Diabetes

Prognosis and treatment of diabetic nephropathy: Recent advances and perspectives

Peter Rossing a,b,∗, Frederik Persson a, Marie Frimodt-Møller a

a Steno Diabetes Center Copenhagen, Niels Steensens Vej 2, 2820 Gentofte, Denmark
b Department of Clinical Medicine, University of Copenhagen, 2200 Copenhagen, Denmark

Article history:
Received 29 December 2017
Accepted 1st February 2018

Keywords:
Diabetes
Nephropathy
Albuminuria
Screening
Epidemiology
Intervention

Abstract

Approximately 20 to 40% of patients with type 1 or type 2 diabetes develop diabetic kidney disease. It is a clinical syndrome characterized by persistent albuminuria (> 300 mg/24 h, or 300 mg/g creatinine), a relentless decline in glomerular filtration rate, raised arterial blood pressure, and enhanced cardiovascular morbidity and mortality. The natural course of classical diabetic nephropathy is initially microalbuminuria or moderately increased urine albumin excretion (30–300 mg/g creatinine). Untreated microalbuminuria may then rise gradually, reaching severely increased albuminuria (macroalbuminuria) over 5 to 15 years. Glomerular filtration rate then begins to decline and end-stage renal failure is reached without treatment in 5 to 7 years. Regular, systematic screening for diabetic kidney disease is needed to identify patients at risk, or with symptomatic stages of diabetic kidney disease. Multifactorial intervention targeting glucose, lipids, and blood pressure including blockade of renin angiotensin system and lifestyle, has improved renal and cardiovascular prognosis and reduced mortality with 50%. Recent data suggest beneficial pleiotropic effects on renal endpoint with new glucose lowering agents. It is also being investigated if blocking aldosterone could be an option as a potential new treatment. Thus, although diabetic nephropathy remains a major burden, prognosis has improved and new options for further improvements are currently tested in phase 3 clinical renal outcome studies.

© 2018 Société francophone de néphrologie, dialyse et transplantation. Published by Elsevier Masson SAS. All rights reserved.

1. Background

Diabetic kidney disease is a major cause of morbidity and mortality in diabetes. Indeed, the excess mortality of diabetes occurs mainly in proteinuric diabetic patients and results not only from end-stage renal disease but also from cardiovascular disease, with the latter being particularly common in type 2 diabetic patients [1–3]. Diabetic kidney disease is clinically characterized by progressive kidney damage reflected by increasing albuminuria, impairment in renal function (decline in glomerular filtration rate), elevated blood pressure and excess morbidity and mortality due to cardiovascular complications. Diabetic kidney disease rarely develops in patients with type 1 diabetes before 10 years after diagnosis, whereas approximately 3% of patients with newly diagnosed type 2 diabetes already have overt nephropathy [4]. Diabetic kidney disease is the single most common cause of end-stage renal disease in many parts of the world including Europe, Japan and the United States, with diabetic patients accounting for 25 to 45% of all patients enrolled in end-stage renal disease programs [5]. While other complications related to diabetes have been reported to decline in recent years, this has only to a smaller extent been the case for diabetic nephropathy, perhaps because people are surviving to end stage renal disease as cardiovascular prognosis has improved, or because there is still an unmet need for better treatment [6].

Since not all persons with diabetes develop all complications, and as many complications are initially without symptoms, relevant systematic screening for occurrence of various complications has become an important part of diabetes care today. Detection of early stages of complications allows for more focused preventive treatment or even specific treatment that can delay further progression of an early manifestation of a complication. A major part of treatment for diabetes is preventive. In essence, the effort to reduce blood glucose and maintain glucose control is a preventive action in order to prevent classical micro- and macrovascular complications.
Screening, diagnosis and treatment of diabetic kidney disease has improved substantially over the last three decades, improving both time to diagnosis of diabetic kidney disease as well as life years gained after diagnosis [7,8]. To further improve these variables, current research seeks to develop new methods for early detection of diabetic kidney disease as well as improved treatment.

2. Definition

Diabetic nephropathy is defined in both type 1 and type 2 diabetes as the presence of persisting severely elevated albuminuria of more than 300 mg/24 h (or more than 200 μg/min) or an albumin/creatinine ratio > 300 mg/g creatinine, confirmed in at least two out of three samples, with concurrent presence of diabetic retinopathy and absence of signs of other forms of renal disease [9]. As such, it is a clinical diagnosis, requiring little more than basic clinical and laboratory evaluations. Normal value for albuminuria has been defined as less than 30 mg/g (or 30 mg/24 h), and abnormal values above 30, but albuminuria is a continuous measurement and increasing values within the normal and abnormal range are associated with elevated risk for renal and cardiovascular disease [10]. Presence of moderately elevated albuminuria (microalbuminuria) (between 30 and 299 mg/g) is widely regarded as a precursor of diabetic nephropathy, both indicating early risk and providing a target for intervention, although in some cases, microalbuminuria can display remission either spontaneously or due to treatment [11–13], an event that indicates better renal risk as compared to progression of albuminuria.

A broader term: ‘kidney disease in diabetes’, is used for diabetes patients with chronic kidney disease (impaired renal function eGFR < 60 mL/min/1.73m² or proteinuria) regardless of the background. Although impaired renal function with normal albuminuria (ACR < 30 mg/g) is prevalent, particularly in elderly subjects, it is much less likely to progress if albuminuria is not present [14,15].

The Italian RIACE study of over 15,000 type 2 diabetic subjects suggested that patients with elevated albuminuria display the typical microvascular phenotype, whereas the nonalbuminuric subjects with impaired renal function had a more cardiovascular or macrovascular phenotype [14].

For chronic kidney disease in general, including diabetes, it has been recommended to stage the severity using a combination of etiology (if known), level of urinary albumin excretion and estimated glomerular filtration rate stage [16].

The National Kidney Foundation KDOQI work group for diabetes and chronic kidney disease suggested that absence of retinopathy, fast deterioration of glomerular filtration rate, rapidly increasing albuminuria or nephrotic range albuminuria (more than 2500 mg/g), active urinary sediments, refractory hypertension and signs or symptoms of other systemic diseases should raise suspicion of non-diabetic causes of chronic kidney disease [17].

3. Prevalence

The global DEMAND study, published in 2006, used a dipstick method to assess presence of albuminuria in a referred cohort of more than 24,000 patients with type 2 diabetes without known albuminuria from 33 countries and found an overall global prevalence of macroalbuminuria of 10% with some variations between regions [18]. Moreover, presence of microalbuminuria was 39%, demonstrating incipient or overt diabetic nephropathy in approximately 50% of the population. Furthermore, 22% had eGFR < 60 mL/min/1.73m². Although the methodology cannot be regarded as robust, it provides one of few global pictures of global prevalence of diabetic nephropathy.

A number of population based cohorts and data from clinical centers have provided more detailed and thorough descriptions of nephropathy in both type 1 and type 2 diabetes. In short, the prevalence of severely elevated albuminuria (macroalbuminuria) in type 2 diabetes clinics ranges from 5 to 48% (median: 14%) and from 8 to 22% (median: 15) in type 1 diabetes patients. Similarly, moderately elevated albuminuria (microalbuminuria) is prevalent in a median 13 and 20% of patients with type 1 and 2 diabetes, respectively [9]. Interestingly however, the most recent publication from NHANES survey points to a declining temporal trend in albuminuria in the US, which may be a results of more focused multifactorial treatment over the last decades [1].

4. Screening

To be able to detect abnormal and/or changing levels of albuminuria and renal function (eGFR), and thereby able to initiate early renoprotective treatment, annual screening of all diabetic patients is recommended [17]. For screening and monitoring early morning spot urine collections are sufficient and most convenient for the patient [10,19]. Due to large (30 to 40%) intraday variability, two out of three spot urine samples within 3 to 6 months must be above the threshold to ascertain the diagnosis. A 24-h collection has been considered gold standard for albuminuria assessment, and can provide additional important information on sodium and protein intake, but complete 24 h urine collection is often difficult and is usually limited to a research setting or to those with established diabetic kidney disease. Urinary albumin excretion may be elevated independent of kidney disease by factors such as severe exercise within 24 h, severe urinary tract infection, menstruation, heart failure and marked hyperglycemia.

The second clinical variable to assess is glomerular filtration rate, in clinical practice most often done by estimation (estimated glomerular filtration rate, eGFR) using serum creatinine-based formulas like the CKD-EPI [20]. This is currently the best validated equation. It has been suggested, that improved estimation can be obtained with an equation including serum creatinine as well as serum cystatin C [21]. A more precise measurement of glomerular filtration rate requires the use of an external marker such as inulin, iothalamate or 99mTc-ethylene diamine tetracetic acid (EDTA) for determination of renal or plasma clearance of the marker [22]. If untreated, the “natural” course of diabetic nephropathy displays a continuing annual decline in estimated glomerular filtration rate between 2 and 20 mL/min/1.73m² (mean 12 mL/min/1.73m²) [23], but proper treatment targeting glycaemia, blood pressure, blocking the renin–angiotensin system and reducing cholesterol and improve life style factors, can reduce progression to 2–5 mL/min/1.73m² per year, demonstrating the importance of screening and intervention [7,8,13].

5. Hyperfiltration

Prior to development of increasing albuminuria, approximately one third of type 1 diabetic patients will have a glomerular filtration rate above the upper normal range for age-matched healthy nondiabetic subjects. The degree of hyperfiltration is less in type 2 diabetic patients and hyperfiltration is even reported to be absent in some studies.

Longitudinal studies suggest that hyperfiltration is a risk factor for subsequent increase in urinary albumin excretion and development of diabetic nephropathy in type 1 diabetic patients (Fig. 1), but conflicting results have also been reported. A meta-