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PERSPECTIVES IN RENAL MEDICINE

Renal disease and hypertension in non–insulin-dependent diabetes mellitus

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Renal disease and hypertension in non–insulin-dependent diabetes mellitus. Recent epidemiologic data demonstrate a dramatic increase in the incidence of end-stage renal disease (ESRD) in patients with non-insulin-dependent diabetes mellitus (NIDDM), thus dispelling the mistaken belief that renal prognosis is benign in NIDDM. Currently, the leading cause of ESRD in the United States, Japan, and in most industrialized Europe is NIDDM, accounting for nearly 90% of all cases of diabetes. In addition to profound economic costs, patients with NIDDM and diabetic nephropathy have a dramatically increased morbidity and premature mortality. NIDDM–related nephropathy varies widely among racial and ethnic groups, genders and lifestyles; and gender may interact with race to affect the disease progression. While the course of insulin-dependent diabetes mellitus (IDDM) progresses through well-defined stages, the natural history of NIDDM is less well characterized. NIDDM patients with coronary heart disease have a higher urinary albumin excretion rate at the time of diagnosis and follow-up. This greater risk may also be associated with hypertension and hyperlipidemia, and genes involved in blood pressure are obvious candidate genes for diabetic nephropathy. Hyperglycemia appears to be an important factor in the development of proteinuria in NIDDM, but its role and the influence of diet are not yet clear. Tobacco smoking can also be deleterious to the diabetic patient, and is also associated with disease progression. Maintaining euglycemia, stopping smoking and controlling blood pressure may prevent or slow the progression of NIDDM-related nephropathy and reduce extrarenal injury. Treatment recommendations include early screening for hyperlipidemia, appropriate exercise and a healthy diet. Cornerstones of management should also include: (1) educating the medical community and more widely disseminating data supporting the value of early treatment of microalbuminuria; (2) developing a comprehensive, multidisciplinary team approach that involves physicians, nurses, diabetes educators and behavioral therapists; and (3) intensifying research in this field.

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States, Japan, and most of industrialized Europe [1–3]. Although attention has focused on renal disease and insulin-dependent diabetes mellitus (IDDM), a silent epidemic of renal disease caused by non–insulin-dependent diabetes mellitus (NIDDM) is mounting [3, 4]. NIDDM accounts for nearly 90% of all cases of diabetes [5]. Nevertheless, NIDDM-related renal disease has been relatively ignored. The epidemiology, natural history, genetics, pathogenesis, and spectrum of renal lesions differ in patients with NIDDM versus IDDM. Progress has been made in preventing the renal complications of IDDM, yet the utility of many of these measures in NIDDM has not been determined.

Key words: ACE gene polymorphism, albuminuria, calcium channel blockers, diabetic nephropathy, hyperglycemia, hyperlipidemia, hypertension, microalbuminuria, urinary albumin excretion.

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DEMOGRAPHIC ASPECTS OF NIDDM AND NEPHROPATHY

There has been an increase in the incidence of ESRD in the past two decades [6] and a concomitant increase in diabetic ESRD patients. Between 1982 and 1992, patients with diabetes as the cause of their ESRD rose from 27% to 36% in the United States and from 11% to 17% in Europe [7].

Data from the 1995 United States Renal Data System showed that nearly 40% of patients receiving renal replacement therapy (RRT) in 1992 had diabetes. In addition, 36.3% of the incident ESRD cases in 1992 were diabetic [1]. A high incidence of diabetic ESRD also was evident in Canada (24%) [8], Australia (14%) [9], Europe (17%) [10], and Japan (28%) [2] in the same year.

Diabetic nephropathy is due predominantly to NIDDM. The prevalence of NIDDM-related ESRD is probably underestimated. Incorrect reporting of NIDDM patients as IDDM when they require insulin therapy complicates classifying diabetes. Indeed, 35% to 45% of NIDDM patients receive insulin [11]. Regional studies suggest that NIDDM contributes significantly to diabetic ESRD. In data from the Michigan Kidney Registry [12], most black patients with diabetic ESRD had NIDDM (77%), whereas white patients more often had IDDM as a cause of diabetic ESRD (58%). In Pima Indians, 95% of diabetic ESRD is due to NIDDM [13]. Similarly, 61% of diabetic ESRD in Australia is due to NIDDM

[14], with a larger percentage in the aboriginal population [85%]. In Europe, NIDDM accounts for 43% of diabetic ESRD. However, in the lower Neckar region of Germany, 90% of diabetic ESRD was NIDDM related [4]. In Italy (national) and Lombardy (regional), NIDDM accounted for 67% and 50% of diabetic ESRD, respectively [15, 16].

Several explanations may account for the growth of NIDDM-related nephropathy. According to a National Health Interview Survey, there was an increase in diabetes in the United States in 1993 [5]. The prevalence for all ages was 3.1%, compared with 0.93% in 1958. NIDDM accounted for almost 95% of this new diabetic population. Similarly, in former communist Germany, the prevalence of diabetes increased from 1% in 1965 to 4% in 1988 [17]. Western societies are also aging. Given the increased incidence of NIDDM with age [18], older patients with ESRD are more likely to have NIDDM. Finally, NIDDM patient survival has improved. In regions of Germany formerly under communist rule, where antihypertensive treatment and treatment for coronary heart disease was not available in the early 1970s, 45% of NIDDM patients died less than four years after the diagnosis of NIDDM [19]. In Heidelberg [20], the five-year survival for NIDDM patients after the onset of proteinuria increased from 35% to 75% between 1966 and 1985, allowing a greater percentage of these patients to experience progression to ESRD.

NIDDM-associated nephropathy varies widely among racial and ethnic groups. NIDDM is more prevalent among African Americans, Hispanic Americans, and Native Americans. African American males have twice the incidence of diabetes, and African American women have four times the incidence of diabetes compared with European Americans [21–24]. Pugh et al found a sixfold higher incidence of diabetic-related ESRD in Mexican Americans compared with non–Hispanic whites and found a fourfold increase in blacks [23]. Cowie et al also showed that diabetic ESRD was more common in blacks [12]. Race-dependent risks of nephropathy may be related to glycemic control, hypertension, or other factors such as differences in the quality and access to medical care [25, 26].

Gender may also affect the prevalence of NIDDM-related nephropathy. According to the EDTA registry [27], 55% of NIDDM patients who began RRT in 1990 were male. These data are similar to those from Minnesota [28] and Heidelberg [4]. However, gender may interact with race. Data from the 1988 United States Renal Data System reported that the relative risk of diabetic ESRD for females compared with males was 1.20 in blacks and 0.85 in whites [29].

There also may be a relationship between lifestyle and renal disease in NIDDM [30]. The incidence and prevalence of NIDDM-associated nephropathy in France are relatively low. However, the prevalence of NIDDM nephropathy is 3.6 times greater in overseas French territories [14]. Even within metropolitan France, the incidence of ESRD in NIDDM patients is lower in areas bordering Italy and Spain (countries with a low incidence of NIDDM-related ESRD) compared with regions bordering Belgium and Germany (countries with a higher incidence of ESRD from NIDDM) [27, 31, 32]. For instance, in Strasbourg, next to the German border, 40% of all patients starting RRT in 1995 had NIDDM (Hannedouche, personal communication). These data suggest that environmental factors may influence the development of ESRD in NIDDM.

NATURAL HISTORY

IDDM-related nephropathy progresses through well-defined stages [33], with ESRD arising 15 to 30 years after the onset of diabetes. The natural history of nephropathy in NIDDM is less well characterized. The date of onset of NIDDM is often unknown, and low-grade albuminuria in NIDDM may be less specific as an indicator of disease progression. Age and hypertension can also affect renal function, and cardiovascular mortality may not allow for the development of nephropathy in NIDDM.

The Pima Indians have provided useful information about NIDDM. This Native American tribe has the highest prevalence of diabetes in the world (≈70% of adults develop diabetes) [34]. They also have high rates of obesity and insulin resistance but rarely develop ketoacidosis. In contrast to most NIDDM patients, the onset of diabetes in Pima Indians usually occurs in the third or fourth decade of life [35], allowing for diabetic complications to manifest themselves without the confounding effects of age and age-related mortality.

Stage I: Hemodynamics of recent-onset NIDDM

Renal vasodilation and hyperfiltration occur early in IDDM [36]. This may not always be the case in NIDDM. Scandinavian investigators, using single-shot ^{51}Cr-EDTA, noted normal glomerular filtration rates (GFR) at the time of diagnosis of diabetes [37]. Nowack et al also noted glomerular hyperfiltration in some (44%), but not all, NIDDM patients [38]. Other investigators have demonstrated hyperfiltration in NIDDM patients [39, 40]. Pima Indians have an average GFR by iothalamate clearance that is 15% greater than nondiabetic control patients [35]. Most of the increase in GFR can be attributed to increased renal plasma flow (RPF) and a slight reduction in serum albumin resulting in decreased glomerular oncotic pressure. However, for any given RPF, GFR was greater in diabetics than in controls, suggesting that glomerular capillary hydrostatic pressure and/or the ultrafiltration coefficient were increased.

Several factors may lead to hyperfiltration in NIDDM. Glucose levels are higher in hyperfiltering patients [38], and a link between hyperglycemia and hyperfiltration has been suggested by the direct correlation between GFR and HbA_1C [35]. Prostaglandins may play a role in hyperfiltration [41], as well as increased sodium (Na^+) glucose reabsorption in the proximal tubule. This reduces Na^+ delivery to the macula densa and alters tubuloglomerular feedback. Furthermore, in IDDM and NIDDM, there is a marked increase in GFR in response to amino acid infusion.

GFR decreases in response to metabolic control in IDDM and NIDDM but usually not to levels found in nondiabetic individuals [37, 42]. A mildly elevated urinary albumin excretion (UAE) is frequently present at the time of diagnosis of diabetes. In 15% of newly diagnosed NIDDM patients, microalbuminuria remains evident despite glycemic control [43]. Moreover, GFR in these patients is generally higher than in patients with normal UAE [44].

Selective glomerular permeability

There is evidence for impaired glomerular charge and size selectivity in NIDDM, and most of this information has been provided by meticulous and regular studies in the Pima Indian tribe. In the process, the authors have provided a paradigm for understanding changes in glomerular function in NIDDM. Myers et al found elevated fractional clearances of high molecular weight dextrans in Pima Indians with NIDDM of recent onset (less than 3 years duration) [35]. Using certain assumptions, they concluded that glomerular pores in NIDDM shifted toward a larger size. Impairment of barrier size selectivity combined with a high GFR appeared to increase the filtered protein load, resulting in a bimodal pore size distribution.

The IgG to IgG4 clearance ratio has been used to estimate charge selectivity in the glomerular capillary wall [45]. Endogenous proteins undergo variable rates of tubular reabsorption; hence, this ratio reflects glomerular and tubular protein handling [46]. Use of this ratio suggests that impairment of the electrostatic barrier in glomeruli, as a consequence of decreased glycosaminoglycans in the glomerular basement membrane (GBM) [47], precedes the size-selective defect [45] and contributes to hyperfiltration early in diabetic renal disease. Interestingly, Tamsma et al recently demonstrated that GBM heparin sulfate was diminished in patients with glomerular disease, including NIDDM [48].

Glomerular size and structure

Renal and glomerular hypertrophy are evident early in diabetes. In IDDM renal hypertrophy correlates with GFR [49, 50], but with insulin treatment there is a reduction in glomerular volume [50]. Glomerular volume is not universally increased in NIDDM [51, 52]. Schmitz, Christensen and Taagehoej found no significant differences in glomerular volume comparing NIDDM patients with normal UAE and matched nondiabetic controls [53]. Interestingly, kidneys were significantly larger in patients with elevated UAE, and the UAE increased to a greater extent in patients with nephromegaly than in those with normal-sized kidneys [54].

Some NIDDM patients, however, do manifest glomerular hypertrophy [26, 55]. Glomeruli in Pima Indians have been shown to be increased in size prior to the onset of diabetes, yet their size does not increase further with the development of diabetes [26]. Pagtalunan et al found that glomerular volume was greater in Pima Indians compared with live kidney donors, yet glomerular volume was not significantly different in patients with and without albuminuria [56]. Osterby et al also examined glomerular ultrastructure in biopsy samples from proteinuric NIDDM patients and found that glomerular hypertrophy correlated with mesangial volume [57].

Stage II: Early renal involvement

The earliest structural abnormality in diabetes is GBM thickening. This occurs in nearly all patients [49], beginning 1.5 to 2.5 years after the onset of IDDM. This may be followed by an increase in fractional mesangial volume (mesangial volume per glomerulus) in those patients whose renal disease progresses. These changes are also present in NIDDM patients, although their timing is less regular [58]. Recent work from Fioretto et al demonstrated that a majority of NIDDM patients with microalbuminuria have normal-appearing glomeruli, or nonspecific changes with interstitial and arteriolar lesions [59]. Typical Kimmelstein-Wilson lesions of diabetic glomerulosclerosis are found in a much smaller proportion of NIDDM patients early in the course of nephropathy. In contrast, nonspecific vascular or interstitial changes are prevalent in these patients. This apparent difference from IDDM may be due to aging, ischemia, or both. There is no doubt, however, that in NIDDM patients who come to autopsy, Kimmelstiel-Wilson lesions are highly prevalent.

The extent of mesangial expansion appears to be linked to the severity of renal dysfunction [49]. Mesangial expansion and occlusion of glomerular capillaries lead to a loss of available surface area for filtration and to a decline in function [60, 61]. Glomerular hypertrophy may initially compensate for this, providing a mechanism for maintaining GFR [62]. Indeed, the rate of progression of diabetic renal disease may be limited by the capacity for glomerular expansion [63].

NIDDM patients with microalbuminuria tend to have more advanced structural lesions than those with normal UAE, although structural abnormalities may not correlate with declining function [64, 65]. Glomerular volume

fraction in diabetic patients with microalbuminuria is greater, suggesting that microalbuminuria is an indicator of diabetic renal disease, regardless of GFR [59].

Stage III: Initial stages of nephropathy (microalbuminuria)

Normal UAE is defined as excretion of less than 30 mg/24 hr (less than 20 μg/min) or an albumin-to-creatinine ratio (A/C) less than 30 mg/g. Microalbuminuria is defined as an albumin excretion rate between 20 and 200 μg/min or 30 to 300 mg/24 hr [66]. Patients with microalbuminuria have a negative urine dipstick for protein and a 24-hour urine protein excretion within the normal range. The greater sensitivity of measurements of urinary albumin is due to the fact that albumin comprises only a small proportion of protein in normal urine.

Microalbuminuria heralding diabetic nephropathy is observed after 5 to 15 years of IDDM. In NIDDM, however, microalbuminuria may be present even before the onset of diabetes. In the Mexico City Diabetes Study, microalbuminuria was evident in nondiabetic individuals with impaired glucose tolerance and in individuals with positive family histories for diabetes [67]. The risk of developing NIDDM was greater in patients with microalbuminuria [67]. Elevated albumin excretion rate was also present in 15% of Pima Indians with impaired glucose tolerance [68]. Certainly, at the time of NIDDM diagnosis, microalbuminuria or frank albuminuria is present in a large proportion of patients. In one study, 19% of newly diagnosed NIDDM patients had microalbuminuria, and 5% even had macroalbuminuria [69]. This was confirmed by the UK Prospective Diabetes Study [70, 71], in which 17% of the patients had microalbuminuria. Keller et al similarly found microalbuminuria in 14% and macroalbuminuria in 2% of patients with newly diagnosed NIDDM [43]. Although essential hypertension may be associated with microalbuminuria, blood pressure is apparently not a major contributor to microalbuminuria in early NIDDM, as similar frequencies of microalbuminuria were found in hypertensive and normotensive patients [43].

The point prevalence of elevated UAE in clinic-based Danish NIDDM patients was 28% versus 14% for IDDM [72]. Higher prevalence rates for microalbuminuria and macroalbuminuria also have been reported in Pima Indians (26% and 21%, respectively) [68]. Microalbuminuria in NIDDM may be more common than in IDDM. The subtle variability in prevalence may depend on the patient population, the duration of diabetes, and the presence of hypertension.

Microalbuminuria is predictive of progression to nephropathy in IDDM [73]. It may not be as predictive in NIDDM. Mogensen noted that after 9.5 years, 22.4% of patients with microalbuminuria developed proteinuria (more than 400 μg/ml) compared with 5.4% of patients with normoalbuminuria [74, 75]. Schmitz, Vaeth and Mogensen followed 278 normoalbuminuric and microalbuminuric NIDDM patients for six years and noted that the change in albuminuria in normoalbuminuric patients (μg albumin/ml 4.2 ± 1.9 to 8.3 ± 2.8) was less than in microalbuminuric patients (36.4 ± 1.9 to 96.9 ± 4.0) [76]. Although in the past microalbuminuric patients were considered destined for nephropathy, better glycemic control and the use of angiotensin (Ang) converting enzyme (ACE) inhibition [77] have altered the risk of progression in IDDM [78]. The same may be true for NIDDM, but microalbuminuria in NIDDM may be less predictive of nephropathy because of comorbid conditions. Its association with cardiovascular mortality (*vide infra*) reduces its predictive sensitivity (that is, death before development of nephropathy).

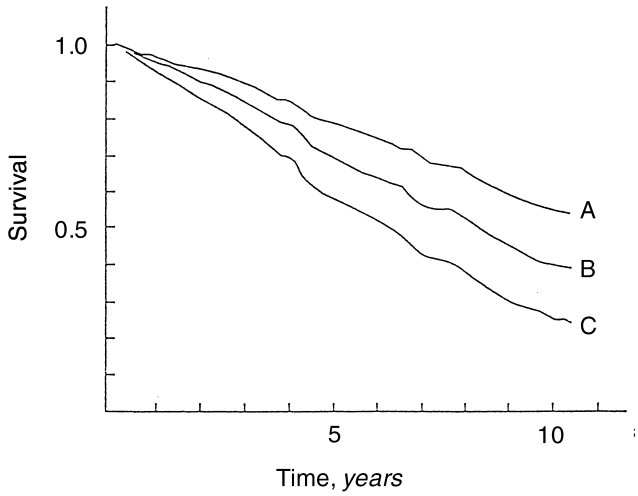

Fig. 1. Ten-year survival by baseline urinary albumin concentrations (UAC in μg/ml) after correction for age, duration of diabetes, and serum creatinine concentration by a Cox regression analysis in 407 patients with NIDDM. Data are from Schmitz and Vaeth [80]. Line A is UAC ≤ 15; line B is 15 < UAC ≤ 40; line C is 40 < UAC ≤ 200.

Elevated UAE as a risk factor for death

Microalbuminuria in IDDM and NIDDM is associated with an increased risk of cardiovascular death [74, 79, 80]. Higher UAE rates were present in NIDDM patients with coronary heart disease at diagnosis of diabetes [81] and in follow-up [72]. In another study, 503 NIDDM patients were followed for 10 years [80]. Two percent died from uremia, whereas 56% died from cardiovascular disease (CVD) or stroke [80]. Figure 1 shows survival curves for UAC after correcting for prognostic variables. Even a minor increase in UAC, that is, 16 to 40 μg/ml, was associated with reduced probability of survival, and the greater the level of albuminuria, the worse the prognosis. The hazard ratios in the elevated UAE groups were 1.65 and 2.41 relative to those with UAE ≤ 15 μg/ml. Interestingly, no further increase in mortality was

Table 1. Mean values of HbA_1C and mean blood pressure and incidence of microalbuminuria

Parameter	Incidence of microalbuminuria	*P* value
$HbA_1C < 9.5\%$	4/22 (18.2%)	< 0.05
$> 9.5\%$	7/12 (58.3%)	
Mean blood pressure < 95 mmHg	4/21 (19.0%)	< 0.05
> 95 mmHg	7/13 (53.8%)	

Adapted from Haneda et al, with permission [86].

detected in patients with UAE more than 200 μg/ml. The association of microalbuminuria with hypertension and hyperlipidemia accounts for part of the cardiovascular risk in NIDDM. The "Steno" hypothesis postulated that albuminuria was a harbinger of endothelial dysfunction and subsequent atherogenesis. A preliminary study lent support to this idea [82], as NIDDM patients with albuminuria had higher plasma levels of von Willebrand factor than patients without albuminuria. This observation was consistent with the concept that microalbuminuria may serve as a surrogate marker of endothelial cell dysfunction [83]. In general, microalbuminuria appears to be a marker for atherosclerotic disease and death in NIDDM. When it precedes a diagnosis of NIDDM, it may be a marker of the prediabetic state, occurring with hypertension, hyperlipidemia, hyperinsulinemia, and insulin resistance [67]. In populations with lower cardiac risk, such as the Japanese or Pima Indians, microalbuminuria may not be as predictive of coronary death [84, 85].

Because microalbuminuria is a predictor of mortality as well as proteinuria in NIDDM, it is important to identify the factor(s) responsible for its development and progression. Poor glycemic control and hypertension are strongly associated with microalbuminuria (Table 1) [86]. Increased levels of atrial natriuretic peptide [87] and renal endothelial dysfunction [88, 89] predate overt nephropathy [89]. Elevated plasma prorenin levels [90] have also been associated with increased albuminuria in NIDDM. Unfortunately, studies evaluating the roles for these factors in predicting progressive microalbuminuria are lacking.

Stage IV: Overt nephropathy

Persistent dipstick albuminuria (UAE $>$ 300 mg/24 hr or $>$ 500 mg/24 hr urinary protein excretion) defines overt nephropathy. It is characterized by a decline in GFR and increased mortality. In IDDM, GFR decreases with stage of overt nephropathy but does not decrease with microalbuminuria. In contrast, in NIDDM, a decline in GFR has been noted in microalbuminuric patients [91] and even in older patients without albuminuria [92]. Overt nephropathy has been reported to appear five years sooner relative to the time of diagnosis of diabetes in NIDDM patients compared with IDDM, although this may be due to a period of unrecognized hyperglycemia prior to the diagnosis of NIDDM [93].

Renal risk was assumed to be less in NIDDM [94]. The Joslin Clinic reported that the cumulative renal mortality rate by the age 75 was 7.5% in NIDDM [95], and the proportion of NIDDM patients dying from renal disease was as low as 1.6% to 2.0% [96]. Furthermore, the relative risk of renal death was increased only twofold compared with the general population [97]. In contrast, diabetic nephropathy with renal failure was the cause of death in 42% of patients with IDDM who were below age 20 at the onset of IDDM [98]. It is not surprising, therefore, that interest in the clinical manifestations and pathophysiology of diabetic nephropathy centered almost exclusively on IDDM until now.

In Pima Indians [99], the incidence of proteinuria was 23% after 15 years of diabetes and 50% after 20 years, refuting the notion that nephropathy was less common in NIDDM. The onset of heavy proteinuria correlated with the duration and severity of diabetes, as in IDDM. The cumulative incidence of proteinuria in two populations with IDDM and in two populations with NIDDM is compared in Figure 2. The incidence in NIDDM is at least as high as in IDDM [100]. Hasslacher et al showed a similar risk for proteinuria at any given duration of diabetes in IDDM and NIDDM patients [101]. The risk of proteinuria after 25 years of disease was 57% in NIDDM and 46% in IDDM. The risk of renal failure, that is, serum creatinine more than 1.4 mg/dl, after five years of persistent proteinuria was 63% and 59% in NIDDM and IDDM, respectively.

High-grade albuminuria correlated with several factors. Males had a higher prevalence of albuminuria (20% males vs. 6% in females) [72], and the prevalence of hypertension increased with escalating degrees of albuminuria [102]. Albuminuria has been linked to the presence of proliferative retinopathy, coronary heart disease, and foot ulcers. In Pima Indians with NIDDM, the presence of heavy proteinuria was associated with duration of diabetes, severity of diabetes, type of treatment (diet vs. oral antihyperglycemic agents or insulin), and blood pressure [99].

Mortality in NIDDM patients with persistent proteinuria is very high [103]. In diabetic Pima Indians with proteinuria, the mean risk of death was 3.5 times greater than in diabetic patients without proteinuria [103]. This is primarily due to CVD or a combination of CVD and renal disease [28, 103].

Stage V: End-stage renal disease

Nelson et al reported that in Pima Indians with NIDDM, the cumulative incidence of ESRD was 40% at 10 years and 61% at 15 years following the onset of proteinuria [13, 44]. This is similar to the 50% incidence of ESRD after 10 years of proteinuria in IDDM patients

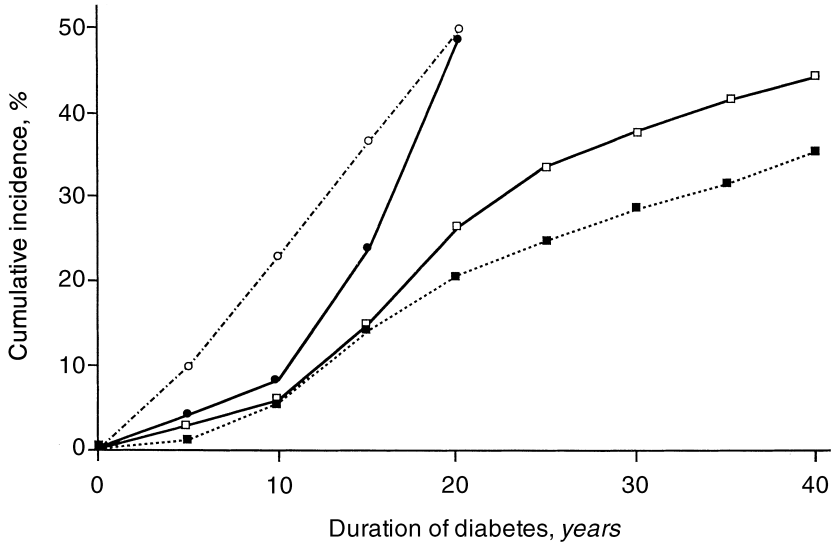

Fig. 2. Cumulative incidence of proteinuria in Japanese patients (○) and Pima Indians (●) with NIDDM and in two studies of white subjects with IDDM [Joslin Clinic, Boston (■) and Steno Memorial Hospital, Denmark (□)]. The incidence in patients with NIDDM was higher through 20 years of diabetes than in those with IDDM. Data are from Knowler and Kunzelman [99].

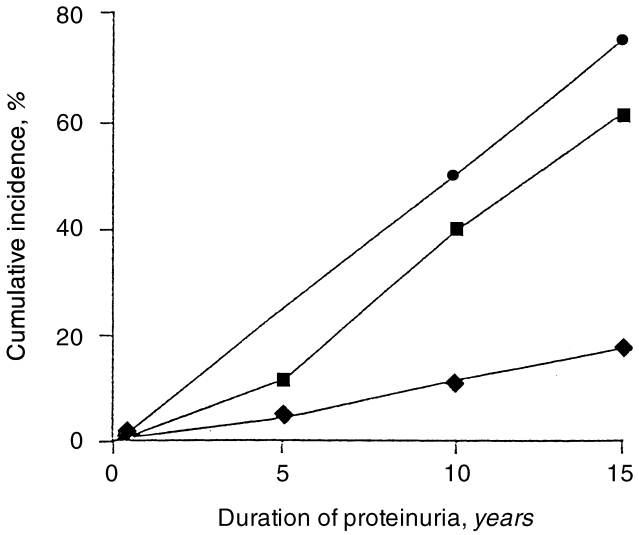

Fig. 3. Cumulative incidence of ESRD by duration of proteinuria in NIDDM and IDDM patients. Data are from Nelson et al [44], Humphrey et al [105], and Krolewski et al [106]. Symbols are: (●) whites with IDDM; (■) Pima Indians with NIDDM; (◆) whites with NIDDM.

at the Joslin Clinic. This high incidence of ESRD does not appear to be unique to the Pima Indians [104], as the same has been observed in most studies examining European and American NIDDM populations.

Figure 3 shows the cumulative incidence of ESRD as a function of duration of proteinuria in Pima Indians [44], in whites with NIDDM [105], and in whites with IDDM [106]. Coronary heart disease is a frequent cause of death in older persons with diabetes and proteinuria, and may account, in part, for the lower incidence of ESRD in whites with NIDDM. Because of the relatively young age at onset of NIDDM in Pima Indians and their lower death rates from CVD [85], the cumulative incidence of ESRD in this population closely resembles that of whites with IDDM.

In the vast majority of patients, GFR begins to decline with the onset of proteinuria. In one study on the natural course of diabetic nephropathy in IDDM, proteinuria appeared on average after 17 years, and ESRD appeared 22 years after the onset of diabetes [107]. The rate of decline in GFR averaged 1 ml/min/month, with 50% of the patients reaching ESRD seven years after the onset of proteinuria [108]. Recent reports suggest that the rate of decline in GFR has slowed in IDDM [106]. This may reflect more effective interventions.

Among Pima Indians, in whom NIDDM develops at a younger age than in other populations, the decline in GFR is similar to that of IDDM (1 ml/min/month from onset of macroalbuminuria) [109]. Ordonez and Hiatt noted that once proteinuria occurred, nephropathy progressed at the same rate in IDDM and NIDDM [110]. Biesenbach, Janko and Zazgornik examined a population of proteinuric NIDDM patients with an average initial creatinine clearance (C_{Cr}) of 81 ± 6 ml/min/1.73 m^2 [111]. Patients developed ESRD after a mean of 81 months (range, 40 to 124 months). The average rate of loss of C_{Cr} in NIDDM patients was similar to IDDM. In patients with NIDDM, the rate of loss of C_{Cr} was twofold greater in patients with systolic blood pressure (SBP) more than 160 mm Hg and in smokers. The latter observation is in keeping with the risk of albuminuria in smokers with IDDM and NIDDM [112].

Gall et al examined albuminuric NIDDM patients with biopsy-proven diabetic glomerulosclerosis [113]. The majority (21 of 26) received antihypertensive treatment. The average rate of decrease of GFR was 5.7 ml/min/year. This rate of decline correlated with blood pressure

Table 2. Comparison of stages of diabetic nephropathy in patients with IDDM and NIDDM

Stage	Clinical term (onset)[e]	Histologic features	Functional/clinical features	Prevalence of renal involvement	
				IDDM	NIDDM
I.	Initial stage (at diagnosis)	Glomerular hypertrophy and increased kidney volume in IDDM; not a constant feature in NIDDM.	• ↑ GFR	90–95%	15–45% (hyperfiltration) 15–20% (MIA) 5–8% (MAA)
				usually normotensive	hypertension frequent
II.	Early renal involvement (1.5–5 years)	GBM thickening, mesangial expansion	• ↑ GFR	90–95%[f] usually normal AER	?50% MIA, MAA, and BP may be present
III.	Incipient[a] nephropathy (5–15 years)	Further GBM thickening and mesangial expansion	• ↑ AER (incidence) • ↑ AER (progression) • ↑ BP	20% 80% 25%	40% 20% 70%
IV.	Overt[b] nephropathy (10–20 years)	Diffuse and/or nodular glomerulosclerosis	• Albuminuria (>300 mg/day) • ↑ BP • Gradual decrease in GRF in both IDDM & NIDDM (untreated) (5–10 ml/min/year)	30–40% 60–65%	30–40% 90–100%
V.	End-stage renal disease (20+ years)	Glomerular closure and obsolescence	• GFR < 15 ml/min[c] • Retinopathy[d] • Neuropathy[d] • Cardiac disease[d] • Vascular disease[d]	30–40% 92% 83% 67% 29%	10–35% 55–65% 82% 75% 21%

Abbreviations are: MIA, microalbuminuria; MAA, macroalbuminuria; AER, albumin excretion rate.
Data are from references [a] 75; [b] 100; [c] 44, 105, and 106; and [d] 5.
[e] Relative to diagnosis of diabetes in IDDM; variable in NIDDM
[f] Percentage refers to GBM thickening

control and albuminuria. Hasslacher et al found an average annual loss of C_{Cr} by the Cockroft-Gault formula of 5.3 ml/min/1.73 m^2 in NIDDM patients with proteinuria followed at the Heidelberg Clinic [114]. Their rate of loss of C_{Cr} correlated with postprandial glucose levels. The last finding provides indirect evidence for a role for glycemic control in progression of NIDDM-related nephropathy.

Overall, the cumulative incidence of ESRD in NIDDM varies between 10% and 35%. The fact that IDDM may carry a higher odds ratio for the development of ESRD [115] does not necessarily imply a more benign renal prognosis in NIDDM. It may reflect greater heterogeneity of renal risk or greater attrition from cardiac death prior to the development of ESRD. Furthermore, although proteinuria in NIDDM might appear sooner relative to the time of diagnosis of diabetes, the average rate of loss of GFR appears to be similar both in NIDDM and IDDM. Table 2 compares the five stages in the natural history of diabetic nephropathy in IDDM and NIDDM.

RISK FACTORS FOR NEPHROPATHY IN NIDDM

Only 20% to 50% of patients with NIDDM develop proteinuria after 20 years of diabetes, depending on the population studied. Therefore, factors other than diabetes obviously are determinants of diabetic renal disease (Table 3).

Table 3. Predictors of nephropathy in NIDDM

Genetic factors
Elevated blood pressure
Smoking
Hyperglycemia
Family history of nephropathy
Family history of cardiovascular events
Parental hypertension
Low birth weight?
Male gender
Advanced age
Microangiopathy (retinopathy)
Macroangiopathy (coronary heart disease, arteriooccluse disease)

Duration of diabetes and age

Duration of diabetes was one of the most important risk factors for diabetic nephropathy in four major studies (Fig. 2). The influence of duration was greater than that of age, gender, or type of diabetes. In the Rochester, Minnesota, cohort [28], older age at onset of diabetes and male gender were risk factors for proteinuria in NIDDM. Separate analyzes controlling for age indicated no association with duration of NIDDM. When patients with NIDDM were matched for years after diagnosis of diabetes, patients diagnosed after age 50 had a higher

prevalence (76%) and degree of microalbuminuria than those diagnosed before age 40 (38%) [116].

Familial and racial factors

Separate inherited risks exist that determine whether a given individual develops diabetes mellitus and whether he or she develops diabetic nephropathy in NIDDM [117]. Pettitt et al found that renal disease clusters in Pima Indian families with NIDDM [118]. Proteinuria occurred in 14% of diabetic offspring in whom neither parent had proteinuria, in 23% of offspring in whom one diabetic parent had proteinuria, and in 46% of offspring in whom both parents had diabetes and proteinuria. Familial clustering of albuminuria is also apparent in whites [67] and in African Americans with NIDDM [119]. In the latter, the risk for developing ESRD was eightfold greater if a close relative with NIDDM had ESRD. Familial clustering of hypertension and CVD in families with NIDDM and nephropathy also occurs [119]. Genetic factors and glycemic control may interact in these families to heighten the frequency of microalbuminuria and overt nephropathy.

Ethnic factors may influence the development of nephropathy in NIDDM. African Americans may be more at risk for ESRD in NIDDM [12, 115]. A greater risk for NIDDM-associated nephropathy has been reported in Maoris [14], Australian aboriginals [14], and Indian immigrants in the United Kingdom [120].

Candidate genes

Because high blood pressure and CVD are related to the risk of nephropathy in NIDDM [43, 121, 122], genes involved in blood pressure regulation and cardiovascular risk are obvious candidate genes for diabetic nephropathy. These include genes encoding the renin-angiotensin system (RAS) [123], the sodium-proton exchanger [124], and components of GBM [125].

ACE gene polymorphism and initiation of nephropathy

The D (deletion) allele of the ACE gene is characterized by higher circulating and tissue levels of ACE, in contrast to the I (insertion) allele. This may result in higher angiotensin (Ang) II concentrations, particularly in tissues in which ACE activity constitutes a rate-limiting step in the RAS cascade. Because Ang II is thought to be involved in the onset and progression of diabetic renal disease, it is reasonable to categorize this polymorphism as a potential determinant of macrovascular and microvascular diabetic complications.

Originally, Cambien et al demonstrated that an insertion (I)/deletion (D) polymorphism of the ACE gene (ACE/ID) was associated with an increased risk for myocardial infarction in nondiabetic patients [126]. This association has been extended to IDDM and NIDDM [127]. The role of this polymorphism in diabetic nephropathy remains unclear. Marre et al reported an association between the ACE I/D genotype and renal disease in diabetes, determining the ACE genotype in IDDM patients with persistent microalbuminuria (30 to 300 mg/24 hr) or macroalbuminuria (more than 300 mg/24 hr) [128]. The II genotype was present in 4% of patients with albuminuria, which was significantly lower than in control patients (15%). Doria, Warram and Krolewski concluded that the ACE I/D genotype in conjunction with a second ACE gene polymorphism contributed to the susceptibility to diabetic nephropathy in white IDDM individuals [129]. Studies from Denmark [130], Germany [131], and the Netherlands [132], however, reported that the ACE genotype distribution in IDDM or NIDDM patients with albuminuria more than 30 mg/day was indistinguishable from that of diabetic patients without albuminuria. A meta-analysis of 11 studies dealing with ACE/ID polymorphisms [133] found no difference in the distribution of D and I alleles between case ($N = 562$) and control patients ($N = 939$). Similar results have been obtained in white NIDDM patients with and without nephropathy [131, 134, 135], although studies in Japanese NIDDM patients suggest that the D allele may be a risk factor for nephropathy [135].

ACE gene polymorphism and progression of nephropathy

There is no firm basis yet that ACE polymorphisms are risk factors for the "initiation" of diabetic nephropathy. However, there is evidence that the RAS may play a role in its "progression" [136, 137]. Yoshida et al found a significantly higher incidence of the DD genotype in NIDDM patients with declining renal function [136]. DD patients had a greater than fourfold risk for progression to ESRD. The DD genotype was not present in patients with overt proteinuria and concurrently stable renal function, implying that proteinuria in diabetic DD patients is incompatible with preservation of renal function. Schmidt et al also noted that there was a higher prevalence of the DD genotype in NIDDM patients on dialysis [138].

Polymorphism of angiotensinogen and Angiotensin receptor genes

There are no solid data yet linking polymorphisms in the angiotensinogen gene (M235T) or the type I Ang II receptor gene to nephropathy in NIDDM [132, 134, 137]. In one study [139], the authors genotyped for the M235T polymorphism in IDDM and NIDDM patients from Northern Ireland and found a significantly higher angiotensinogen TT genotype (20%) in IDDM patients with nephropathy versus IDDM without nephropathy (8%). TT was found in 8% of the general population. There were no significant differences in the M235T polymor-

phism in NIDDM patients compared with the general population. Data from Schmidt et al also revealed no significant differences in allele frequency for angiotensinogen M or T in European NIDDM patients with and without albuminuria more than 30 mg/24 hr [137].

Sodium/lithium countertransport

Increased red blood cell (RBC) sodium/lithium exchange (Na^+/Li^+), as a surrogate for sodium/proton cotransport, has been proposed as a genetic marker for hypertension in nondiabetic patients. Two [140, 141] of four studies in NIDDM patients [140–143] reported an increased Na^+/Li^+ exchange. In the study from Rutherford et al, NIDDM patients with nephropathy had significantly reduced K_m and V_{max} for Na^+/Li^+ exchange compared with uncomplicated diabetic and nondiabetic control patients [141]. Considerable overlap existed between the different groups, and the predictive power of Na^+/Li^+ exchanger activity was dependent on long-term glycemic control [144]. Several nongenetic factors also influence Na^+/Li^+ exchanger activity, including hyperlipidemia, insulin resistance, hypokalemia, oral contraceptive use, and membrane fluidity [145]. The first two are often associated with NIDDM. A propensity to hypertension may also be part of the genetic predisposition to nephropathy in NIDDM [142]. Pietruck et al recently described enhanced G-protein coupling in B lymphoblast cell lines of IDDM patients with diabetic nephropathy [146]. In ongoing studies, the G-protein abnormality has been examined in conjunction with NIDDM-related renal and cardiovascular complications. Preliminary results are compatible with the idea that these changes are related to Na^+-H^+ exchanger abnormality.

Hypertension

The relationship between blood pressure and renal disease is problematic because elevated blood pressure may be a cause or consequence of renal disease. The deleterious effects of systemic blood pressure on glomeruli were reported more than 20 years ago in a patient with NIDDM and unilateral renal artery stenosis in whom nodular diabetic glomerulosclerosis was present in the nonischemic kidney [147]. Because abnormal metabolic conditions would affect both kidneys, it seems likely that the stenosis protected the ipsilateral kidney. Animal studies also suggest that hemodynamic changes may influence diabetic nephropathy. Uninephrectomy in animals, leading to hyperfiltration in the remaining kidney, markedly accelerates experimental diabetic nephropathy [148].

Hypertension appears to play a role in the nephropathy of NIDDM [121, 149]. The relationship between hypertension and renal disease is different in IDDM and NIDDM. Although in IDDM the presence of hypertension usually indicates renal involvement, the same is not true for NIDDM. Up to the time of diagnosis of NIDDM, many patients are hypertensive even without albuminuria. This is possibly due to the fact [150] that patients genetically predisposed to NIDDM may have been hypertensive for years prior to the onset of diabetes as part of a metabolic syndrome [151] characterized by insulin resistance, obesity, dyslipidemia, and hypertension.

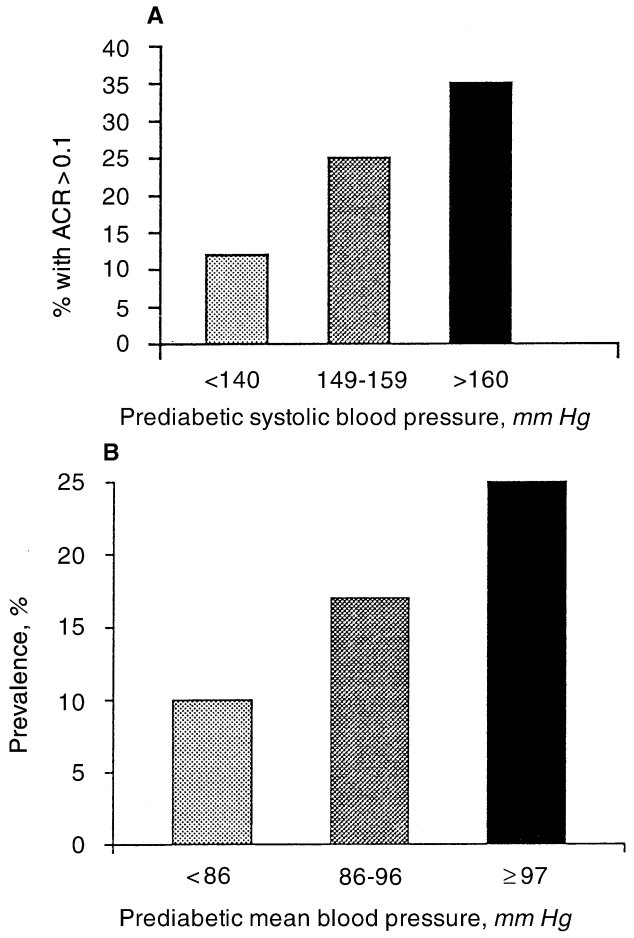

Fig. 4. Prediabetic systolic blood pressure and prevalence of A/C ratio (g/g) of greater than 0.1 in 356 Pima Indians (*A*). Data are from Viberti and Earle [149]. Prevalence of abnormal albumin exertion [albumin (mg)-to-creatinine (g) ratio = 100] after the diagnosis of diabetes by prediabetic mean blood pressure (*B*). Data are from Nelson et al [121].

Hypertension before the onset of diabetes in Pima Indians conferred a greater risk of postdiabetic renal disease [149]. Similarly, hypertension prior to the diagnosis of diabetes was associated with an abnormal UAE after the diagnosis of NIDDM [121] (Fig. 4). Higher prediabetic blood pressure could reflect susceptibility to renal disease in the presence of diabetes or, alternatively, be a risk factor for more severe NIDDM [152]. Recent studies compared offspring of NIDDM parents with or without diabetic nephropathy and found that in nonobese adult individuals, ambulatory SBP averaged 8 mm Hg higher

Table 4. Hypertension as a predictor of nephropathy in type II diabetes during the preproteinuric phase

Patients	Median (*range*) Post-prandial glucose *mg/dl*	Blood pressure *mmHg*	Patients Normotensive	Patients Hypertensive
Developing persistent proteinuria ($N = 63$)	208 (130–295)	164 (105–215)[a] 87 (70–106)[b]	19/63 (30%)[c]	44/63 (70%)
Not developing persistent proteinuria ($N = 63$)	199 (104–272)	149 (122–183)[a] 84 (68–97)[b]	36/63 (57%)	27/63 (43%)

Modified, with permission, from Hasslacher [153].
[a] Systolic blood pressure
[b] Diastolic blood pressure
[c] $P < 0.05$

in offspring of parents with diabetic nephropathy [122]. Hasslacher et al found that diabetic patients who developed proteinuria later were more frequently hypertensive in the preproteinuric state than patients who failed to develop proteinuria (Table 4) [153].

The finding of a high prevalence of hypertension in NIDDM is not a new one. Pell and D'Alonzo reported an increased frequency of hypertension in NIDDM in 1967 [154]. Their case-control study demonstrated a 50% greater prevalence of hypertension in NIDDM compared with matched nondiabetic controls. The increased frequency of hypertension was independent of obesity and occurred more commonly in patients with NIDDM even in the absence of proteinuria or renal disease. Ritz et al noted that up to 70% of NIDDM patients without persistent proteinuria were hypertensive according to the World Health Organization definition (Fig. 5) [155]. More recently, they used ambulatory blood pressure monitoring in 85 newly diagnosed NIDDM patients. Sixty percent of these patients were hypertensive, and 61% had an attenuated nocturnal decrease in blood pressure. A normal blood pressure profile was found in only 21% of the patients [43]. Hypertension is thus a feature of early NIDDM, acting as a risk factor for nephropathy and a contributor to progression. Several studies have noted a more rapid decline in GFR in hypertensive compared with normotensive NIDDM patients. Biesenbach et al also found a more rapid progression at SBP more than 160 mm Hg [111], and Perneger et al noted that adjusting for hypertension decreased the odds ratio for developing ESRD in NIDDM [115].

It should be pointed out that obesity, in and by itself, is associated with abnormal renal physiology, which is highly relevant to any discussion of NIDDM. Patients with upper-body obesity have a high incidence of hypertension. Several recent studies cast doubt on the idea that insulin resistance and hyperinsulinemia are the initial triggers of the cascade of defective mechanisms described in obesity-related hypertension. However, insulin resistance enhanced activity of both the RAS and sympathetic nervous systems, a decrease in the secretory response of atrial natriuretic factors, and increased intravascular volume, cardiac output, and stroke volume continue to be considered as pathogenetic mechanisms leading to obesity-related hypertension [156]. In addition to salt-dependent hypertension, obesity may be associated with interstitial and glomerular disease in the absence of hyperglycemia and hyperfiltration. This must contribute to the fact that the vasculopathies of IDDM and NIDDM are not quite the same. In the same vein, the glomerular pathologies of the two states are different, and the tubulointerstitial changes of NIDDM are more prominent in the early stages of the disease, suggestive that different forces are at work, even if the outcome is the same.

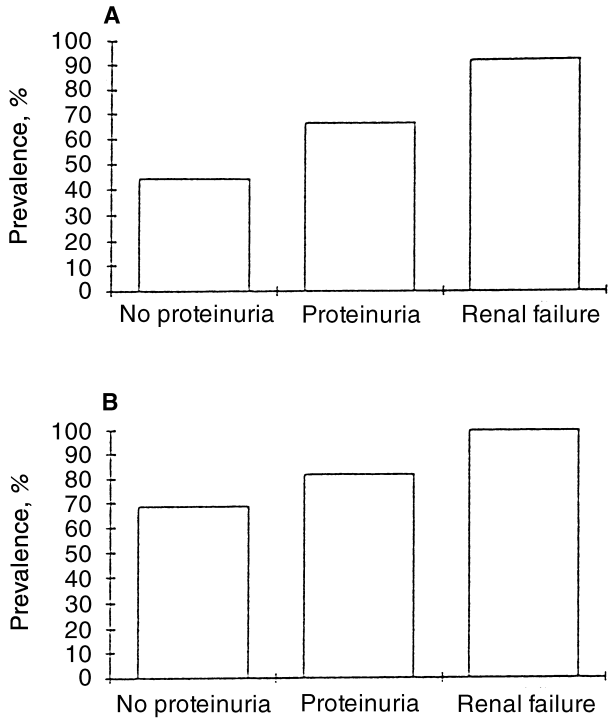

Fig. 5. Prevalence of hypertension by the World Health Organization criteria in type I (IDDM; *A*) and type II diabetes (NIDDM; *B*) in different stages of diabetic nephropathy. Data are from Ritz et al [155].

Hyperglycemia

Hyperglycemia appears to be important for the development of proteinuria in NIDDM. Ballard et al highlighted this association using a proportional hazards analysis to define significant predictors of proteinuria in NIDDM patients [28]. Hyperglycemia was a significant risk factor, especially in younger (>60 years) diabetic patients, perhaps because of a competing risk of death in older (<60 years) patients.

Vasquez et al noted a reduction in proteinuria when NIDDM patients were placed on a hypocaloric diet decreasing hyperglycemia [157]. However, the effect of the dietary intervention must also be considered as a confounding variable. Insulin resistance, another aspect of NIDDM, precedes the onset of microalbuminuria in NIDDM [158], and greater degrees of insulin resistance are evident when UAE is elevated in NIDDM [159]. It has been suggested that hyperglycemia and hyperinsulinemia in the prediabetic state may contribute to microalbuminuria in NIDDM [160]. Further evidence for a role of hyperglycemia in the development of proteinuria in NIDDM comes from the Kumamoto study [161], which documented significantly less nephropathy in NIDDM patients with intensive insulin treatment.

The role of hyperglycemia in the progression of NIDDM-related nephropathy is not clear. Many of the aforementioned studies suggested that poor glycemic control was associated with an increasing rate of decline in GFR. Certainly, the pathogenesis of hypertension in NIDDM may be related in part to hyperglycemia, sodium retention, and insulin resistance [162]. The Appropriate Blood Pressure Control in Diabetes Trial analyzed glycemic control and progression in NIDDM [102]. Mean fasting blood glucose and HbA_1C values were lower in normoalbuminuric patients compared with microalbuminuric patients or patients with overt nephropathy.

The association between glycemic control and NIDDM-associated nephropathy was further substantiated in the Oklahoma Indian Diabetes Study [163]. Individuals in this study with a fasting blood glucose more than 200 mg/dl had a 2.9-fold increased risk of ESRD compared with patients with normal fasting glucose values. This same increased risk for ESRD is evident in Pima Indians [164]. This may not be a universal association, as studies in African Americans with NIDDM failed to demonstrate a direct link between hyperglycemia and nephropathy [165, 166]. Nevertheless, the Diabetes Control and Complication Trial (DCCT) confirmed a role for hyperglycemia in renal disease in IDDM patients [167], and a similar role for glycemic control in NIDDM is likely. Hopefully, data from the United Kingdom Prospective Diabetes Study (UKPDS) in 1998 will provide an answer to this question.

Smoking

Smoking, a strong predictor of renal risk in IDDM [168], is also associated with progression in NIDDM [169]. It has also been noted that NIDDM patients with microalbuminuria were more frequently smokers than nonsmokers. Olivarius et al, examining male patients with newly diagnosed NIDDM, found that heavy albuminuria (that is, A/C ratio more than 20 μg/mmol) was more common in smokers (8.2%) and former smokers (7.3%) than in nonsmokers (2.1%) [112]. It is of interest that smoking is also an independent risk factor for albuminuria in patients with essential hypertension [170].

Tobacco smoking can cause vasoconstriction, impaired platelet function, and abnormal regulation of coagulation and blood pressure [171], accelerating the processes of vascular damage that often affect diabetic patients [172].

PATHOGENESIS

Intrarenal determinants of elevated GFR and their relationship to the glomerulosclerosis have been tested extensively in experimental models of diabetes. Increased RPF and glomerular capillary pressure mediate hyperfiltration. Glomerular hypertension (independent of systemic hypertension) may be an important factor in the initiation and progression of diabetic nephropathy [173]. A reduction in intrarenal vascular resistance favors the occurrence of glomerular hypertension, and this increases shear stress. Damage to endothelial and epithelial cells will ensue and disrupt the filtration barrier.

That hyperfiltration is not the only factor leading to renal disease in NIDDM is demonstrated again in data from Pima Indians. Diabetic Pima Indians have elevated GFR at early stages of NIDDM. However, baseline GFR was not predictive of increasing UAE nor declining GFR during a four-year follow-up, suggesting that other factors contributed to the progression of nephropathy [109]. Certainly, the abnormal biochemical milieu is important. Elevated ambient glucose concentrations alter many cellular functions relevant to diabetic nephropathy. They stimulate the sorbitol pathway [174], induce advanced glycation end-product formation [175], disrupt synthesis of glycosaminoglycans [176], and activate protein kinase C [177].

Some of these changes may affect the GBM. Diabetic nephropathy is characterized by GBM thickening and mesangial expansion, primarily as a result of extracellular matrix protein accumulation. The extent of mesangial expansion correlates with the clinical disease state. Quantitative studies have demonstrated that the early appearance of microalbuminuria is closely correlated with mesangial matrix expansion and GBM thickness [178].

Experimental models have shed light on some of the mechanisms leading to the development of diabetic ne-

phropathy. Investigators, however, have focused on insulinopenic models (analogous to IDDM), rather than hyperinsulinemic models (analogous to NIDDM). Glomerular lesions occur in some models of NIDDM but not in others [179]. Mesangial expansion and GBM thickening are found in many, but nodular lesions are found in only a few. Animals in these models do not develop renal failure. For example, Zucker diabetic fatty rats have hyperglycemia, hyperinsulinemia, and hyperlipidemia and develop progressive albuminuria. However, they develop hydronephrosis and interstitial disease, not glomerular disease [180].

Spontaneous focal segmental glomerulosclerosis has been observed in autosomal recessive obese Zucker rats [181]. Obese rats demonstrate glucose intolerance and insulin resistance [182], preceding albuminuria and renal injury. Glomerular hemodynamics are not significantly different between young obese Zucker rats and their lean litter mates [183], a finding of interest in view of abnormal GFR in insulinopenic models of diabetes.

Diabetic nephropathy is strongly influenced by genetic background. Wistar fatty rats (fa/fa), derived from crossing Zucker with Wistar-Kyoto rats, are obese with hyperinsulinemia, glucose intolerance, hyperlipidemia, hyperphagia, hyperglycemia, polydipsia, and glycosuria [184]. Sodium excretion is impaired, and the natriuretic effect of atrial natriuretic peptide [185] is reduced in these animals.

Hyperlipidemia

Dyslipidemia could play a role in the development of diabetic glomerular lesions. Treatment with clofibric acid and mevinolin, structurally unrelated lipid-lowering agents, altered the appearance of glomerular lesions [186] in experimental studies. It is currently unknown whether the same is true for NIDDM. There has been much excitement concerning an observation [187] that found that four weeks of pravastatin treatment reduced proteinuria in hypercholesterolemic patients with NIDDM.

Nondiabetic renal disease in NIDDM

The diagnosis of diabetic nephropathy is almost always based on clinical grounds. The diagnosis is supported by a long history of diabetes, evidence of target organ damage, and proteinuria preceding azotemia. The validity of this clinical approach is well established in IDDM [188, 189] but not in NIDDM.

The renal-retinal relationship in NIDDM. There is a dearth of information on retinopathy in NIDDM patients with renal disease. The available studies are flawed by a lack of uniform methodology, absence of fluorescence angiography, etc. Some clinically useful information, however, can be drawn from these studies. Ninety to 95% of IDDM patients with diabetic nephropathy have retinopathy. Forty to 75% of NIDDM patients with nephropathy have retinopathy [80, 113, 190–192]. In the study of Gall et al, one third of NIDDM patients with biopsy-proven nephropathy did not have evidence of retinopathy [113]. Parving et al noted that 41% of proteinuric NIDDM patients with nephropathy lacked retinopathy [190] compared with 60% or more of proteinuric NIDDM patients in studies from Marshall and Alberti [191] and Schmitz and Vaeth [80].

In the study by Parving, glomerulosclerosis was evident in all albuminuric patients with retinopathy. The specificity of retinopathy for the presence of nephropathy was 100%, whereas the sensitivity was 40%. The majority of patients with diabetic renal disease have retinopathy, however, the reverse is not true. The percentage of NIDDM patients with concurrent retinopathy and nephropathy is unknown. The incidence of retinal disease is greater than nephropathy. This discrepancy may reflect a greater sensitivity of fundoscopic examination for the presence of microangiopathy compared with the clinical diagnosis of nephropathy.

Specificity of albuminuria in NIDDM. Biopsy studies suggest that 25% to 50% of patients with NIDDM have a glomerular lesions unrelated to or in addition to diabetic nephropathy [113, 190, 192–194] (Table 5). Nondiabetic renal disease in IDDM is much less prevalent (5%). Recruitment bias and lack of uniform criteria for biopsy interpretation may have overestimated nondiabetic nephropathy in NIDDM. Schwartz et al found nondiabetic renal disease in only 3 of 32 NIDDM patients [192]. Parving et al found a high incidence (77%) of diffuse or nodular diabetic glomerulosclerosis in 27 of 35 NIDDM patients with persistent albuminuria [190]. Similarly, Lipkin et al noted that 25 of 82 patients had nondiabetic renal lesions.

In another study, biopsy specimens from 52 proteinuric NIDDM patients were examined [193]. Diffuse or global glomerulosclerosis, glomerular hypertrophy, and arteriolar hyalinosis were present in 19 patients. Sixteen patients had nonspecific glomerular changes. Exudative lesions (fibrin caps or capsular drops) and GBM thickening were also present. The remaining 17 patients had a form of glomerular disease superimposed on diabetic glomerulosclerosis. Thus, nondiabetic renal disease is present with some variability in NIDDM.

Because proteinuria in NIDDM is less specific than in IDDM, a lack of retinopathy, autonomic neuropathy, or a short interval between onset of diabetes (less than 5 years) and proteinuria raises the possibility of a nondiabetic renal lesion [190, 195]. These findings warrant strong consideration for renal biopsy (Table 6). Many studies have documented a primary glomerulonephritis, particularly membranous or IgA glomerulonephritis in patients with NIDDM [190, 195, 196]. However, superimposed glomerulonephritis in NIDDM is not frequent in systematic postmortem or biopsy studies (for example,

Table 5. Diabetic and non-diabetic renal disease in patients with NIDDM

Author [reference]	No. of patients	Nature of study and/or reason for biopsy	Renal histology		
			DGS	DGS & other	Other
Amoah [195]	60	Retrospective analysis, evaluation of renal dysfunction	72%	7%	22%
Parving [190]	35	Evaluation of albuminuria	77%		23%
Gambara [193]	52	Evaluation of albuminuria and renal dysfunction	36%	33%	30%
Fabre [94]	50	Natural history, retrospective	82%	18%	
Waldherr [197]	205	Autopsy	80%		
Lipkin [194]	82	Evaluation of albuminuria	61%	9%	30%
Schwartz [192]	32	Evaluation of albuminuria	91%		9%

DGS is diabetic glomerulosclerosis.

Table 6. Findings suggestive of non-diabetic renal disease in NIDDM

- Proteinuria without retinopathy
- Overt nephropathy with NIDDM <5 years
- Renal failure without significant proteinuria
- Sudden onset nephrotic syndrome
- Rapid decline in GFR (>1 ml/min/month)
- Persistent gross and microhematuria unexplained by urologic pathology
- RBC casts

Table 7. Strategies in the prevention of progression of nephropathy in type II diabetes

Antihypertensive treatment
Glycemic control
Discontinuation of smoking
Dietary protein restriction?
Treatment of hyperlipidemia
Avoidance of nephrotoxins
Radiocontrast agents: avoid unless absolutely indicated, modify dose, non-ionic agents (nephropathy with renal failure)

Waldherr et al [197] and Pinel et al [198]), and its occurrence may simply reflect coincidence.

Microhematuria in NIDDM

Microscopic hematuria with or without RBC casts has been reported in diabetic nephropathy [199]. One survey of 30 patients with diabetic nephropathy revealed hematuria in 30% and RBC casts in 13%. In a separate group, renal biopsy tissue from eight diabetic patients with RBC casts was examined. Five individuals had only diabetic nephropathy, and three patients had a disease other than diabetic nephropathy. Other series have suggested that a large fraction of diabetic patients with hematuria have superimposed glomerulonephritis [200]. Consequently, hematuria, and particularly RBC casts, requires further evaluation.

Hyperkalemia and hyporeninemic-hypoaldosteronism

Angiotensin-converting enzyme inhibitors are now standard medications for diabetic patients with proteinuria. Hyperkalemia has become more problematic with their increased use. Some patients may demonstrate a voltage-dependent distal renal tubular acidosis with normal or increased aldosterone levels and a hyperchloremic metabolic acidosis with sodium wasting and increased serum potassium [201]. More commonly, patients will have hyporeninemic-hypoaldosteronism as the cause of their hyperkalemia [202]. Recent studies suggest that deficiency in prostacyclin production and a concomitant increase in 12-hydroxyeicosatetraenoic acid (12-HETE) may underlie hyporeninemic-hypoaldosteronism and hyperkalemia in NIDDM. Antonipillai et al studied the urinary excretion rate of prostaglandin $F_{1\alpha}$ and 12-HETE in NIDDM patients with hyporeninemic-hypoaldosteronism and in control patients [203]. Excretion of 12-HETE was increased in the diabetic patients in general. Moreover, the NIDDM patients with hyporeninemic-hypoaldosteronism had a marked reduction in prostaglandin $F_{1\alpha}$ excretion despite increased 12-HETE excretion. This may be one mechanism contributing to hyperkalemia in NIDDM.

INTERVENTIONS IN NIDDM

Diabetes is a costly illness with frightening morbidity and premature mortality as illustrated by the fact that NIDDM patient survival on dialysis is equivalent to that of patients with gastric carcinoma. The magnitude of the problem and its economic impact have led to efforts to identify preventive and therapeutic options. It is logical to assume that maintaining euglycemia, stopping smoking, and controlling blood pressure may prevent the onset or slow progression of diabetic nephropathy and may reduce extrarenal injury (Table 7).

Blood pressure control

Consensus statements have emphasized the importance of antihypertensive therapy in preventing the development and progression of diabetic nephropathy [66, 204]. The kidney appears to be injured by elevated blood pressure, including even values that are normotensive according to World Health Organization or Joint National Commission criteria in diabetic and nondiabetic

renal disease [205]. Consequently, recommendations include treating even normotensive IDDM and NIDDM patients once microalbuminuria is present. Evidence for a beneficial effect of this strategy in NIDDM is less conclusive than in IDDM [206]. However, this approach seems reasonable in an effort to limit renal damage [101, 207].

Practical points concerning management of hypertension in NIDDM include the following:

(I) Salt balance. Exchangeable sodium is increased in IDDM and NIDDM patients [208]. Blood pressure is frequently salt sensitive even in nonalbuminuric diabetic patients [209]. Reducing dietary sodium intake and diuretic treatment are therefore logical therapeutic approaches. It is widely believed that diuretic monotherapy is not advisable [210]. However, this concern may not apply when low doses of diuretics are used [211]. The adverse metabolic effects of diuretic monotherapy may be prevented by concomitant use of ACE inhibitors.

The importance of reversing sodium retention (and extracellular volume expansion) is illustrated by the observation that reduction of proteinuria was most pronounced in studies using ACE inhibitors in which the highest doses of diuretics were given [212]. The antiproteinuric and antihypertensive effects of ACE inhibitors are amplified by sodium restriction [213, 214], as is the antiproteinuric effect of calcium channel blockers (CCBs) [215]. Control of hypervolemia is particularly important to prevent nighttime elevation in blood pressure [216].

Diuretic treatment is frequently neglected in the antihypertensive management of NIDDM patients, although one obviously has to avoid the risk of hypovolemia. In the initial stages of diabetic nephropathy, thiazides are usually sufficient, but with impaired renal function, loop diuretics are necessary. Uncontrolled clinical experience indicates that in NIDDM, the combination of loop diuretics and thiazides increases diuretic potency as it does in nondiabetic renal disease [217, 218]. Because of the high prevalence of hyporeninemic hypoaldosteronism, potassium-sparing diuretics must be used more cautiously, particularly when patients are treated with ACE inhibitors. These drugs are contraindicated when serum creatinine is elevated.

(II) Antihypertensive medication. Antihypertensive treatment studies differ with respect to endpoints: proteinuria or loss of GFR in NIDDM. Studies using prevention or modification of structural lesions as endpoints are not available. Studies also differ with respect to patient recruitment, blood pressure measurement, duration of observation, and goals of therapy. Despite these caveats, there is general agreement that lowering blood pressure is important regardless of the agent used. The most significant decrease in albuminuria occurred in studies with the largest reductions in blood pressure [212, 219]. Blood pressure values in the low to normal range should be targeted [66, 204, 205]. The selection of antihypertensive agents is also important because of the renoprotective effect of ACE inhibitors [220, 221] and, less uniformly, that of CCBs [222].

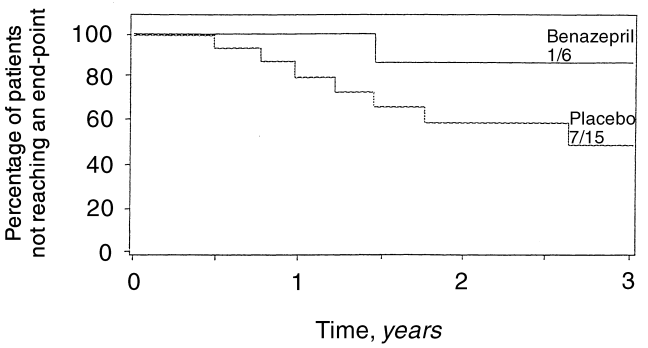

Fig. 6. Renal end point (doubling of serum creatinine or renal death) in 21 NIDDM patients in the AIPRI. Six patients were on the ACE inhibitor benazepril, and 15 patients were on placebo. Data are from Maschio et al [230].

(IIa) ACE inhibitors and AT_1 blockers. Two meta-analyses [220, 221] concluded that ACE inhibitors were renoprotective in diabetic patients. In addition, prospective placebo-controlled trials in normotensive microalbuminuric NIDDM have shown a diminished rate of progression of proteinuria with ACE-inhibitor treatment [223]. Captopril has been administered to normoalbuminuric, normotensive NIDDM patients in small short-term studies. ACE inhibition appeared to prevent even the onset of microalbuminuria [224], but this will require further analysis. There is no doubt that in hypertensive microalbuminuric NIDDM patients, ACE inhibitors diminish the UAE [219, 223, 225–227] or at least prevent an increase in UAE [60, 226]. In general, ACE inhibitors are relatively safe despite risks of unrecognized renal artery stenosis and hyperkalemia in NIDDM. It is important, too, that ACE inhibitors improve glucose uptake in peripheral tissue in NIDDM patients [228] with beneficial effects on glycemic control, although this may slightly increase the risk of hypoglycemia.

Angiotensin-converting enzyme inhibition is effective in reducing the increase in S_{Cr} [223] or measured loss of GFR [222] in diabetics and may even increase GFR [229]. The small subgroup of NIDDM patients in the Angiontensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study [230] showed possible long-term benefits (Fig. 6). Nevertheless, no prospective controlled study has documented a benefit from ACE inhibitors on definite endpoints in NIDDM patients with renal failure. In general, the ACE inhibitors' antiproteinuric effect is superior to diuretics, β blockers and short-acting CCB. Information is currently not available on AT_1 blockers in NIDDM, but two major prospective

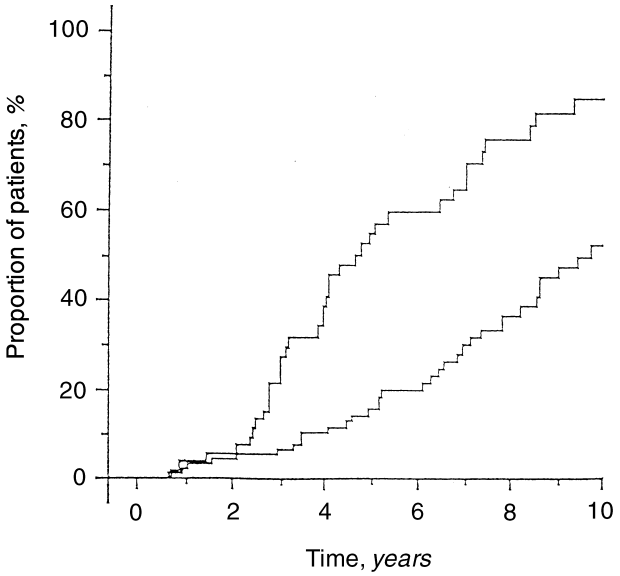

Fig. 7. Renal end point (loss of 40% of initial GFR) as a function of diastolic blood pressure in 158 patients with diabetic nephropathy. Comparison of patients with diastolic blood pressure of 85 mm Hg (upper line) or more and less than 85 mm Hg (lower line). $P < 0.001$. Data are from Bjorck [212].

trials are currently underway to assess their effects on NIDDM-related nephropathy in NIDDM.

Angiotensin-converting enzyme inhibitors progressively lose their antiproteinuric advantage over other agents as blood pressure control increases [221]. Analysis of an extension of the captopril trial in IDDM [206] showed that the event rate (renal end points) between the ACE inhibitor and the placebo arms became identical once treated blood pressure values were less than 95 mm Hg mean arterial pressure (E. Lewis, personal communication). The benefit of aggressive blood pressure control was also shown by Bjorck [212], as significantly less renal endpoints were observed when diastolic blood pressure was less than 85 mm Hg (Fig. 7).

(IIb) Calcium channel blockers (CCBs). CCBs inhibit vasoconstrictive, hypertrophic, and hyperplastic effects of Ang II through blockade of postreceptor calcium-dependent signaling events [231]. CCBs differ with respect to interactions with voltage-gated L channels, duration of action, and activation of the sympathetic nervous system complicating a generalized assessment of their efficacy in NIDDM [229, 232]. ACE inhibitors have been compared with nifedipine, nitrendipine, or amlodipine in microalbuminuric NIDDM patients. ACE inhibitors were superior when UAE was used as a surrogate endpoint [219, 232–235]. In other studies, ACE inhibitors have also proven more beneficial than CCB with respect to UAE [222, 236]. The rationale for CCB use comes from data in IDDM patients that demonstrated a significant lowering of albuminuria with verapamil and diltiazem [222] to an extent similar to that noted with ACE inhibitors [237, 238]. In NIDDM patients with overt nephropathy, a comparison between nifedipine and enalapril showed different effects on C_{Cr} and proteinuria despite similar degrees of blood pressure control. However, a recent comparison of cilazapril and amlodipine in hypertensive NIDDM patients using Cr^{51}-EDTA clearance found similar efficacy for cilazapril and amlodipine in delaying the slope of GFR decline at blood pressure values of less than 140/85 mm Hg. This is in agreement with Bakris et al's recent finding that lisinopril and nondihydropyridine CCB (verapamil or diltiazem) were superior to atenolol in attenuating the rate of decline of C_{Cr} and in reducing proteinuria in NIDDM [222].

(IIc) Combination ACE inhibitors and CCB. Several authors have suggested that CCB and ACE inhibitor used together would be superior to monotherapy with either drug [231, 239]. When nonhypotensive doses of verapamil and the ACE inhibitor, trandolapril, were administered together in spontaneously hypertensive stroke-prone (SHR-sp) rats, less proteinuria and glomerulosclerosis were noted than with either drug alone.

(III) Practical points. Atherosclerotic cerebrovascular disease should be excluded before blood pressure is lowered. Cerebral autoregulation is impaired in elderly hypertensive individuals with NIDDM, and rapid lowering of blood pressure poses the risk of cerebral underperfusion. Thus, it is advisable to choose a low initial medication dose that can be increased gradually.

Coronary heart disease also is frequent in NIDDM, leading to consideration of the J-curve phenomenon [240]. It has been argued that coronary oxygen extraction is maximal already under normal conditions so that lowering perfusion pressure below 85 mm Hg diastolic BP will lead to cardiac ischemia. However, Fletcher and Bulpitt concluded that cardiac mortality was higher even in the placebo arm of trials [241]. Hence, a low diastolic blood pressure may be no more than a marker of a sick patient with a high risk to die. In the Modification of Diet in Renal Disease Trial, there was no evidence of a J-curve phenomenon [242]. This is plausible because reducing blood pressure decreases afterload and wall stress. Nevertheless, cardiac ischemia may develop in individuals with severe coronary artery disease. Such patients must be carefully monitored during treatment.

Antihypertensive therapy has several uses in NIDDM in limiting end-organ renal and cardiovascular disease. Beta blockers have been grossly underused in dialyzed NIDDM patients with coronary heart disease [243]. Cardiac death rates in NIDDM patients on dialysis not receiving β blockers approached 30%. As such, the cardiac benefit derived from β blockade may be significant in NIDDM patients [244].

Orthostatic hypotension is frequent in NIDDM patients with autonomic neuropathy. It poses complex

problems, as it has been associated with increased mortality. The risk of hypotension is increased by aggressive diuretic treatment. It is therefore useful to give a major proportion of antihypertensive medication at bedtime to avoid nighttime hypertension and pronounced daytime hypotension.

Glycemic control

The DCCT in IDDM patients suggested that rigorous glycemic control interfered with the onset of diabetic nephropathy, that is, the development of microalbuminuria [167]. Data from renal transplant patients also support the conclusion that glycemic control can affect diabetic nephropathy. Barbosa et al randomized 48 diabetic renal transplant recipients to maximal or standard glucose control and assessed renal pathology by biopsy [245]. There was a significant increase in mesangial matrix expansion, arteriolar hyalinosis, and GBM widening in standard therapy patients compared with the maximal control group.

Normoglycemia in NIDDM appears to reduce or retard microvascular or macrovascular complications. A six-year prospective study from Japan evaluated intensive glycemic control (HbA_1C levels 7.1%) in NIDDM patients [161]. Patients were separated into a primary prevention cohort (retinopathy and microalbuminuria not present) and a secondary intervention cohort (patients with mild retinopathy and microalbuminuria). The percentage of patients developing nephropathy in the prevention cohort was 8% in the intensive group versus 28% in the conventional (HbA_1c levels 9.4%) group. In the intensive control cohort, 12% of patients progressed to nephropathy versus 28% in the conventional group. The Kumamoto study also suggested that glycemic control may affect the development and progression of microangiopathy in NIDDM. It is of interest that poor predialysis glycemic control is a predictor of morbidity on maintenance hemodialysis [246]. Not surprising is the view of the striking impact of glycemia on cardiovascular survival in NIDDM with cardiac disease [247]. The UKPDS, a large prospective trial evaluating glucose control in newly diagnosed NIDDM patients, will hopefully settle the question of glycemic control in NIDDM [248].

Intensive insulin therapy is not without potential adverse consequences. Several studies have demonstrated a paradoxical risk of progression and albuminuria in patients treated with insulin [44, 102]. Patients with nephropathy demonstrate insulin resistance more so than patients without nephropathy. A pilot study examining intensive insulin therapy in NIDDM patients who failed oral agents found that these patients were well controlled on insulin with little weight gain [249]. It has been suggested that improving insulin resistance without intensive insulin therapy would be ideal [16]. Medications such as metformin [248] and thiozolidinediones [250] may obviate the need for intensive insulin treatment early in NIDDM in the future and will hopefully improve renal outcomes. Interestingly, in the nine-year UKPDS update, metformin, alone or combined with insulin or sulfonylureas, was associated with less weight gain than sulfonylurea or insulin treatment alone [248]. Metformin appears to be a good choice for the treatment of obese NIDDM patients as long as renal function is normal. A recent study that compared metformin and glyburide demonstrated equivalent glycemic control for each; however, metformin did so without increasing body weight [236].

Recommendations about intensive glycemic control in NIDDM

Glycemic control in NIDDM should be taken as seriously as in IDDM [251]. We recommend target levels of glucose control as shown in Figure 8, but the goals and methods of treatment should be individualized. Aggressive glycemic control may be inappropriate in certain patients, for example, the aged, those with dementia, those with advanced renal failure, and those with advanced cardiovascular or cerebrovascular disease.

Protein restriction

Several studies have suggested that protein restriction can attenuate the evolution of nephropathy in IDDM. Raal et al prospectively followed two well-matched cohorts for six months on different diets [252]. Patients who received moderate protein restriction (0.8 g/kg/day) had a marked decrease in proteinuria and stabilized their GFR, in contrast to the patients who received the unrestricted diet (more than 1.6 g/kg/day). Dullaart et al also noted that dietary protein restriction in diabetic patients with albuminuria reduced the degree of albuminuria [253].

Few studies have focused on protein restriction in patients with NIDDM. Interestingly, an epidemiologic analysis of a cohort in the San Antonio Heart Study determined that high protein intake was not a risk factor for proteinuria in patients with NIDDM [254]. However, in a randomized crossover trial [255], moderate protein intake (0.8 g/kg/day) was compared with a high-protein diet (2.0 g/kg/day) to evaluate its effects on renal function and glycemic control. The moderate protein diet was associated with improvements in GFR and less proteinuria.

Despite the aforementioned data, the findings from the largest trial to date examining dietary protein restriction and progression of renal disease, the Modification of Diet in Renal Disease Study failed to demonstrate an unequivocal benefit of protein restriction in mostly nondiabetic patients with renal failure [256]. Certainly, catabolic patients with advanced diabetic nephropathy approaching ESRD may be at risk for malnutrition [257]. Based on the evidence in IDDM [258], however, it is

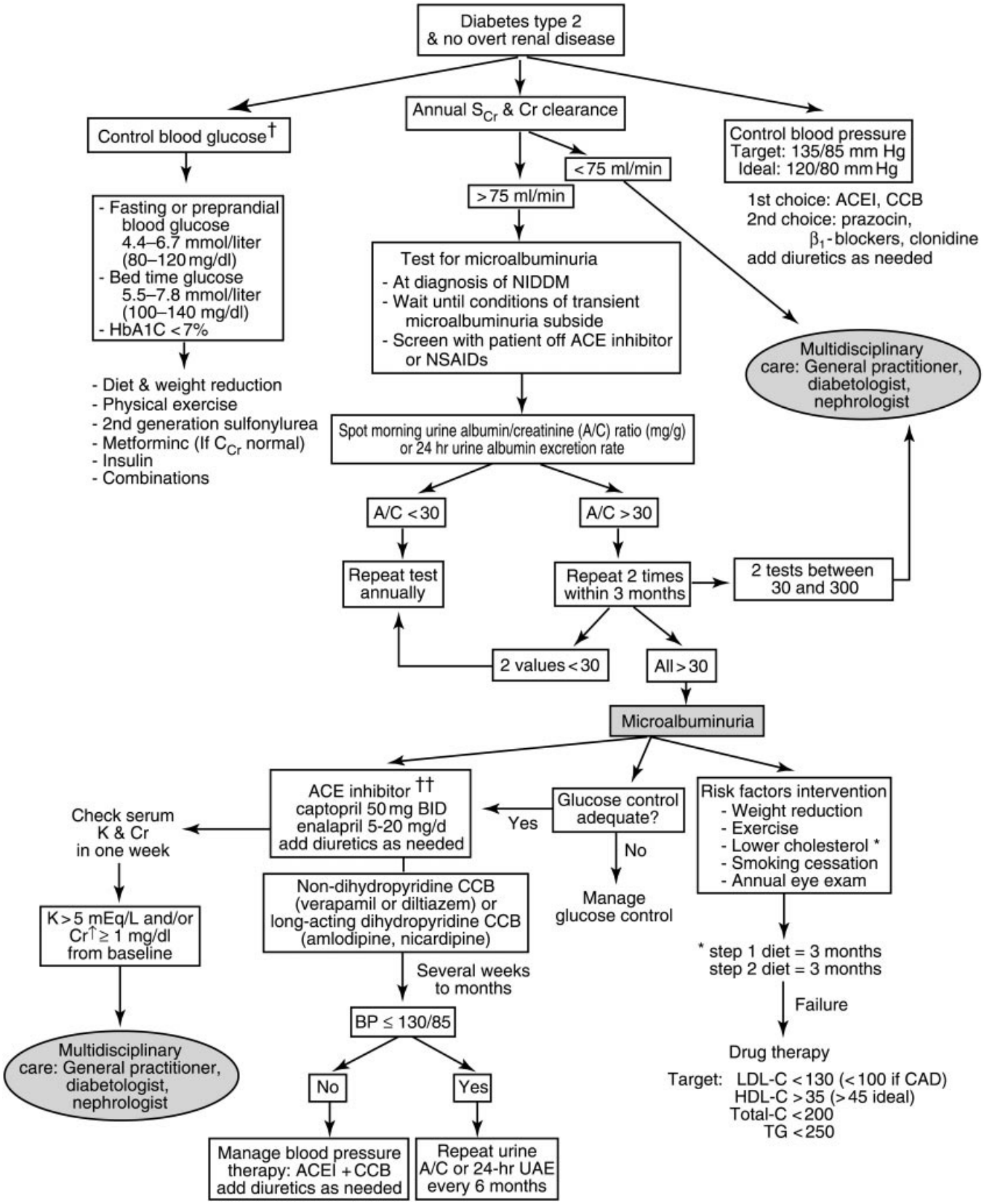

Fig. 8. Algorithm for prevention of nephropathy or progressive renal disease in patients with NIDDM. Data are from the Ad Hoc Committee for the Council on Diabetes Mellitus of the National Kidney Foundation [66], the American Diabetes Association [304], and the Forum One of the Fifth Regenstrief Conference (†) [251]. (††) Other ACE inhibitors may also be appropriate.

reasonable to recommend a dietary protein intake of 0.75 to 0.85 g/kg/day in early stages of diabetic nephropathy.

RISK FACTOR INTERVENTIONS

Lipid disorders

Cardiovascular risk is increased by a factor of approximately 3 in NIDDM [259], and this increase is particularly marked in the presence of proteinuria [103]. Indeed, 50% to 70% of NIDDM patients die in the preterminal stage of renal failure, mainly from CVD [4].

Cardiovascular disease in NIDDM is excessive even in nonproteinuric patients [260]. Proteinuria increases the risk [103]. Dyslipidemia appears to be a primary abnormality in NIDDM and is demonstrable even in prediabetic patients and in individuals with a genetic predisposition to NIDDM [261]. These patients have elevated total cholesterol and very low-density lipoprotein (VLDL) triglycerides and low high-density lipoprotein cholesterol, whereas LDL cholesterol is usually normal, at least when glycemic control is adequate. It has been suggested that hypertriglyceridemia results from increased hepatic synthesis of VLDL particles [262]. Decreased high-density lipoprotein cholesterol has been related to decreased postheparin [263] and adipose tissue lipoprotein lipase activity [264].

Nephropathy in NIDDM appears to alter the lipid profile in a more atherogenic direction. Total triglyceride and VLDL triglyceride concentrations increase markedly [265], whereas total cholesterol is not elevated, at least when adjustments are made for gender, age, and duration of diabetes [266].

Lp(a) is highly atherogenic [267, 268], and consequently its changes in NIDDM are of considerable interest. Unfortunately, the available data regarding Lp(a) are confounded by genetic heterogeneity. Small studies have failed to find a difference in median Lp(a) concentrations in nondiabetic controls and diabetic patients, including NIDDM patients with or without nephropathy [265, 269, 270]. Although one study did find higher apo(a) levels in NIDDM patients with microalbuminuria or macroalbuminuria, this observation was not confirmed in a more recent case-control study [265].

In nondiabetic patients on dialysis, high cholesterol concentrations paradoxically predict better survival [271], presumably because they are an indication of adequate nutrition. However, higher total cholesterol and LDL cholesterol strongly predict cardiac death in dialyzed diabetic patients [272]. Treatment with ACE inhibitors may lower plasma cholesterol [273], in part by reducing proteinuria. In addition, nonpharmacological interventions, that is, exercise [274], weight loss, and diet, are important. Nevertheless, it may be necessary to use fibrates or HMG-CoA reductase inhibitors to lower lipid levels further. Few studies on pharmacological lipid lowering have been carried out in NIDDM [275]. There is a consensus that in NIDDM patients with no other risk factors, pharmacological lipid lowering should be considered if LDL or triglycerides (TG) remain in the high-risk range [LDL-cholesterol (LDL-C) 160 mg/dl, TG greater than 400 mg/dl] [276, 277]. Target levels should be LDL-C 130 mg/dl, TG less than 200 mg/dl, and in patients with cardiac risk factors, for example, hypertension, smoking, family history of premature CVD or evidence of microvascular disease, treatment should be started at even lower concentrations and lower targets should be aimed for (that is, LDL-C 100 mg/dl and TG $<$ 150 mg/dl). Given the high cardiovascular risk in NIDDM [259], it is appropriate to lower plasma lipid concentrations in all NIDDM patients with renal involvement and aim for LDL-C of less than 100 mg/dl [277].

Fibric-acid derivatives have been studied in NIDDM patients with diabetic dyslipidemia, but in patients with renal involvement, these drugs can have significant untoward effects. HMG-CoA reductase inhibitors are highly effective in lowering cholesterol in NIDDM [273] without adversely affecting glycemic control. A risk of drug-induced myopathy is present in patients with renal failure [278, 279] and in patients taking cyclosporine, gemfibrozil, or other lipid-lowering agents. Because diabetic patients are already predisposed to cataract formation, HMG-CoA-reductase inhibitors may potentiate this condition.

SUMMARY

The incidence of ESRD in NIDDM has dramatically increased, dispelling the mistaken belief that NIDDM had a benign renal prognosis. Although similar clinical and histologic features characterize nephropathy in IDDM and NIDDM, the two diseases have distinct differences. Proteinuria may be less sensitive for detecting nephropathy in NIDDM. Moreover, nearly one third of patients with NIDDM with albuminuria have nondiabetic renal disease. Furthermore, although the absence of retinopathy in IDDM almost excludes diabetic nephropathy, patients with NIDDM without diabetic retinopathy may still be at risk for diabetic nephropathy. Finally, the nephropathy of NIDDM occurs at an older age, and the time span between diagnosis and development of renal disease (5 to 10 years) in NIDDM is shorter than in IDDM (15 to 25 years).

Lebovitz et al showed that the rate of loss of GFR was significantly greater in patients with overt proteinuria at baseline compared with patients with subclinical proteinuria (Fig. 9) [227]. Because of the adverse impact of microalbuminuria and clinical albuminuria on survival in patients with NIDDM, screening and intervention programs in NIDDM should be implemented early, at the stage of microalbuminuria. Ravid et al extended recom-

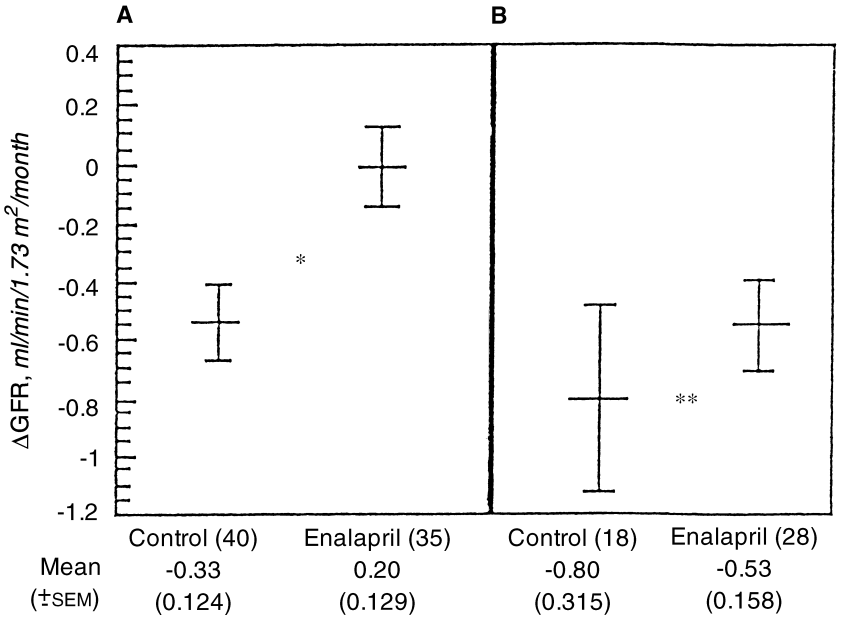

Fig. 9. Effect of baseline UAE on rate of change of GFR during antihypertensive therapy with enalapril in patients with microalbuminuria (*A*) and overt albuminuria (*B*). Data are from Lebovitz [227]. *$P = 0.0044$; **P = NS

mendations for early interventions even to normotensive NIDDM patients with microalbuminuria [223].

Cost-benefit analyses for managing IDDM patients with microalbuminuria projected considerable benefits with early interventions [280]. Similar analyses for NIDDM have not yet been undertaken, but it is expected that comparable savings would be achieved [66].

RECOMMENDATIONS

Screening for microalbuminuria

Urinary albumin excretion (UAE) should be measured at diagnosis and then annually in all patients with NIDDM [281]. Standard dipsticks give positive results only when the UAE is greater than 250 mg/minute [360 mg/day]. Products such as Micral Test (Boehringer-Mannheim, Mannheim, Germany) and Microbumintest (Ames, Miles, Elkhart, IN, USA) have been introduced to detect smaller amounts of albumin. Their specificities are fairly low: 82% and 87%, respectively [282]. Microbumintest is a qualitative test with a positive or negative result; a positive result corresponds to an albumin concentration greater than 40 mg/liter. Micral is a semiquantitative test with a range from 0 to 100 mg/liter. A value of 20 mg/liter or more is considered positive. These are useful screening tests, but microalbuminuria is best diagnosed using quantitative assays [281, 282]. These correlate well with 24-hour measurements in terms of sensitivity (94%) and specificity (96%) [282]. Thus, albumin levels in single-voided urine samples can be used to estimate 24-hour excretion.

Transient causes of microalbuminuria such as hyperglycemia, hypertension, cardiac failure, urinary tract infection, and excessive exercise must be considered when evaluating microalbuminuria. ACE inhibitors and some CCBs decrease UAE and may interfere with testing. These drugs should be avoided at initial screening. During therapeutic interventions, however, UAE rates can be determined without withholding these drugs. Persistent microalbuminuria needs to be documented by two or three elevated values over a three to six month period. A single elevated collection is not adequate [66].

Management of microalbuminuria

The best glycemic control possible should be the goal in microalbuminuric NIDDM patients [66]. If glycemic control is adequate and an increased urinary A/C ratio persists, an ACE inhibitor is appropriate in normotensive and hypertensive patients. Serum creatinine and potassium (K^+) levels should be evaluated within one week after initiating ACE inhibitor therapy. If serum K^+ increases to greater than 5.0 mEq/liter or creatinine increases to greater than 1 mg/dl from baseline, the patient should be referred to a nephrologist for further evaluation. In patients with microalbuminuria, a blood pressure of less than of equal to 130/85 mm Hg should be targeted [281]. A low-dose diuretic can be added if this is not achieved with an ACE inhibitor alone [66]. Additional interventions include treatment for dyslipidemia and smoking cessation. A comprehensive time course for diagnostic and therapeutic interventions in NIDDM patients is summarized in Figure 8.

Therapy of hypertension

Angiotensin-converting enzyme inhibitors or CCBs are the first choice for antihypertensive therapy in diabetic

patients with renal disease. For control of hypertension in patients with albuminuria (overt diabetic nephropathy), ACE inhibitors or nondihydropyridine CCBs (diltiazem, verapamil) are preferred agents [283, 284]. Because reducing albuminuria delays progression in IDDM- and NIDDM-related nephropathy, this parameter should be used as a benchmark for measuring efficacy of therapeutic interventions [285].

PERSPECTIVES

Insights into the pathogenesis of diabetic nephropathy have provided opportunities for specific therapeutic interventions. Thromboxane receptor antagonists have been tried in experimental diabetic nephropathy with some success [286]. Kinin-receptor antagonists may block the early hemodynamic effects of insulin-like growth factor-1 [287]. Anti-transforming growth factor β antibodies may abrogate renal hypertrophy and glomerulosclerosis [288]. Aminoguanidine, an inhibitor of advanced glycosylation and inducible nitric oxide synthase [289], is currently undergoing phase II/III clinical trials in diabetic nephropathy and may offer a means for reducing the formation and toxicity of advanced glycation end products. Lovastatin, by inhibiting the mevalonate pathway, matrix synthesis, and transforming growth factor β mRNA expression, may retard diabetic glomerulosclerosis [291]. Use of naturally occurring glycosaminoglycans (Sulodexide®) in NIDDM may also be of benefit in decreasing UAE [292]. All of these treatment strategies portend possible shifts in the epidemic of NIDDM-related kidney disease.

Screening for a genetic predisposition to progressive renal dysfunction should be considered in the future. ACE polymorphisms may play a deleterious role in the progression of renal dysfunction in NIDDM [123, 136]. Therefore, aggressive ACE inhibition (or perhaps Ang II receptor blockade) may be warranted for patients who are homozygous for the D allele of the ACE polymorphism [133].

Although it is a rational strategy to prevent diabetic nephropathy in NIDDM patients, it would obviously be more efficacious to prevent NIDDM *per se.* O'Dea observed normalization of glycemia when diabetic Australian aboriginals were re-exposed to their traditional lifestyle [293]. Eriksson and Lindgarde followed a population of 181 middle-aged men with impaired glucose tolerance [294]. Some of the patients were given a low-calorie diet and physical exercise, and the others were maintained on their habitual lifestyle. After five years, the prevalence of diabetes was markedly less in those who had been switched to a healthier lifestyle (10% vs. 28.6%).

Sadly, Western societies face problems of physical inactivity and obesity on a massive scale. According to one study, in 1991 the frequency of a body mass index above 25 kg/m^2 was 51.4% in the adult German population and 75% in individuals aged between 55 and 64 years [4]. This can be easily confirmed by a casual glimpse at a beach with German tourists or at leading German politicians. The same is true for the United States; to quote Klein, "The richest nation in the world is the fattest and growing fatter. Our behinds, seen on television or on tourists, have become the butt of jokes in every culture but our own" [295].

Paradigm shift in NIDDM practices

Medical care for patients with NIDDM in general, and for proteinuric NIDDM patient in particular, is suboptimal [296]. ESRD associated with NIDDM (at least in the United States) is mainly a disease of poor, older African Americans, Hispanics, and Native Americans who have endured substandard medical care during the interval between the diagnosis of diabetes and the onset of ESRD [297].

Most patients with NIDDM are currently being cared for by generalists. Many investigators have reported poor adherence to treatment and screening guidelines for patients with NIDDM [298, 299]. Only 26% of NIDDM patients taking insulin and 5% not taking insulin monitored their blood glucose daily, and education classes were attended by only 35% of patients. Diabetes care is lacking, further evidenced by data from the Indian Health Service [300]. Uncontrolled hypertension was present in 33% of patients and metabolic control (HbA_1C was 7.5% or less or mean blood glucose was 9.2 mmol/liters or less) in only 29%. There is little evidence that state-of-the-art treatment is provided to the majority of diabetic patients with renal disease [301]. A survey by Pommer et al documented suboptimal glycemic control, blood pressure control, and delayed timing of referral to a nephrologist in the majority of diabetic patients with renal disease in Berlin [301]. Initiatives to educate primary care providers as to the true renal risk of NIDDM are crucial.

The DCCT trial showed that achieving and maintaining near normal glycemia significantly reduced complications, yet it required close monitoring and ongoing support from health care teams, ample financial resources, and patient knowledge and motivation [165]. What has to change to reduce the burden of renal disease in NIDDM? To optimize the care of the NIDDM patient, we recommend the following: (a) data supporting the value of early treatment of microalbuminuria must be more widely disseminated; (b) education programs fostering information about diabetes treatment should continue to be developed and expanded [302, 303]; (c) sufficient resources and funding by governmental agencies should be available to all payors that provide health care to diabetics; and (d) NIDDM management can be

optimized by using a comprehensive, multidisciplinary team approach that involves physicians, nurses, diabetes educators, and behavioral therapists.

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APPENDIX

Abbreviations used in this article are: A/C, albumin-to-creatinine ratio; ACE, angiotensin converting enzyme; Ang, angiotensin; CCBs, calcium channel blockers; C_{Cr}, creatinine clearance; CVD, cardiovascular disease; DCCT, Diabetes Control and Complication Trial; ESRD, end-stage renal disease; 12-HETE, 12-hydroxyeicosatetraenoic acid; IDDM, insulin-dependent diabetes mellitus; GBM, glomerular basement membrane; GFR, glomerular filtration rate; NIDDM, non-insulin-dependent diabetes mellitus; RAS, renin-angiotensin system; RBC, red blood cell; RPF, renal plasma flow; RRT, renal replacement therapy; SBP, systolic blood pressure; UAE, urinary albumin excretion; UKPDS, United Kingdom Prospective Diabetes Study.

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