Perspectives in Diabetes

The Need for Early Predictors of Diabetic Nephropathy Risk

Is Albumin Excretion Rate Sufficient?

M. Luiza Caramori, Paola Fioretto, and Michael Mauer

Initial studies showing an ~80% rate of progression from microalbuminuria (MA) to proteinuria in type 1 diabetic patients led to the broad acceptance of MA as a useful clinical predictor of increased diabetic nephropathy (DN) risk. Some MA patients, however, have quite advanced renal structural changes, and MA may, in these cases, be a marker rather than a predictor of DN. More recent studies have observed only about a 30–45% risk of progression of MA to proteinuria over 10 years, while about 30% of type 1 diabetic patients with MA became normoalbuminuric and the rest remained microalbuminuric. The finding that some MA patients have only mild diabetic renal lesions is consistent with the lower than originally estimated risk of progression from MA to proteinuria and with the notion that some MA patients revert to normoalbuminuria. To increase the complexity of the scenario, some normoalbuminuric long-standing type 1 diabetic patients have well-established DN lesions and ~40% of all patients destined to progress to proteinuria are normoalbuminuric at initial screening, despite many years of diabetes. A similar picture is emerging in type 2 diabetic patients, although fewer studies have been conducted. Thus, the predictive precision for MA to progress to overt nephropathy over the subsequent decade or so is considerably less than originally described. It is unclear whether this is due to changes in the natural history of DN resulting from improved glycemia and blood pressure control, or whether there were overestimates of risk in the original studies due to the small sample sizes, post hoc analyses, and variable MA definitions. Albumin excretion rate (AER) remains the best available noninvasive predictor of DN risk and should be regularly measured according to established guidelines. However, AER may be unable to define patients who are safe from or at risk of DN with an accuracy that is adequate for optimal clinical decision making or for the design of certain clinical trials. Investigations into new risk markers or into the combined use of several currently available predictive parameters are needed. *Diabetes* **49:1399–1408, 2000**

From the Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota; and the Department of Medical and Surgical Sciences, University of Padova, Padova, Italy.

Address correspondence and reprint requests to Michael Mauer, MD, MMC 491, 420 Delaware St. SE, Minneapolis, MN 55455. E-mail: mauer002@tc.umn.edu.

ACEI, ACE inhibitors; AER, albumin excretion rates; DCCT, Diabetes Control and Complications Trial; DN, diabetic nephropathy; ESRD, end-stage renal disease; GBM, glomerular basement membrane; GFR, glomerular filtration rate; JDFI, Juvenile Diabetes Foundation International; MA, microalbuminuria; Vv(Mes/glom), mesangial fractional volume.

The proportion of patients with end-stage renal disease (ESRD) caused by diabetes has progressively increased during the last few decades, and diabetic nephropathy (DN) is now the single most common cause of ESRD in the Western world. In fact, in 1997, 44% of all new cases of ESRD in the U.S. were diagnosed in diabetic patients, >80% of whom have type 2 diabetes (1). Although a recent study from Sweden (2) in which patients were maintained under strict glycemic control reported a decrease in the incidence of DN in type 1 diabetic patients, this result has not been confirmed (3).

Based on studies in type 1 diabetes, it had been generally considered that once overt DN, manifesting as persistent proteinuria, is present, it was only possible to slow, but not halt, the progression toward ESRD (4–6). This led investigators during the early 1980s to search for early predictors of DN through the measurement of low concentrations of albumin in the urine. Some diabetic patients were found to have increased urinary albumin excretion rates (AER) not detectable by standard laboratory methods, and this condition was termed *microalbuminuria* (MA). Initial retrospective studies in type 1 diabetic patients (7–9) observed a risk of progression from MA to proteinuria of ~80% over the subsequent 6–14 years. These early studies, each of which used different AER criteria for MA, led to a consensus conference in which a general agreement was reached on the definition of MA (AER, 20–200 ng/min) (10). Since then, there has been broad acceptance of MA as a marker of increased DN risk. However, concern has been raised that there is a wide range of underlying diabetic glomerular lesions among long-standing type 1 diabetic patients (11,12). For some patients with persistent MA, renal lesions are quite advanced (11–13) and treatment for these patients could be less effective than at earlier stages of the disease. Thus, for these patients, MA may be a marker rather than a predictor of advanced renal structural changes. Therefore, it is not surprising that patients with MA may progress to proteinuria despite strict glycemic control

(14) and effective antihypertensive treatment. Thus, it would make sense to try to identify normoalbuminuric patients at increased DN risk in order to select those at early stages still amenable to aggressive intervention strategies such as strict glycemic control.

Although MA remains the best available marker for DN risk, we will review more recent studies suggesting that the percentage of MA patients progressing to proteinuria over ~10 years is 30–45%, much less than the initial reports of ~80% (7–9). Also, some MA patients may revert to normoalbuminuria. Although these differences may represent changes in the disease's natural history with improvements in treatment, MA is still a less precise predictor of DN risk than originally suggested. In fact, MA patients often have only mild diabetic renal injury (11,12), a finding consistent with a lower risk of progression from MA to proteinuria.

The presence of normal AER in long-standing diabetic patients has been said to identify patients at low risk of DN. However, a significant proportion of normoalbuminuric long-standing diabetic patients have well-established DN lesions (11,12), and ~40% of those who are ultimately at risk of progression to proteinuria are normoalbuminuric, despite many years of diabetes. Thus, it will be argued that AER, albeit the best currently available noninvasive predictor of DN risk, is unable to define patients who are safe from DN with an accuracy optimal for clinical decision making or for the design of certain clinical trials. For these reasons, it is suggested that investigations into new risk markers or into the combined use of several currently available markers may lead to important advances in this field.

METHODS

For a predictor of DN to be optimally useful, it should identify individuals at increased risk of the development of serious diabetic renal disease early enough in the natural history of the disorder that the evolution of the process can be influenced by intervention strategies. MA is uncommon in the first decade of type 1 diabetes, especially during the first 5 years (15–20), and by 20–25 years much of the natural history of the disorder has already declared itself within a patient population. Therefore, we used data derived from patients with 10–15 years of type 1 diabetes duration to determine the prevalence of normoalbuminuria, MA, and proteinuria in cross-sectional studies. Because the duration of type 2 diabetes is usually not accurately known, diabetes duration was not considered in the selection of prevalence data for our calculations. Longitudinal studies using AER as a predictor of the subsequent development of proteinuria and studies from which such information could be extracted (e.g., control populations in clinical trials) were also reviewed. We attempted to review all pertinent published articles in this area but, rather than performing meta-analyses, we selected those longitudinal studies for review which met the criteria outlined below. Omitted were articles with unorthodox definitions of MA, short follow-up times, or inadequate descriptions of the methods. It was considered important that patients be followed for at least 5 years from the baseline evaluation. This long follow-up was selected to improve the likelihood that the patient's final outcome would be reflected by the follow-up data. Shorter durations of follow-up were not extrapolated to longer follow-up times because data on patterns of progression of MA patients over time (e.g., linear and log linear)

were not available. We divided these studies into 3 groups. Group A consisted of studies that adopted the consensus (10) definition of MA (AER of 20–200 µg/min in at least 2 of 3 sequential timed urine collections performed over 1–6 months) in which only patients with 5 or more years of follow-up were included. In group B studies, baseline AER was defined on the basis of a single urine sample and/or the follow-up was a mean or median of 5 years. Studies that would have been in group A or group B but that used different AER criteria to define MA were put in group C. Studies with a mean or median follow-up of <5 years were not included. Studies in type 1 diabetic patients were included only if baseline diabetes duration for all patients in these longitudinal studies was at least 7 years. We considered type 1 and type 2 diabetes studies separately.

TYPE 1 DIABETES

Diabetic nephropathy risk in normoalbuminuric type 1 diabetic patients. Three landmark studies placed the issue of AER measurements in diabetic patients at center stage. Two of the studies met the criteria for inclusion in this review (7,9), while 1 study included normoalbuminuric patients with as little as 1 year of diabetes duration at baseline (8). The 2 included studies were in group C (Table 1). One study found progression from normoalbuminuria to MA (defined as AER 15–150 µg/min) in ~14% (9) and another found progression to proteinuria in ~12% of patients (7).

Three studies were included in group A. Forsblom et al. (21), in a small well-designed study, found that ~7% of normoalbuminuric patients progressed to proteinuria and 14% to MA over 10 years of follow-up. Drs. Peter Rossing and Hans-Henrik Parving (personal communication), at our request, reanalyzed their extensive data based on criteria we imposed for group A studies. This study, which is by far the largest to date, found progression rates similar to those of Forsblom et al. (21) (Table 1). Moreover, there was no difference in diabetes duration at baseline in the patients remaining normoalbuminuric compared with those progressing to MA or proteinuria at follow-up. Mathiesen et al. (22) found somewhat lower progression rates (Table 1) but excluded some hypertensive patients. Interestingly, Mathiesen et al. noted that the rate of progression from normoalbuminuria to MA and proteinuria was almost constant throughout the 10 years of the study. The progression risk was somewhat lower in the normoalbuminuric younger patients of Chiarelli et al.'s study (23) (Table 1).

Drs. Michael Steffes and William Thomas facilitated our access to Diabetes Control and Complications Trial (DCCT) data. Normoalbuminuric patients randomized to conventional insulin treatment with at least 5 years of follow-up were selected for group B studies (DCCT, unpublished data). The DCCT used a single baseline urine sample for initial classification (14). Nonetheless, the DCCT results are identical to those of Rossing and Parving (Table 1). The study by Rudberg et al. (24) in children and adolescents showed somewhat higher rates of progression to MA (Table 1).

Based on these studies, we estimate that 5% of normoalbuminuric patients with at least 7 years of type 1 diabetes will progress to proteinuria over the next 5–10 years, whereas 17% will progress to MA. Progression from normoalbuminuria to proteinuria presumes at least the transient presence of MA. Thus, careful follow-up and repeated measures of AER are

TABLE 1
Risk of progression from normoalbuminuria to microalbuminuria or proteinuria in type 1 diabetic patients

Patient group and study	n	Diabetes duration (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of microalbuminuria (%)
Group A					
Forsblom et al. (21)	29	22.1 ± 5.4 (15–38)	10	6.9	13.8
Rossing and Parving (personal communication)	453	19.7 ± 9.3 (7–40)	9.0 ± 1.3 (5–10)	5	17
Mathiesen et al. (22)	209	17 ± 5 (10–30)	10	3.8	10
Chiarelli et al. (23)	170	~9.3 (7.1–23.2)	~8 (8.1–9.3)	0	10.6
Group B					
DCCT (unpublished data)	204	10.6 ± 2.3 (7–15)	6.8 ± 1.5 (5–9)	5	17
Rudberg et al. (24)	53	~11.5 >8	8	5.7	28.3
Group C					
Mogensen and Christensen (9)	29	— (7–19)	— (7–14)	0	13.8
Parving et al. (7)	17	15 ± 4 (10–24)	6	11.8	0

Data are n, %, or means ± SD (range).

necessary to detect increasing AER in these patients. In fact, studies show that AER values in the higher range of normoalbuminuria indicate greater risk of progression to MA (25), and these findings should be considered in clinical and clinical research settings.

Glomerular structure in normoalbuminuric type 1 diabetic patients. Glomerular structure is normal at onset of diabetes, and changes can be detected by morphometric measurements within 1.5–2.5 years after onset (26). However, because the normal range for glomerular structures, such as glomerular basement membrane (GBM) width or mesangial fractional volume (Vv[Mes/glom]) is quite wide, it may take some time for some individuals to progress from the normal to the abnormal range. However, glomerular changes in long-standing diabetes are always discernible as evidenced by direct comparison with measures from the patient's non-diabetic identical twin (27). Thus, all patients with type 1 diabetes appear to be developing glomerular structural changes of diabetes, albeit some at very slow rates. Others develop lesions so fast that they result in overt DN in as little as 10 years. Therefore, it is not surprising that long-standing normoalbuminuric type 1 diabetic patients have increased GBM width and Vv(Mes/glom) compared with age- and sex-matched nondiabetic normal control subjects. In the largest study performed (12), 66 nonproteinuric patients were divided into 4 groups on the basis of their AER as follows: I) normoalbuminuric with AER <15 μg/min, $n = 33$; II) low level MA with AER 15–30 μg/min, $n = 11$; III) MA with AER 31–70 μg/min, $n = 13$; and IV) MA with AER 71–150 μg/min, $n = 9$. Glomerular structural parameters were compared with 52 age- and gender-matched normal control subjects. Because MA is uncommon during the first decade of diabetes and the degree of glomerulopathy is directly related to the duration of diabetes (28), only patients with diabetes duration of at least 10 years were included. All parameters of glomerulopathy were abnormal in the normoalbuminuric group, although approximately half of the patients fell into the normal range. Figure 1 shows data on Vv(Mes/glom) in these patients, but similar results were obtained for GBM width. Note that in many of the group I (normoalbuminuric) patients, Vv(Mes/glom), the structural parameter most

closely related to renal functional disturbances in diabetes (29), overlapped with values in patients in the MA groups (groups III and IV) and, in some instances, approached levels regularly associated with overt DN. Note also that several of the normoalbuminuric patients (group I) with Vv(Mes/glom) above the normal range had a reduced glomerular filtration rate (GFR) (<90 ml/min/1.73 m^2), hypertension, or both (Fig. 1). The combination of normoalbuminuria and reduced GFR is more likely to occur in type 1 diabetic women (30,31) and may be related to a self-selected low-protein diet. Whether some of these patients would have been MA on a normal protein diet is not known.

Other studies have shown that significant glomerular lesions can be present in normoalbuminuric patients. Berg et al. (32) found that 36 normoalbuminuric adolescents (median diabetes duration 10.8 years, range 7.5–19.2) had greater GBM width and mesangial matrix fractional volume than normal control subjects, but Berg et al. did not report an increase in Vv(Mes/glom) in these patients with approximately half of the diabetes duration of our cohort (12). Using pooled data from
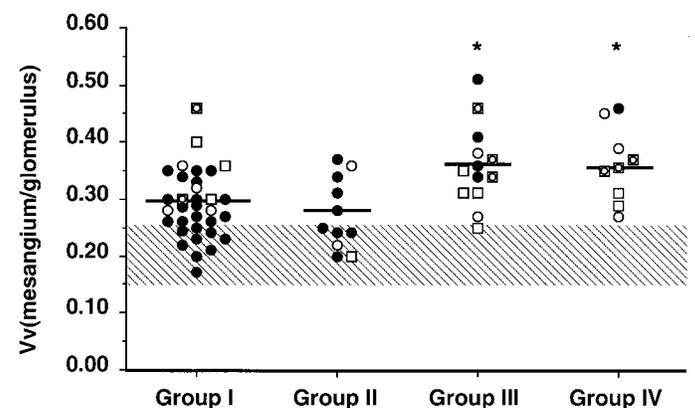

FIG. 1. Mesangial fractional volume (Vv[mesangium/glomerulus]) in the 4 groups of patients. The shaded area represents the means ± 2 SD in a group of 52 age-matched normal control subjects. ●, Normal BP and GFR; ○, reduced GFR (<90 ml · min^{-1} · 1.73m^{-2}); □, hypertension (≥140/85); ▣, reduced GFR and hypertension. *$P < 0.005$ vs. groups I and II (12).

TABLE 2
Risk of progression from microalbuminuria to proteinuria in type 1 diabetic patients

Patient group and study	n	Diabetes duration (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of normoalbuminuria (%)
Group A					
Forsblom et al. (21)	20	25.7 ± 5.7 (16–36)	10	25	35
Rossing and Parving (personal communication)	132	20.3 ± 8.7 (7–40)	9.1 ± 1.3 (5–10)	30	20
Group B					
DCCT (unpublished data)	30	11.4 ± 2.3 (7–15)	7.3 ± 1.6 (5–9)	23	43
Rudberg et al. (24)	11	~11.5 >8	8	18.2	36.4
Group C					
Mogensen and Christensen (9)	14	— (7–19)	~10 (7–14)	85.7	7.1
Viberti et al. (8)	8	14.1 ± 2.9 (7–33)	14	87.5	0
Parving et al. (7)	8	19 ± 5 (13–25)	6	62.5	25

Data are *n*, %, or means ± SD (range).

several studies from her laboratories, Østerby (28) described an increase in GBM width in normoalbuminuric type 1 diabetic patients, whereas Vv(Mes/glom) was similar in control subjects and normoalbuminuric patients. However, the differences in our results (12) compared with Østerby's (28) results are best explained by the marked differences in duration of diabetes in the 2 groups of normoalbuminuric patients (12 years in the Aarhus cohort versus 21 years in the Minnesota cohort). It should also be pointed out that the results of the normoalbuminuric patients shown in Fig. 1 were confirmatory of our earlier study (11). However, different structural definitions were used in our earlier study (11), and this has led to some confusion in the interpretation of our results (32a). In fact, our findings of advanced lesions in some normoalbuminuric patients are also entirely consistent with the natural history data previously described. Thus, it is not surprising that some patients, who are normoalbuminuric after many years of type 1 diabetes but have advanced glomerular lesions, may progress to MA and proteinuria. In fact, in a preliminary 5- to 17-year follow-up study of normoalbuminuric patients with long-standing diabetes, we found that those progressing to MA or proteinuria had worse glomerular lesions at baseline than those who remained normoalbuminuric (33). The increase in AER at early clinical stages is related primarily to increasing Vv(Mes/glom). Thus, we previously showed that changes in AER over 5 years correlated with changes in Vv(Mes/glom) over this time, but not with other structural variables (34).

Diabetic nephropathy risk in microalbuminuric type 1 diabetic patients. The 3 original articles (7–9) on this subject studied a total of 30 patients, used 3 different ranges of AER to define MA, may have used post hoc methods to select those ranges, and included some patients whose baseline status was defined by a single urine sample (7,8). Progression to proteinuria from MA over 6–14 years occurred in ~80% of these patients (group C) (Table 2).

The prospective study by Forsblom et al. (21) suggested that these 3 initial studies may have overestimated the risk of progression from MA to proteinuria. This study evaluated 20 MA type 1 diabetic patients with 16–36 years of diabetes duration using group A criteria (Table 2) and found progression to proteinuria 10 years later in only 25%, whereas 35% reverted to normoalbuminuria and 40% remained microalbuminuric. One argument that could be raised against the conclusions of this study is that by selecting patients with at least 15 years of disease duration, the study was biased toward patients less likely to progress, because most patients destined to develop proteinuria will do so before 20 years of duration. Drs. Peter Rossing and Hans-Henrik Parving (personal communication) performed analyses that we requested on their extensive patient population and permitted the use of the data for this review (Table 2). Using group A criteria, they followed 132 MA patients with 20.3 ± 8.7 (range 7–40) years' duration for a mean of 9.1 years. Thirty percent had developed proteinuria, 20% became normoalbuminuric, and 50% remained microalbuminuric at follow-up. Duration of diabetes was, in fact, shorter at baseline in those with MA progressing to proteinuria (17 ± 8 years) than those remaining with MA (22 ± 9 years, *P* < 0.005) but was not different from those becoming normoalbuminuric (20 ± 9 years). These data are consistent with an earlier abstract by Rossing et al. (35) indicating a 45% risk of progression to proteinuria in MA patients with <15 years of diabetes duration vs. 26% progression rate in patients with >15 years' duration. Indeed, these studies confirmed Forsblom et al.'s (21) observations of a 25% risk of progression of patients with 15 or more years of diabetes duration. Interestingly, data extracted from conventionally treated MA DCCT patients (group B) (Table 2) revealed progression rates to proteinuria similar to those of the group A studies (Table 2). However, duration of diabetes in this DCCT cohort was 7–15 years and progression to proteinuria was only 23%. This was less than the 45% progression rate in the similar but much larger cohort of Rossing et al. (35). These differences could be due to the less rigorous definition of MA at baseline in the DCCT study or could represent population differences. Rudberg et al. (24) found an even lower progression rate (18.2%) (Table 2) in MA children and adolescents. The reason for this is not clear, but it may be age related (see also Chiarelli et al [23], Table 1) or a consequence of the small sample size.

Based on these more recent studies, we estimate the rate of progression from MA to proteinuria over 5–10 years to be ~30%, perhaps 15% higher in patients with <15 years' dia-

TABLE 3
Risk of progression from normoalbuminuria to microalbuminuria or proteinuria in type 2 diabetic patients

Patient group and study	*n*	Age (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of microalbuminuria (%)
Group A					
Forsblom et al. (39)	108	~58 (35–70)	9	8.3	20.4
Tanaka et al. (40)	74	~61 (60–75)	6	0	32.4
Ravid et al. (41)	97	54.4 ± 2.9 (38–59)	6	0	15.5
Group B					
Gall et al. (43)	191	55 (20–65)	5.8 (1.5–6.0)	2.6	18.8
Ravid et al. (44)	621	47.7 ± 4.5 (40–60)	7.8 ± 0.9 (2–9)	14.5	17.9
Group C					
Mogensen (38)	128	~66 (50–75)	10	5.5	—
Kawazu et al. (45)	33	~54	8	0	57.6
Jerums et al. (46)	51	57 ± 7.1	6.4 ± 2.1 (3–10.3)	11.8	5.9
Haneda et al. (47)	34	~57	5	2.9	29.4
Niskanen et al. (48)	92	~56 (45–64)	5	0	10.9

Data are *n*, %, or means ± SD (range).

betes duration, but considerably lower than originally estimated. It is possible, of course, that with a follow-up >10 years, more MA patients would progress to proteinuria. However, it is also possible that more progression would be seen with longer follow-up in the normoalbuminuric patients. These long-term data are needed but are currently not available. One hypothesis that could explain these reduced progression rates is the recent change in the natural history of this disorder based on newer treatment strategies such as improved systemic blood pressure control. Although currently available data are not conclusive, Drs. Rossing and Parving did not find a different rate of return to normoalbuminuria from MA in patients treated or not treated with antihypertensive medications (P. Rossing, H-H. Parving, personal communication), including ACE inhibitors (ACEI). Another suggestion is that overall management of glycemia has improved since the original observations. There are no studies with adequate statistical power to address this hypothesis with confidence. Nonetheless, the DCCT could not demonstrate that improved glycemia has a beneficial effect on the risk of progression from MA to proteinuria (14).

Glomerular structure in microalbuminuric type 1 diabetic patients. Unlike the controversies regarding normoalbuminuric patients, there is general consensus that, on average, MA patients have increased GBM width and Vv(Mes/glom) compared with normoalbuminuric patients (11–13,36) and control subjects (11–13). However, all studies have shown wide ranges of glomerular structure among type 1 diabetic patients with MA. Thus, GBM width ranges from the upper limits of normal to markedly increased. Moreover, there is no significant increase in GBM width in patients with different levels of MA (12). The same is true for Vv(Mes/glom) (Fig. 1) when the values in MA patients in groups III and IV ranged from the upper limits of normal (12) to levels that overlapped with those observed in patients with proteinuria (P.F., M.M., unpublished data). The values in the patients in groups III and IV were greater than in patients with lower levels of increased AER (15–30 μg/min, group II) and normoalbuminuric patients (group 1), whereas groups I and II overlapped completely (12). Østerby (28)

found some MA patients with Vv(Mes/glom) in the normal range. We also found this to be true when patients with AER in the range of 15–30 μg/min were examined (group II) (Fig. 1). However, at higher levels of MA, Vv(Mes/glom) was increased in virtually all patients. Also, we found that patients with AER >30 μg/min had a relatively high incidence of hypertension, decreased GFR (<90 ml · min^{-1} · 1.73 m^{-2}), or both (12). Nonetheless, even among these patients, the range of Vv(Mes/glom) was quite wide and the values in the MA patients overlapped with those of the normoalbuminuric patients (Fig. 1). In longitudinal studies of MA patients, Bangstad et al. (37) found that GBM width at baseline biopsy was predictive ($r^2 = 0.67$, $P < 0.0001$) of AER after 6 years of follow-up, whereas Vv(Mes/glom) was a significant but less precise predictor.

In summary, the presence of serious diabetic glomerular lesions in some normoalbuminuric patients suggests that altered glomerular permeability to proteins is not a necessary precondition for the development of these lesions. It is unlikely that established diabetic glomerular lesions are of little prognostic value in normoalbuminuric patients. On the contrary, preliminary studies indicate a greater risk of progression in normoalbuminuric patients with more advanced lesions (33). The risk of progression to proteinuria over the next decade of long-standing type 1 diabetic patients with persistent MA is less than originally estimated. Moreover, approximately one-third of MA patients will return to normoalbuminuria. On the other hand, because 5% of long-standing normoalbuminuric patients will be proteinuric and 17% will be microalbuminuric after 5–10 years of follow-up, and because ~75% of long-standing type 1 diabetic patients will be normoalbuminuric at initial evaluation (15–19), one can estimate that 40% of those patients at risk of DN will be normoalbuminuric at baseline. This variable outcome could reflect the wide range of glomerular structural measures seen among normoalbuminuric and MA patients; however, this hypothesis has not been adequately tested. Finally, these observations should be taken into account in discussing prognosis with individual patients and, perhaps, in making decisions about treatment. Certainly, these data must be

TABLE 4
Risk of progression from microalbuminuria to proteinuria in type 2 diabetic patients

Patient group and study	n	Age (years)	Observation period (years)	Cumulative incidence of proteinuria (%)	Cumulative incidence of normoalbuminuria (%)
Group A					
Tanaka et al. (40)	49	~65 (60–75)	6	53.1	0
Ravid et al. (52)	52	44.8 ± 3.5 (36–49)	5	36.5	—
Ahmad et al. (53)	58	50.3 ± 2.1 (45–55)	5	20.7	—
Group B					
Gall and Parving (personal communication)	86	58 (28–65)	5	34.8	—
Group C					
Mogensen (38)	76	~66 (50–75)	10	22.4	—
Yajima et al. (54)	59	—	9	35.6	—
Kawazu et al. (45)	15	~56	8	40	0
Haneda et al. (47)	18	—	5	33.3	0
Niskanen et al. (48)	21	~56 (45–64)	5	0	42.9

Data are n, %, or means ± SD (range).

carefully considered when designing intervention trials for MA patients.

TYPE 2 DIABETES
Diabetic nephropathy risk in normoalbuminuric type 2 diabetic patients. Mogensen (38) first studied the prognostic value of AER in type 2 diabetic patients (Table 3). AER was measured on spot urines and on single samples from 32% of the case subjects. In this 10-year retrospective study, MA was defined as urinary albumin concentration of 30–140 μg/ml. Progression from normoalbuminuria to proteinuria occurred in 5.5% of these patients. The risk of progression to MA was not stated. The 48% death rate in these initially normoalbuminuric patients was remarkably high. Thus, the data from this study could not be used to estimate the risk of renal progression among normoalbuminuric type 2 diabetic patients.

For this review, we used the 3 published reports that met the group A studies' criteria except for duration, which cannot be accurately determined in type 2 diabetic patients (Table 3). These studies (39–41) followed patients for 6 to 9 years from the baseline AER measurement and found a 15–30% incidence of progression from normoalbuminuria to MA and from 0 to 8% from normoalbuminuria to proteinuria. Table 3 excludes 1 study with similar outcomes in which >20% of case subjects were lost during follow-up (42).

Two papers were categorized in group B. One produced similar (43) and the other produced higher values (44) of progression to proteinuria than the group A studies (Table 3). Five papers (38,45–48) were in group C because of the MA definition used (Table 3). Progression from normoalbuminuria to MA varied markedly from 5.9 to 57.6%, whereas progression from normoalbuminuria to proteinuria varied from 0 to 11.8%. Only the data from group A studies were used for the risk calculation.

Glomerular structure in normoalbuminuric type 2 diabetic patients. There are few published papers on renal structure in normoalbuminuric type 2 diabetic patients compared with control subjects, so information was also extracted from published abstracts.

The rate of development of DN lesions is less clear in type 2 compared with type 1 diabetic patients because, with the exception of the Pima Indian studies (49), duration is usually not precisely established in these patients. Nonetheless, GBM width and Vv(Mes/glom) are increased in normoalbuminuric Caucasian (50), Pima Indian (49), and Japanese (51) long-term type 2 diabetic patients. As in type 1 diabetic patients, there is considerable overlap with normal control subjects, and some normoalbuminuric type 2 diabetic patients have relatively advanced glomerular lesions (50,51). Thus, as is true for type 1 diabetic patients, there is a structural basis for explaining the progression to MA and proteinuria among some normoalbuminuric type 2 diabetic patients. Whether normoalbuminuric type 2 diabetic patients with more advanced diabetic renal lesions are at greater risk of progression needs to be determined. In Pima Indians, glomerular structure was not different in MA patients compared with normoalbuminuric patients with long diabetes duration, whereas MA patients had more advanced glomerulopathy than normoalbuminuric patients with short duration. These results might explain the observation that some long-term normoalbuminuric patients are at high risk of progression. Further, as discussed below, there are more varied renal structural patterns and patterns of functional progression among microalbuminuric, and also proteinuric, type 2 diabetic patients compared with type 1 diabetic patients, and the final outcome of these patients remains to be fully established.

Diabetic nephropathy risk in microalbuminuric type 2 diabetic patients. For reasons outlined above, the initial retrospective examination of outcomes in 76 MA type 2 diabetic patients by Mogensen (38) was a group C study (Table 4). MA patients in this study had a 77.6% 10-year mortality rate, mostly from cardiovascular disease, whereas 22% progressed to proteinuria.

Subsequently, 3 prospective group A studies (40,52,53) with much lower mortality rates among MA type 2 diabetic patients have been published. These studies included a total of 159 MA patients followed for 5–6 years with an average risk of progression to proteinuria of ~40% (Table 4). The risk of proteinuria over a longer term follow-up is not known but is presumably greater. One of these studies (40) reported that no patients were normoalbuminuric at follow-up (Table 4). The other 2 studies (52,53) did not provide these data.

One group B study evaluating 86 MA patients (M.-A. Gall., H.-H. Parving, personal communication) observed, after 5 years of follow-up, approximately the same progression rate to proteinuria as seen in group A studies, but return to normoalbuminuria was not defined in this cohort (Table 4). Five studies were classified as group C because of MA definitions (38,45,47,48,54) (Table 4). In these studies, the progression rates from MA to proteinuria ranged from 0 to 40%, and these articles were not used in the risk calculations.

Glomerular structure in microalbuminuric type 2 diabetic patients. Caucasian type 2 diabetic patients with MA have more complex patterns of renal structural changes than MA type 1 diabetic patients. A light microscopic study of 34 unselected MA type 2 diabetic patients described that 10 (29.4%) had normal or near-normal renal structure (55), a finding uncommon in type 1 diabetes. Ten patients had renal structural changes typical of those seen in type 1 diabetic patients with more or less balanced severity of glomerular, tubulointerstitial, vascular, and global glomerulosclerosis lesions. However, 14 subjects (41.2%) had atypical patterns of renal injury with absent or only mild diabetic glomerular changes associated with other disproportionately severe renal structural changes, including important tubulointerstitial lesions with or without arteriolar hyalinosis and with or without increased global glomerular sclerosis. Patients with proliferative retinopathy all had typical and well-established glomerulopathy lesions. None of the patients without retinopathy had typical lesions. However, background retinopathy could be associated with any of the 3 structural categories defined above. These studies were confirmed by electron microscopic observations (56) showing that MA type 2 diabetic patients more frequently had electron microscopic morphometric glomerular structural measures in the normal range and, as a group, had less severe lesions than MA type 1 diabetic patients. Many of these observations have been confirmed in Japanese type 2 diabetic patients (51). On the other hand, Pima Indian type 2 diabetic patients at very high risk of ESRD from diabetes appear to have lesions more similar to those seen in type 1 diabetic patients. One study has argued that the underlying pattern of renal injury does not predict the rate of GFR decline among a Caucasian cohort of already proteinuric type 2 diabetic patients (57). In contrast, a large 4.3-year follow-up study of ACEI-treated Caucasian type 2 diabetic patients with MA and proteinuria observed that patients with more rapid GFR decline had greater GBM width and Vv(Mes/glom) at baseline (58).

In summary, assuming the risk of progression from MA to proteinuria in type 2 diabetic patients to be ~40% (Table 4), then the risk of developing proteinuria over the next 10–15 years in normoalbuminuric type 2 diabetic patients would be ~12% (Table 3). Based on studies of >6,000 patients, ~70% of screened type 2 diabetic patients are normoalbuminuric (42,59–67). It can then be estimated that ~40% of the dipstick-negative type 2 diabetic patients who are ultimately destined to develop proteinuria will be normoalbuminuric at initial screening, whereas ~60% will be microalbuminuric. Thus, the predictive value of AER below the range of overt proteinuria appears to be similar among type 1 and type 2 diabetic patients. This similarity in prognostic value of AER emerges despite the fact that knowledge of duration in type 2 diabetes is less precise than in type 1 diabetes, and the follow-up period in the type 2 diabetes studies has tended to be shorter than in type 1 studies. Whether risk of progression in type 2 diabetic patients would be even greater if the follow-up period were extended is an important but unanswered question. The study of type 2 diabetes is further complicated by the findings of greater renal structural heterogeneity among type 2 diabetic patients than type 1 MA and proteinuric patients (50,51,56,68). The regularity with which type 2 diabetic patients with proteinuria progress to ESRD is less well known than for type 1 diabetic patients. Nelson et al. (69) suggested that the rate of decline of GFR among type 2 diabetic Pima Indian patients is similar to that of Caucasian type 1 diabetic patients. However, in contrast to Pima Indians and type 1 diabetic patients, some proteinuric Caucasian and Japanese type 2 diabetic patients have normal or near-normal glomerular structure and they seem not to progress toward ESRD at the same rate as patients with advanced lesions (58). At any rate, the prognostic value of proteinuria is less clear in type 2 diabetes versus type 1 diabetes and, consequently, so is the meaning of progression from MA to proteinuria in these patients. The higher cardiovascular death rate among type 2 diabetic patients with MA may further obscure nephropathy risk. There is also a higher incidence of hypertension among normoalbuminuric and microalbuminuric type 2 diabetic patients compared with type 1 diabetic patients. On one hand, left untreated, this could superimpose hypertensive renal injury on the diabetic nephropathy lesions. Theoretically, hypertension could also accelerate diabetic lesions. Further, hypertension could be associated with increased urinary AER (70–72). Thus, the greater incidence of hypertension in type 2 diabetic patients could complicate the predictive value of AER for DN risk in these patients. On the other hand, antihypertensive treatment with drugs, such as ACEI, could directly influence AER (73) and obscure outcomes defined by this measure. Finally, racial factors may have greater influence in nephropathy risk in type 2 diabetes than in type 1 diabetes (74). Perhaps even more than for type 1 diabetes, examination of renal structure may provide a substantial basis for understanding the heterogeneity in outcome among type 2 diabetic patients with MA. For these reasons, it is considered vital that well-designed large longitudinal natural history and renal biopsy studies be carried out among various ethnic and racial groups with type 2 diabetes. It is worth reiterating that >35% of all new ESRD patients in the U.S. have type 2 diabetes, yet their underlying renal disease is still poorly understood.

NEED FOR NEW MARKERS AND PREDICTORS OF DIABETIC NEPHROPATHY RISK

DN has rapidly become an important public health problem. Early detection of risk leading to the possibility of intervention before advanced renal damage has occurred is an obviously important goal. This goal is made difficult by the fact that much of the important diabetic renal structural injury can occur in absolute clinical silence. It may not be practical to treat all diabetic patients with all potentially useful therapies (e.g., strict glycemic control and antihypertensive medications), because of issues of cost and inadequate health care infrastructure, and because those without risk of renal complications would be needlessly exposed to the risk of these treatments. It would be far better to focus the available health care resources on those most likely to benefit. Measurement of AER in the subproteinuric range has been a very

important advance in this field. This review confirms that AER is the strongest broadly available marker or predictor of DN risk. However, we need improved markers and predictors of DN risk. These will be addressed in 2 general categories as follows: *1*) better use of existing methods and *2*) development of new technologies.

Existing methods. Longitudinal studies are indicated in type 1 and type 2 diabetes, which would examine the potential value of using repeated measures of AER over time, different set points for the definition of MA, or both. In addition, the combination of measures of AER with multiple clinical and renal structural parameters may lead to the development of more precise risk estimates for DN. These additional variables could include age, diabetes duration, blood pressure (including 24-h blood pressure monitoring), GFR, HbA_{1c}, retinopathy, and renal biopsy measurements. Prospective studies in type 1 and type 2 diabetic patients generally support the concept that normoalbuminuric and MA patients who progress have significantly higher baseline levels of blood pressure (25,39,43,44,47,75–77) and HbA_{1c} (14,21,22,25, 39,40,43–45,47,77–79) compared with patients that do not progress. However, there is still controversy as to whether increased baseline GFR is a predictor of progression (9,24,80–85). Preliminary results of our prospective study in normoalbuminuric type 1 diabetic patients have shown that patients who progress to MA or proteinuria have worse baseline glomerular lesions, lower GFR, and are more frequently hypertensive than patients remaining normoalbuminuric (33). Other variables, in a list by no means meant to be exhaustive, could include plasma prorenin (86,87), erythrocyte sodium/lithium countertransport activity (23), lipid levels, smoking history, and family history of cardiovascular disease and DN. A multivariate risk-assessment scheme far more exact than AER alone could emerge from such studies.

Development of new technologies. New tests are needed to provide accurate DN risk estimates before renal functional disturbances are well established (88). Initially, these tests will need to be validated, at least in part, by their association with important renal lesions as ascertained in renal biopsies. If sufficiently precise, these early predictors could obviate the need for renal biopsy except as a research tool. There are many possibilities for such new approaches to this problem and only a few are suggested as follows: *1*) identification of genes associated with increased or decreased DN risk; *2*) measures of substances in blood or urine, such as extracellular matrix molecules, products of glycation, or growth factors; *3*) measurements of tubular function; *4*) measurements of cellular functions (e.g., in cultured skin fibroblasts), which may be associated with DN risk, including extracellular matrix molecules and growth factors; *5*) less invasive methods such as fine needle aspiration to sample renal tissues for structural or biochemical changes associated with nephropathy risk; and *6*) development and application of new imaging technologies (e.g., positron emission tomography and magnetic resonance imaging) as tools to detect early renal diabetic biochemical or structural changes.

CONCLUSIONS

The measurement of urinary AER has led to very important advances in the field of DN. AER is currently the best available noninvasive means of following the course of kidney disease in nonproteinuric diabetic patients; therefore, this review strongly supports the current recommendation that urinary AER should be monitored on a regular basis, in accordance with accepted protocols and procedures (89,90). Moreover, given their increased risk of progression, patients with persistent MA should be considered for antihypertensive therapy and improved glycemic control. However, concerns have been previously raised (39,51,91), and this study concurs, that AER does not predict DN risk with the accuracy suggested by the original studies in this field (7–9) and that changes in the natural history of this disease may not fully explain these discrepancies. Moreover, AER as a predictor in nonproteinuric diabetic patients may not be sufficient for optimal clinical decision making, clinical research design, or public health policy development. Improved predictors could come from existing methodologies or from technologies not yet fully developed. The growing magnitude of the DN problem and its huge human and social costs mandate that we commit far greater basic and clinical research resources to this problem. The value of long-term continuous research support can be seen in the use by the National Institutes of Health of intramural funding studies of the Pima Indian population, and this concept should be expanded to the study of other important patient groups. This need is dictated by the very long and largely silent natural history of DN, and this natural history will not be changed by wishful thinking.

REFERENCES

1. 1999 United States Renal Data System Annual Report: National Technical Information Service. US Department of Health and Human Services, Springfield, VA
2. Bojestig M, Arnqvist HJ, Hermansson G, Karlberg BE, Ludvigsson J: Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 330:15–18, 1994
3. Rossing P, Rossing K, Jacobsen P, Parving HH: Unchanged incidence of diabetic nephropathy in IDDM patients. *Diabetes* 44:739–743, 1995
4. Mogensen CE: Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. *Br Med J* 285:685–688, 1982
5. Parving H-H, Andersen AR, Smidt UM, Svendsen PA: Early and aggressive antihypertensive treatment reduces the rate of decline in kidney function in diabetic nephropathy. *Lancet* 1:1175–1179, 1983
6. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy: the Collaborative Study Group. *N Engl J Med* 329:1456–1462, 1993
7. Parving H-H, Oxenbøll B, Svendsen PA, Christiansen JS, Andersen AR: Early detection of patients at risk of developing diabetic nephropathy: a longitudinal study of urinary albumin excretion. *Acta Endocrinol (Copenh)* 100:550–555, 1982
8. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H: Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1:1430–1432, 1982
9. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 311:89–93, 1984
10. Mogensen CE, Chachati A, Christensen CK, Close CF, Deckert T, Hommel E, Kastrup J, Lefebvre P, Mathiesen ER, Feldt-Rasmussen B, Schmitz A, Viberti GC: Microalbuminuria: an early marker of renal involvement in diabetes. *Uremia Invest* 9:85–95, 1985–1986

11. Chavers BM, Bilous RW, Ellis EN, Steffes MW, Mauer SM: Glomerular lesions and urinary albumin excretion in type I diabetic patients without overt proteinuria. *N Engl J Med* 320:966–970, 1989

12. Fioretto P, Steffes MW, Mauer SM: Glomerular structure in nonproteinuric insulin-dependent diabetic patients with various levels of albuminuria. *Diabetes* 43:1358–1364, 1994

13. Bangstad HJ, Østerby R, Dahl-Jorgensen K, Berg KJ, Hartmann A, Nyberg G, Frahm Bjorn S, Hanssen KF: Early glomerulopathy is present in young, type 1 (insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia* 36:523–529, 1993

14. The Diabetes Control and Complications Trial Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 47:1703–1720, 1995

15. Parving H-H, Hommel E, Mathiesen E, Skøtt P, Edsberg B, Bahnsen M, Lauritzen M, Hougaard P, Lauritizen E: Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. *Br Med J* 296:156–160, 1988

16. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH: Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 39:1116–1124, 1990

17. Mangili R, Deferrari G, DiMario U, Giampietro O, Navalesi R, Nosadini R, Rigamonti G, Spezia R, Crepaldi G: Arterial hypertension and microalbuminuria in IDDM: the Italian Microalbuminuria Study. *Diabetologia* 37:1015–1024, 1994

18. Olsen BS, Johannesen J, Sjølie AK, Borch-Johnsen K, Hougaard P, Thorsteinsson B, Pramming S, Marinelli K, Mortensen HB, the Danish Study Group of Diabetes in Childhood: Metabolic control and prevalence of microvascular complications in young patients with type 1 diabetes mellitus. *Diabet Med* 16:79–85, 1999

19. Warram JH, Gearin G, Laffel L, Krolewski AS: Effect of duration of type 1 diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 7:930–937, 1996

20. Microalbuminuria Collaborative Study Group: Microalbuminuria in type 1 diabetic patients: prevalence and clinical characteristics. *Diabetes Care* 15:495–501, 1992

21. Forsblom CM, Groop P-H, Ekstrand A, Groop LC: Predictive value of microalbuminuria in patients with insulin dependent diabetes of long duration. *BMJ* 305:1051–1053, 1992

22. Mathiesen ER, Rønn B, Storm B, Foght H, Deckert T: The natural course of microalbuminuria in insulin dependent diabetes: a 10-year prospective study. *Diabet Med* 12:482–487, 1995

23. Chiarelli F, Catino M, Tumini S, Martino M, Mezzetti A, Varrotti A, Vanelli M: Increased Na^+/Li^+ countertransport activity may help to identify type 1 diabetic adolescents and young adults at risk for developing persistent microalbuminuria. *Diabetes Care* 22:1158–1164, 1999

24. Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy: an 8-year prospective study. *Kidney Int* 41:822–828, 1992

25. Microalbuminuria Collaborative Study Group: Predictors of the development of microalbuminuria in patients with type 1 diabetes mellitus: a seven-year prospective study. *Diabet Med* 16:918–925, 1999

26. Østerby R: Morphometric studies of the peripheral glomerular basement membrane in early juvenile diabetes. I. Development of initial basement membrane thickening. *Diabetologia* 8:84–92, 1972

27. Steffes MW, Sutherland DER, Goetz FC, Rich SS, Mauer SM: Studies of kidney and muscle biopsy specimens from identical twins discordant for type I diabetes mellitus. *N Engl J Med* 312:1282–1287, 1985

28. Østerby R: Glomerular structural changes in type 1 (insulin-dependent) diabetes mellitus: causes, consequences, and prevention. *Diabetologia* 35:803–812, 1992

29. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC: Structural-functional relationships in diabetic nephropathy. *J Clin Invest* 74:1143–1155, 1984

30. Lane PH, Steffes MW, Mauer M: Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. *Diabetes* 41:581–586, 1992

31. Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, Jerums G: Progressive decline in renal function in diabetic patients with and without albuminuria. *Diabetes* 43:649–655, 1994

32. Berg UB, Torbjörnsdotter TB, Jaremko G, Thalme B: Kidney morphological changes in relation to long-term renal function and metabolic control in adolescents with IDDM. *Diabetologia* 41:1047–1056, 1998

32a. Mogensen CE: Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. Diabetelogia 42:263–285, 1999

33. Caramori ML, Fioretto P, Mauer M: Long-term follow-up of normoalbuminuric longstanding type 1 diabetic patients: progression is associated with worse baseline glomerular lesions and lower glomerular filtration rate (Abstract). *J Am Soc Nephrol* 10:126A, 1999

34. Fioretto P, Steffes MW, Sutherland DER, Mauer M: Sequential renal biopsies in insulin-dependent diabetic patients: structural factors associated with clinical progression. *Kidney Int* 48:1929–1935, 1995

35. Rossing P, Hougaard P, Borch-Johnsen K, Parving H-H: Progression from microalbuminuria to diabetic nephropathy in IDDM (Abstract). *J Am Soc Nephrol* 8:117A, 1997

36. Walker JD, Close CF, Jones SH, Rafferty M, Keen H, Viberti GC, Østerby R: Glomerular structure in type 1 (insulin-dependent) diabetic patients with normo- and microalbuminuria. *Kidney Int* 41:741–748, 1992

37. Bangstad HJ, Østerby R, Hartmann A, Berg TJ, Hanssen KF: Severity of glomerulopathy predicts long-term urinary albumin excretion rate in patients with type 1 diabetes and microalbuminuria. *Diabetes Care* 22:314–319, 1999

38. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–360, 1984

39. Forsblom CM, Groop P-H, Ekstrand A, Totterman KJ, Sane T, Saloranta C, Groop L: Predictors of progression from normoalbuminuria to microalbuminuria in NIDDM. *Diabetes Care* 21:1932–1938, 1998

40. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998

41. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R: Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 128:982–988, 1998

42. John L, Sunder Rao PSS, Kanagasabapathy AS: Rate of progression of albuminuria in type II diabetes: five-year prospective study from South India. *Diabetes Care* 17:888–890, 1994

43. Gall MA, Hougaard P, Borch-Johnsen K, Parving H-H: Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 314:783–788, 1997

44. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R: Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch Intern Med* 158:998–1004, 1998

45. Kawazu S, Tomono S, Shimizu M, Kato N, Ohno T, Ishii C, Murata K, Watanabe T, Negishi K, Suzuki M, Takahashi M, Ishii J: The relationship between early diabetic nephropathy and control of plasma glucose in non-insulin-dependent diabetes mellitus: the effect of glycemic control on the development and progression of diabetic nephropathy in an 8-year follow-up study. *J Diabetes Complications* 8:13–17, 1994

46. Jerums G, Cooper ME, Seeman E, Murray RML, McNeil J: Spectrum of proteinuria in type I and type II diabetes. *Diabetes Care* 10:419–427, 1987

47. Haneda M, Kikkawa R, Togawa M, Koya D, Kajiwara N, Uzu T, Shigeta Y: High blood pressure is a risk factor for the development of microalbuminuria in Japanese subjects with non-insulin-dependent diabetes mellitus. *J Diabetes Complications* 6:181–185, 1992

48. Niskanen L, Uusitupa M, Siitonen O, Voutilainen E, Penttilä I, Pyörälä K: Microalbuminuria predicts the development of serum lipoprotein abnormalities favoring atherogenesis in newly diagnosed type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 33:237–243, 1990

49. Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, Coplon NS, Sun L, Meyer TW: Podocyte loss and progressive glomerular injury in type II diabetes. *J Clin Invest* 99:342–348, 1997

50. Fioretto P, Mauer M, Velussi M, Carraro A, Muollo B, Baggio B, Crepaldi G, Nosadini R: Ultrastructural measures of glomerular extracellular matrix accumulation in non-proteinuric type 2 diabetic patients (Abstract). *J Am Soc Nephrol* 7:1356–1357, 1996

51. Moriya T, Moryia R, Yajima Y, Steffes MW, Mauer M: Urinary albumin is a weaker predictor of diabetic nephropathy lesions in Japanese NIDDM patients than in Caucasians IDDM patients (Abstract). *J Am Soc Nephrol* 8:116A, 1997

52. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M: Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 118:577–581, 1993

53. Ahmad J, Siddiqui MA, Ahmad H: Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 20:1576–1581, 1997

54. Yajima Y, Jim Y, Moriya T, Matoba K: Progression from microalbuminuria to overt nephropathy in NIDDM: the receiver operating characteristics curve

analysis (Abstract). *Diabetologia* 41 (Suppl. 1):A287, 1998

55. Fioretto P, Mauer M, Brocco E, Velussi M, Frigato F, Muollo B, Sambataro M, Abaterusso C, Baggio B, Crepaldi G, Nosadini R: Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia* 39:1569–1576, 1996

56. Fioretto P, Mauer M, Bortoloso E, Barzon I, Saller A, Dalla Vestra M, Abaterusso C, Baggio B, Nosadini R: Glomerular ultrastructure in type 2 diabetes (Abstract). *J Am Soc Nephrol* 9:114A, 1998

57. Ruggenenti P, Gambara V, Perna A, Bertani T, Remuzzi G: The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. *J Am Soc Nephrol* 9:2336–2343, 1998

58. Nosadini R, Velussi M, Brocco E, Bruseguin M, Abaterusso C, Saller A, Della Vestra M, Carraro A, Bortoloso E, Sambataro M, Barzon I, Frigato F, Muollo B, Chiesura-Corona M, Pacini G, Baggio B, Piarulli F, Sfriso A, Fioretto P: Course of renal function in type 2 diabetic patients with abnormalities of albumin excretion rate. *Diabetes* 49:476–484, 2000

59. Verthoeven S, van Ballegooie E, Casparie AF: Impact of late complications in type 2 diabetes in a Dutch population. *Diabet Med* 8:435–438, 1991

60. Bruno G, Cavallo Perin P, Bargero G, Borra M, Calvi V, Derrico N, Deambrogio P, Pagano G: Prevalence and risk factors for micro- and macroalbuminuria in an Italian population-based cohort of NIDDM subjects. *Diabetes Care* 19:43–47, 1996.

61. Piehlmeier W, Renner R, Schramm W, Kimmerling T, Garbe S, Proetzch R, Fahn J, Piwernetz K, Landgraf R: Screening of diabetic patients for microalbuminuria in primary care: the PROSIT-Project Proteinuria Screening and Intervention. *Exp Clin Endocrinol Diabetes* 107:244–251, 1999

62. Klein R, Klein BE, Moss SE: Prevalence of microalbuminuria in older-onset diabetes. *Diabetes Care* 16:1325–1330, 1993

63. Gall MA, Rossing P, Skott P, Damsbo P, Vaag A, Bech K, Dejgaard A, Lauritzen M, Lauritzen E, Hougaard P, Beck-Nielsen H, Parving H-H: Prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease in European type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 34:655–661, 1991

64. Schmitz A, Vaeth M: Microalbuminuria: a major risk factor in non-insulin-dependent diabetes: a 10-year follow-up study of 503 patients. *Diabet Med* 5:126–134, 1988

65. Esmatjes E, Castell C, Gonzales T, Tresseras R, Lloveras G: Epidemiology of renal involvment in type II diabetics (NIDDM) in Catalonia: the Catalan Diabetic Nephropathy Study Group. *Diabetes Res Clin Pract* 32:157–163, 1996

66. Delcourt C, Vauzelle Kervroedan F, Cathelineau G, Papoz L: Low prevalence of long-term complications in non-insulin dependent diabetes mellitus in France: a multicenter study: CODIAB-INSERM-ZENECA Pharma Study Group. *J Diabetes Complications* 12:88–95, 1998

67. Torffvit O, Agardh E, Agardh CD: Albuminuria and associated medical risk factors: a cross-sectional study in 451 type II (non-insulin-dependent) diabetic patients. Part 2. *J Diabetes Complications* 5:29–34, 1991

68. Østerby R, Gall M-A, Schmitz A, Nielsen FS, Nyberg G, Parving H-H: Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36:1064–1070, 1993

69. Nelson RG, Meyer TW, Myers BD, Bennett PH: Course of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. *Kidney Int* 52 (Suppl. 63):S45–S48, 1997

70. Metcalf P, Baker J, Scott A, Wild C, Scragg R, Dryson E: Albuminuria in people at least 40 years old: effect of obesity, hypertension, and hyperlipidaemia. *Clin Chem* 38:1802–1808, 1992

71. Bigazzi R, Bianchi S, Campese VM, Baldari G: Prevalence of microalbuminuria in a large population of patients with mild to moderate essential hypertension. *Nephron* 61:94–97, 1992

72. Rambausek M, Fliser D, Ritz E: Albuminuria of hypertensive patients. *Clin Nephrol* 38 (Suppl. 1):S40–S45, 1992

73. U.K. Prospective Diabetes Study Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: United Kingdom Prospective Diabetes Study 39. *BMJ* 317:713–720, 1998

74. Cowie CC, Port FK, Wolfe RA, Savage PA, Moll PA, Hawthorne VM: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–1079, 1989

75. Poulsen PL, Hansen KW, Mogensen CE: Ambulatory blood pressure in the transition from normo- to microalbuminuria: a longitudinal study in IDDM patients. *Diabetes* 43:1248–1253, 1996

76. U.K. Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703–713, 1998

77. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, Ryan L, Krolewski AS: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 49:94–100, 2000

78. U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998

79. U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998

80. Mogensen CE: Early glomerular hyperfiltration in insulin-dependent diabetes and late nephropathy. *Scand J Clin Lab Invest* 46:201–206, 1986

81. Chiarelli F, Verrotti A, Morgese E: Glomerular hyperfiltration increases the risk of developing microalbuminuria in diabetic children. *Pediatr Nephrol* 9:154–158, 1995

82. Caramori MLA, Pecis M, Gross JL, de Azevedo MJ: Glomerular filtration rate, urinary albumin excretion rate, and blood pressure changes in normoalbuminuric normotensive type 1 diabetic patients: an 8-year follow-up study. *Diabetes Care* 22:1512–1516, 1999

83. Yip JW, Jones SL, Wiseman MJ, Hill C, Viberti GC: Glomerular hyperfiltration in the prediction of nephropathy in IDDM: a 10-year follow-up study. *Diabetes* 45:1729–1733, 1996

84. Bognetti E, Meschi F, Bonfanti R, Gianolli L, Chiumello G: Decrease of glomerular hyperfiltration in short-term diabetic adolescents without microalbuminuria. *Diabetes Care* 16:120–124, 1993

85. Lervang H-H, Jensen S, Brøchner-Mortensen J, Ditzel J: Early glomerular hyperfiltration and the development of late nephropathy in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 31:723–729, 1988

86. Allen TJ, Cooper ME, Gilbert RE, Winikoff J, Skinner SJ, Jerums G: Serum total renin is increased before microalbuminuria in diabetes. *Kidney Int* 50:902–907, 1996

87. Deinum J, Rønn B, Mathiesen E, Derkx FHM, Hop WCP, Schalekamp MADH: Increase in serum prorenin precedes onset of microalbuminuria in patients with insulin-dependent diabetes mellitus. *Diabetologia* 42:1006–1010, 1999

88. *Conquering Diabetes: A Report of the Congressionally-Established Diabetes Research Working Group 1999* (NIH publ. no. 99-4398) National Diabetes Information Clearinghouse, Bethesda, MD

89. American Diabetes Association: Diabetic nephropathy. *Diabetes Care* 23 (Suppl. 1):S69–S72, 2000

90. Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D: 1998 Clinical practice guidelines for the management of diabetes in Canada: Canadian Diabetes Association. *Can Med Assoc J* 159 (Suppl. 8):S1–S29, 1998

91. Danne T, Kordonouri O, Hövener G, Weber B: Diabetic angiopathy in children. *Diabet Med* 14:1012–1025, 1997