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Review Article

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Risk Factors and Pathogenesis of Diabetic Nephropathy

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Abstract

Nephropathy is a chronic complication characterized by increased urinary albumin excretion (proteinuria) or reduced kidney glomerular filtration rate in both forms of diabetic mellitus, type 1 diabetes mellitus and type 1 diabetes mellitus. Diabetic nephropathy is categorized into stages so called microalbuminuria (urinary albumin excretion greater than 20 g/min and less than or equal to 199 g/min) and macroalbuminuria (urinary albumin excretion greater than or equal to 200 g/min). Hyperglycemia, increased blood pressure levels, and genetic predispositions are the main risk factors for the development of diabetic nephropathy. Nephropathy occurs as a result of an interaction between metabolic and hemodynamic factors, which activate diverse pathways that lead to renal damage. Growing evidence highlights the importance of inflammatory mechanisms in the development and progression of diabetic nephropathy. Therefore, investigation into antiinflammatory strategies may offer new approaches of further effect.

Keywords: Diabetic nephropathy; Pathogenesis, Risk factors

Introduction

Diabetes mellitus is a serious, chronic metabolic disorders that characterized by high sugar level either when the pancreas does not produce enough insulin, or when the body cannot effectively use insulin [1]. Complications of diabetes mellitus are progressive and almost resulting by chronic exposure to high blood levels of glucose caused by impairments in insulin metabolism and biological macromolecules such as carbohydrates, lipids, proteins and nucleic acids [1]. Nephropathy is a chronic complication characterized by increased urinary albumin excretion (proteinuria) or reduced kidney glomerular filtration rate in both forms of diabetic mellitus, type 1 diabetes mellitus and type 1 diabetes mellitus [2, 3]. This nephropathy has a long natural history in type 1 diabetes. Initially, the patient shows hyperfiltration, represented by high values of glomerular filtration rate, approximately doubling of the normal value, and occasional occurrence of microalbuminuria [4]. Diabetic nephropathy is a major cause of end stage renal disease, and the incidence of diabetes mellitus is rising rapidly [5]. The natural history of diabetic nephropathy differs according to the type of diabetes and whether microalbuminuria (defined as >30 mg but 300 mg albumin excreted daily), whereas only 20–40% of those with type 2 diabetes over a period of 15 years will progress [6, 7]. 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 in the absence of other renal diseases. Diabetic nephropathy is categorized into stages so called microalbuminuria (urinary albumin excretion greater than 20 g/min and less than or equal to 199 g/min) and macroalbuminuria (urinary albumin excretion greater than or equal to 200 g/min). The cutoff values adopted by the American Diabetes Association (time, 24-hour, and spot urine collection) for the diagnosis of micro- and macroalbuminuria. Progression to micro- or macroalbuminuria was more frequent in patients with type 2 diabetes with baseline urinary albumin excretion above the median (2.5 mg/24 hour). After 10 years of follow-up, the risk of diabetic nephropathy was 29 times greater in patients with type 2 diabetes with urinary albumin excretion values 10 g/min. Hyperglycemia, increased blood pressure levels, and genetic predispositions are the main risk factors for the development of diabetic nephropathy. Hypertension, poor glycemic control, and albuminuria, the main known risk factors for diabetic nephropathy, do not explain all of the inter-individual variability for the rates of developing nephropathy. Elevated serum lipids, smoking habits, and the amount and origin of dietary protein also seem to play a role as risk factors [8]. Proteinuria was seen in about 30% of type 1 diabetes patients and 40% of type 2 diabetes patients. It's also the major source of end-stage renal disease development in the world, accounting for about 40% of new renal replacement therapies [2, 9].

Table 1: Diabetic nephropathy stages: cutoff values of urine albumin for diagnosis and main clinical characteristics [8].

Stages	Albuminuria cutoff values	Clinical characteristics
Microalbuminuria	20–199 g/min	Increased frequency of metabolic syndrome components
	30–299 mg/24 h	Endothelial dysfunction
	30–299 mg/g*	Association with diabetic retinopathy, amputation, and cardiovascular disease Increased cardiovascular mortality Stable GFR Abnormal nocturnal decrease of blood pressure and increased blood pressure levels Increased triglycerides, total and LDL cholesterol, and saturated fatty acids
Macroalbuminuria	200 g/min	Hypertension
	300 mg/24 h	Increased triglycerides and total and LDL cholesterol
	300 mg/g*	Asymptomatic myocardial ischemia Progressive GFR decline

Diabetes causes unique changes in kidney structure. Classic glomerulosclerosis is characterized by increased glomerular basement membrane width, diffuse mesangial sclerosis, hyalinosis microaneurysm, and hyaline arteriosclerosis. Micro- and macroalbuminuric patients with type 2 diabetes mellitus have more structural heterogeneity than patients with type 1 diabetes mellitus. Diabetic nephropathy is characterized by glomerular hypertrophy, thickness of basement, tubular and glomerular membranes and accumulation of extracellular matrix in these membranes that finally cause tubulointerstitial and glomerular fibrosis and sclerosis. There is a response for hyperglycemia from the system, the transcription factors regulate the gene encoding some cytokines like transforming growth factor β, chemokine C-C motif ligand 2, fibronectin, osteopontin, decorin, thrombospondin, aldose reductase and plasminogen activator inhibitor 1, all these molecules involved in inflammation, extracellular matrix synthesis and its degradation are increased in type-2 diabetes mellitus. Diabetic patients then could have albuminuria since early phases or stages of organ damage, it is also considered as a very sensible marker of kidney disease progression. As a result, there are many glomerular abnormalities including podocyte structure alteration, reduction of nephrin expression and increase of filtration rate, a hallmark of diabetic retinopathy [10-15].

Multiple mechanisms contribute to the development and outcomes of diabetic nephropathy, such as an interaction between hyperglycemia induced metabolic and hemodynamic changes and genetic predisposition, which sets the stage for kidney injury.8 Hemodynamic factors are the activation of various vasoactive systems, such as the renin–angiotensin–aldosterone and endothelin systems. In response, secretion of profibrotic cytokines, such as transforming growth factor β1, is increased and further hemodynamic changes occur, such as increased systemic and intraglomerular pressure. Metabolic pathway involvement, among other features, leads to non-enzymatic glycosylation, increased protein kinase C activity, and abnormal polyol metabolism [16, 17]. Sustained prorenin-receptor blockade abolished mitogen-activated protein kinases activation and prevented the development of nephropathy despite an unaltered increase in angiotensin II activity [18-20]. Nephropathy occurs as a result of an interaction between metabolic and hemodynamic factors, which activate diverse pathways that lead to renal damage. Growing evidence highlights the importance of inflammatory mechanisms in the development and progression of diabetic nephropathy. Therefore, investigation into antiinflammatory strategies may offer new approaches of further effect [21-25].

Conclusion

Diabetic nephropathy is a major cause of end stage renal disease, and the incidence of diabetes mellitus is rising rapidly. Elevated serum lipids, smoking habits, and the amount and origin of dietary protein also seem to play a role as risk factors. Diabetic nephropathy is characterized by glomerular hypertrophy, thickness of basement, tubular and glomerular membranes and accumulation of extracellular matrix in these membranes that finally cause tubulointerstitial and glomerular fibrosis and sclerosis. There is a response for hyperglycemia from the system, the transcription factors regulate the gene encoding some cytokines like transforming growth factor β, chemokine C-C motif ligand 2, fibronectin, osteopontin, decorin, thrombospondin, aldose reductase and plasminogen activator inhibitor 1, all these molecules involved in inflammation, extracellular matrix synthesis and its degradation are increased in type-2 diabetes mellitus.

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