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Review

Management of diabetic nephropathy: Recent progress and future perspective

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ABSTRACT

Diabetic nephropathy (DN), a leading cause of end-stage renal disease (ESRD) affecting ~20–30% diabetics, is associated with increased cardiovascular mortality. The progression of kidney disease in patients with diabetes can take many years. It occurs as a result of interaction between both genetic and environmental factors in individuals with both type 1 and type 2 diabetes. Hyperglycaemia, hypertension, and genetic pre-disposition are the main risk factors besides elevated serum lipids, smoking habits, and the amount of dietary proteins. Interventions such as glycaemic control, blood pressure control and inhibition of the renin–angiotensin–aldosterone system have been shown to slow this progression. Despite the implementation of these strategies, the number of patients with diabetes that ultimately develop end-stage renal disease remains high. The treatment of DN, therefore, has posed a formidable challenge besides optimization of renin–angiotensin–aldosterone system blockade in patients with DN; additional investigation has focused on the potential of novel therapies that target various pathways upregulated by hyperglycaemia or other targets believed to promote the progression of DN such as oxidative stress, inflammation, endothelin system and vitamin D receptors. This review article addresses the pathogenesis and some of the well established principles regarding the progression and accepted management of DN, and also includes the perspectives of novel anti-DN agents and the future directions for the prevention of DN.

Contents

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1. Introduction

With the worldwide increase in the prevalence of diabetes in recent years, diabetic nephropathy (DN), a common complication in patients with both type 1 and type 2 diabetes, is the leading cause of end-stage renal disease (ESRD). In 2013, there were 347 million people with diabetes all over the world, and WHO projects that diabetes will be the seventh leading cause of death by 2030 [1]. The incidence is increasing particularly with the improvement of living standard and the change in lifestyle. Approximately one-third of all diabetic individuals are affected by DN [2], which produces significant social and economic burden.

Glycaemic control, blood pressure control, and inhibition of the renin–angiotensin–aldosterone system (RAAS) have been shown to slow the progression of DN; however, the specific regimes to use, which optimally implement these strategies, remain uncertain, and the incidence of the overall progression of DN to ESRD remain unacceptably high. This article will review and discuss the natural progression of DN, pathogenesis, management and the recent trials involving some of the emerging therapeutic options that may potentially impact the management of DN [3].

2. Definition and epidemiology

Diabetic nephropathy (DN) is typically defined by macroalbuminuria (>300 mg in a 24-h collection) or microalbuminuria and abnormal renal function as represented by abnormality in serum creatinine, calculated creatinine clearance, or glomerular filtration rate (GFR). Clinically DN is characterized by hypertension, progressive albuminuria, decline in GFR, and a high risk of cardiovascular morbidity and mortality.

Attributing impaired renal function to diabetes typically requires either a biopsy diagnosed (gold standard) or presence of constellation of clinical findings. The classic features of DN most commonly seen in patients with type 2 diabetes mellitus are Kimmelstiel–Wilson nodules and nodular glomerulosclerosis. The likelihood that this pattern will be present on renal biopsy is increased in the context of both albuminuria and diabetic retinopathy [4]. Lesions that can be seen earlier in the course of DN in patients with both type 1 and type 2 diabetes include glomerular basement membrane thickening and mesangial expansion [5]. A renal biopsy may be deferred with the assumed diagnosis of DN in the context of macroalbuminuria that has developed progressively and microalbuminuria in patients with diabetes for more than 10 years [6]. The presence of hematuria, nephrotic range proteinuria at the time of diagnosis of diabetes, or the presence of other systemic disease process including autoimmune disease warrant the consideration of another potentially treatable condition that will require a renal biopsy to diagnose.

In the early 1980s, seminal studies from Europe revealed that small amounts of albumin in the urine, not usually detected by conventional method, were predictive of proteinuria in type 1 [7–9] and type 2 (10) diabetic patients. This stage of renal involvement was termed microalbuminuria or incipient nephropathy. The cumulative incidence of microalbuminuria in type 1 diabetic patients was 12.6% over 7.3 years according to the European Diabetes (EURODIAB) Prospective Complication Study Group [11] and ~33% in an 18-year follow-up study in Denmark [12]. In patients with type 2 diabetes, the incidence of microalbuminuria was 20% per year and the prevalence was of 25%, 10 years after the diagnosis in U.K. Prospective Diabetes Society [13]. Proteinuria occurs in 15–40% of patients with type 2 diabetes; the prevalence is highly variable, ranging from 5% to 20% [13,14].

3. Stages of kidney disease in diabetes

Diabetic nephropathy has been categorized into stages based on the values of urinary albumin excretion (UAER): microalbuminuria and macroalbuminuria. Microalbuminuria is an early sign of renal microvascular disease in diabetes, being a powerful predictor of cardiovascular disease and early mortality. The evolution of DN proceeds through several distinct but interconnected phases, an early phase, and a clinical phase of persistent clinical albuminuria progressing to a decline in GFR and ultimately to ESRD (Table 1).

3.1. Hyperfiltration

Soon after the diagnosis of type 1 diabetes, several renal abnormalities may be observed. Supra-normal values of renal plasma flow and glomerular hyperfiltration (GFR above 135 ml/min/m^2) are found in 20–40% of patients [16]. Hypertension and albuminuria are typically not present in this phase. Although included as the first of five categories in Mogenson's Classification of DN [17], hypertension is not specifically addressed in the five categories of CKD in the KDOQ 1 guidelines. This could be in part because creatinine-based formulas underestimate GFR at high levels and because direct measurements of GFR are not used routinely. The hyperfiltration is partially related to poor metabolic control and intensification of glycaemic control reduces GFR towards normal. An increase in kidney size (nephromegaly) is a pre-requisite for hyperfiltration but its prognostic significance remains unclear. The increase in GFR is accounted for by an