The Need for Early Predictors of Diabetic Nephropathy Risk

Is Albumin Excretion Rate Sufficient?

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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

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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 nondiabetic 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

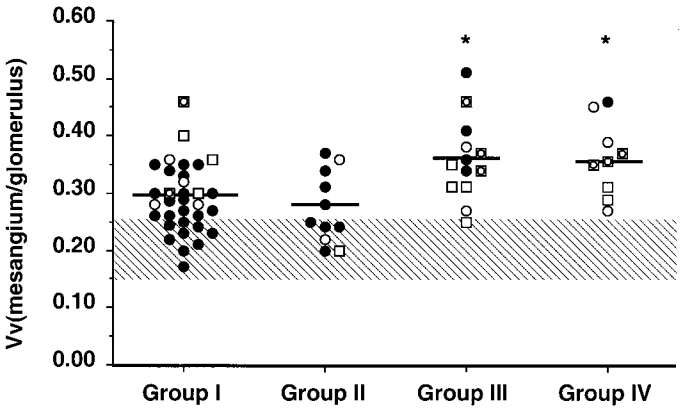

FIG. 1. Mesangial fractional volume (Vv[mesangium/glomerulus]) in the 4 groups of patients. The shaded area represents the means ± 2 SD in a group of 52 age-matched normal control subjects. ●, Normal BP and GFR; ○, reduced GFR (<90 ml · min^{-1} · 1.73m^{-2}); □, hypertension (≥140/85); ⧇, reduced GFR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

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