azotaemia, and culminating in end-stage renal failure (ESRF). However, not all subjects with diabetic nephropathy progress through these stages***(Gross et al., 2005).***

Table (1): Stages of diabetic nephropathy***(Gross et al., 2005).***

	Designation	Characteristics	GFR (minimum)	Albumin Excretion
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>300 mg/d
Stage 5	Uremic	ESRD	0-10	Decreasing

Renal Pathology Society classification of diabetic nephropathy

Four classes of glomerular lesions were defined:

Class I: Isolated glomerular basement membrane thickening. Basement membranes are greater than 430 nm in males older than age 9 and 395 nm in females. There is no evidence of mesangial expansion, increased mesangial matrix, or global glomerulosclerosis involving >50 percent of glomeruli.

Class II: Mild (class IIa) or severe (class IIb) mesangial expansion. A lesion is considered severe if areas of expansion larger than the mean area of a capillary lumen are present in >25 percent of the total mesangium.

Class III: At least one Kimmelstiel-Wilson lesion (nodular intercapillary glomerulosclerosis) is observed on biopsy and there is <50 percent global glomerulosclerosis.

Class IV: Advanced diabetic sclerosis. There is >50 percent global glomerulosclerosis that attributable to diabetic nephropathy ***(Tervaert et al., 2010).***

Pathogenesis of diabetic nephropathy

Diabetic nephropathy is also known as Kimmelstiel Wilson syndrome and it was discovered in 1936 by Clifford Wilson and Paul Kimmelstiel. It occurs as a result of an interaction between hemodynamic and metabolic factors ***(Arya et al., 2010).***

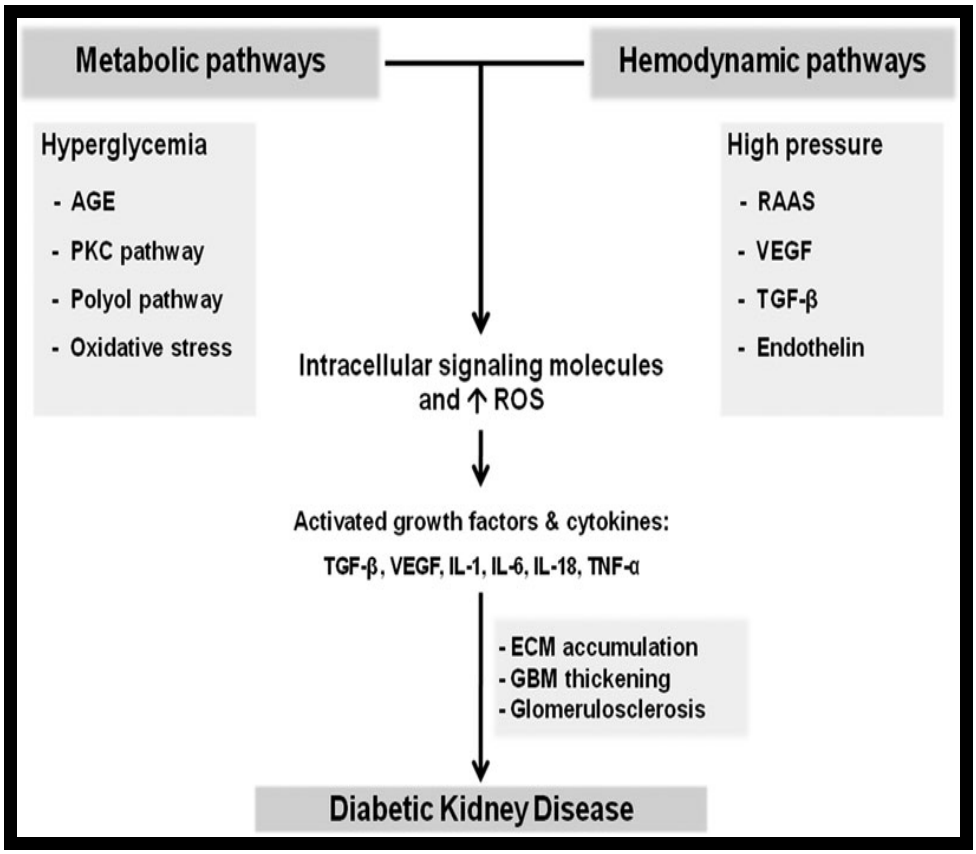

Fig (1):Pathogenesis of diabetic nephropathy. Diabetic nephropathy occurs as a result of an interaction between hemodynamic and metabolic factors ***(Arya et al., 2010)***

HEMODYNAMIC PATHWAYS

Glomerular hyperperfusion and hyperfiltration are the early signs resulted from decreased resistance in both the afferent and efferent arterioles of the glomerulus. Afferent arteriole seems to have agreater decrease in resistance than the efferent. Many factors have been reported to be involved in this faulty autoregulation , including nitric oxide ,prostanoids ,vascular endothelial growth factor (VEGF), TGF-β1, and the rennin angiotensin system, specifically angiotensinII. These early hemodynamic changes alleviate albumin leakage from the glomerular capillaries and overproduction of mesangial cell matrix, as well as thickening of the glomerular basement membrane and injury to podocytes ***(Ziyadeh and Wolf, 2008).***

In addition, increased mechanical strain from these hemodynamic changes can induce localized release of certain cytokines and growth factors ***(Wolf and Ziyadeh, 2007).***

Hemodynamic factors that contribute to the development of diabetic nephropathy include increased systemic and intraglomerular pressure, as well as activation of vasoactive hormone pathways including the renin angiotensin system and endothelin. These hemodynamic pathways activate intracellular second messengers such as protein kinase C (PKC), Mitogen-activated protein (MAP kinase), nuclear transcription factors such as NF-kB, and various growth factors such as the prosclerotic cytokine, TGF-β , permeability