Diabetic Nephropathy

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INTRODUCTION

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States. The frequency of diabetic nephropathy–induced ESRD has increased dramatically, from 7000 new cases in 1984 to more than 41,000 in 2003. This trend has begun to slow somewhat in recent years. However, the number of Americans with diabetes mellitus (DM) rose from 5.8 million in 1980 to 13.8 million in 2003 and is expected to double in the coming decade, mostly as a result of the increased incidence of type 2 DM. In 2003, Medicare spent nearly $17 billion to cover the health expenses of more than 400,000 patients with ESRD, and experts predict an increase in this expenditure to $28.3 billion by 2010.

Nephropathy also is an independent risk factor for development of other diabetic complications, including cardiovascular disease and retinopathy, and it imparts an increased overall risk of morbidity and mortality compared with diabetes alone. Strategies that prevent the development or delay the progression of diabetic nephropathy are of paramount importance.

Between 25% and 40% of patients with diabetes will develop diabetic nephropathy. Risk factors that increase the likelihood of renal complications include persistently elevated blood pressure (BP), poor glycemic control, genetic predisposition including family history and race, hyperlipidemia, and smoking (Table 1). In addition, the degree of albuminuria (proteinuria) predicts the rate of progression of renal dysfunction, with a more rapid decline in kidney function occurring in diabetic patients excreting higher amounts of urinary protein.

Over the past decade and a half, several studies have led to the development of specific interventions that delay progression of diabetic nephropathy. These therapies are most effective when instituted early, making timely detection during the asymptomatic phase crucial for at-risk individuals. This manual presents an overview of diabetic nephropathy and discusses several relevant clinical studies that have evaluated the efficacy of common therapies, with a focus on type 2 DM. In addition, recent recommendations of the American Diabetes Association (ADA), the National Kidney Foundation, and other expert bodies will be discussed.

CLINICAL STAGES OF DIABETIC NEPHROPATHY

Diabetic nephropathy is a disorder characterized by the presence of increased urinary albumin excretion and/or persistently reduced glomerular filtration rate (GFR). The natural progression of diabetic nephropathy has classically been divided into 5 stages (Table 2). Stage 1 is characterized by normal-sized or mildly enlarged kidneys with normal or mildly elevated GFR. Stage 2 is distinguished by the presence of glomerular basement membrane thickening and mesangial expansion on microscopic evaluation of renal biopsy tissue. Stages 1 and 2 are generally clinically silent.

By stage 3, microalbuminuria is present, usually occurring at least 5 to 10 years after the onset of diabetes. A fraction of patients with stage 3 diabetic nephropathy will have spontaneous regression of microalbuminuria. Without treatment, however, patients may progress to stage 4, with overt albuminuria (also referred to as macroalbuminuria or proteinuria) detectable by routine dipstick urinalysis. Stage 4 is associated with a decline in renal function, and the albuminuria is predictive of further decline in GFR. Subsequently, some patients evolve to stage 5, defined as ESRD requiring renal replacement therapy.

This natural history and timeline has been best described in patients with type 1 DM. In the general clinic population, the time of onset of type 2 DM is often unclear and may be delayed by many years. Hence, this group of patients may present with advanced stages of diabetic nephropathy at the time of initial diabetes diagnosis. Additionally, death from cardiovascular disease often precedes progression to advanced renal dysfunction or renal failure in patients with type 2 DM.

SCREENING FOR DIABETIC NEPHROPATHY

Initial screening for diabetic nephropathy requires checking serum creatinine levels and dipstick urinalysis,