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# Enhancing the Predictive Value of Urinary Albumin for Diabetic Nephropathy

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**Diabetic nephropathy (DN) is a growing cause of ESRD despite widely known recommendations for improved glycemic and BP control. Perhaps earlier identification of patients who have diabetes and are at high risk for DN could reverse these epidemiologic trends. Albumin excretion rate (AER), the mainstay of early detection of DN, is not a sufficiently precise predictor of DN risk. Careful family history, smoking history, consideration of absolute *versus* categorical AER values, more frequent AER measures, ambulatory BP monitoring, precise GFR measurements, diabetic retinopathy assessments, and plasma lipid levels all can add to predictive accuracy for DN. Thus, although further research in DN biomarkers and predictors is greatly needed, a careful integrated evaluation of currently available parameters can improve our ability to predict DN risk in individual patients.**

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Recent analyses of the United States Renal Data System data demonstrated a dramatic increase in the incidence of ESRD that is caused by diabetes (1). Between 1999 and 2003, diabetes was responsible for >44.8% of all new cases of ESRD in the United States. This increase could not be explained fully by changes in assignment of causes of ESRD, rising prevalence of diabetes, increased access to renal replacement therapy (RRT), increased acceptance of individuals with diabetes to ESRD programs, or increased survival of patients with diabetes (2), suggesting that external factors might be responsible for this growth in diabetic nephropathy (DN) incidence. Thus, whereas the population with diabetes grew 40% between 1984 and 1996, the number of people who initiated treatment for ESRD as a result of diabetes increased by 400%. Between 1996 and 2003, the annual U.S. incidence grew by another 37%, from approximately 32,000 to approximately 44,000 new cases per year (1). On the basis of these data, we expect the burden of DN to increase further in the next years, although perhaps at a less accelerated growth rate (2). This expansion of ESRD that is caused by diabetes occurred despite well-publicized studies showing that improved glucose (3) and BP (4) control and renin-angiotensin system (RAS) blockade (5–9) might slow the development or progression of DN. Although these therapies have been developed on the basis of sound pathophysiologic concepts and well-done clinical trials, we have, to date, not been able to prevent the near-epidemic rise in severe kidney damage caused by diabetes. Thus, new approaches are urgently needed, including the possibility that for interventions to be effective in the prevention of ESRD in diabetes, they would need to be initiated much earlier in the disease. For these reasons, early and accurate DN risk markers are of great importance.

In the early 1980s, independent investigators reported that some patients with diabetes had increased urinary albumin excretion rates (AER) that were not detectable by standard laboratory methods and termed this microalbuminuria (MA). Initial retrospective studies reported that approximately 80% of patients with type 1 diabetes would progress from MA to proteinuria (P) over 6 to 14 yr (10–12). Because the *post hoc* values for MA that are predictive of progression to P differed among these initial investigations, a conference was convened to achieve consensus on the definition of MA (13), and these values have been used up to the present time.

## DN Risk in Patients with Type 1 Diabetes

Initial studies reported that between 10 and 15% of patients with type 1 diabetes and normoalbuminuria (NA) progressed to MA (10) or P (11) after 6 to 14 yr of follow-up. As we have previously reviewed (14), similar results were found in subsequent studies, with progression rates from NA to MA ranging from 10 to 28% and to P from 4 to 7% over 8 to 10 yr of follow-up. More variable progression rates have been reported in children and adolescents (15–17). On the basis of these studies, we estimated that 5% of patients with NA and at least 7 yr of type 1 diabetes would progress to P over the next 5 to 10 yr, whereas 17% would progress to MA (14), one third of whom then would progress to P, for a total P risk of 10%.

More recent data from the Steno Diabetes Center showed

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higher progression rates in an inception cohort of patients who had type 1 diabetes with a much older age of onset (approximately 27 yr) than is typical for type 1 diabetes (18). In this study (18), 79 (28.5%) of 277 patients progressed from NA to MA and 27 (9.7%) progressed to P over a median follow-up period from type 1 diabetes onset of 18 yr (1.0 to 21.5). However, it is important to consider that >30% of the patients who progressed to MA later reverted back to NA, either transiently (15 patients) or permanently (13 patients). Thus, at the end of the study, progression from NA to MA was approximately 24%.

Although MA remains the best available marker for DN risk, recent studies suggested that the percentage of patients who have MA and progress to P over approximately 10 yr is approximately 30% (14), much less than the initial reports of approximately 80% (10–12). Forsblom *et al.* (19) were the first to suggest that patients with MA might revert to NA. He evaluated 20 patients with type 1 diabetes and MA and 16 to 36 yr of type 1 diabetes duration and found progression to P 10 yr later in only 25%, whereas 35% had NA on follow-up and 40% still had MA. Rossing *et al.* (20) indicated that the risk for progression to P in patients with MA and <15 yr of diabetes duration was 45 *versus* 26% progression rate in patients with >15 yr duration. Drs. Peter Rossing and Hans-Henrik Parving performed analyses that we had requested (14) and found that only 30% of 132 patients with MA and with diabetes duration of 20.3 ± 8.7 yr (7 to 40) developed P after a mean follow-up period of 9.1 yr. Moreover, 20% of these patients returned to NA, and 50% still had MA on follow-up. Duration of diabetes was shorter at baseline in patients whose MA progressed to P (17 ± 8 yr) than in those who still had MA (22 ± 9 yr; $P < 0.005$) but not different from those who reverted to NA (20 ± 9 yr). It is interesting that data that were extracted from conventionally treated patients who were in the Diabetes Control and Complications Trial (DCCT) and had MA after 7 to 15 yr of diabetes duration (14) revealed a 23% progression rate from MA to P over the 7 yr of this study. This was less than the 45% progression rate in the similar but much larger cohort of Rossing *et al.* (20). Rudberg *et al.* (15) found an even lower progression rate (18%) in children and adolescents who had MA and were followed for 8 yr. Since we published a review of the predictive value of AER for DN risk (14), several additional papers on his topic have been published. Perkins *et al.* (21) followed for 6 yr 220 patients who had type 1 diabetes and MA and found that 40% of them had reverted to NA and only 15% had progressed to P. Similarly, 35% of patients with MA in the Steno Diabetes Center inception cohort reverted to NA (half of them permanently) and 34% progressed to P, after a median follow-up of 7.5 yr (0.1 to 15.8) (18). In the large EURODIAB study, 50.6% of the patients who had MA reverted to NA whereas only 13.9% progressed to P after 7 yr of follow-up (22).

Thus, these more recent studies suggest that the rate of progression from MA to P over 5 to 10 yr is approximately 15 to 30%, although as high as 45% in patients with <15 yr of diabetes duration but considerably lower than originally estimated. As mentioned, the Steno cohort study did find that many of the patients who had MA that reverted to NA during follow-up had redeveloped MA by the end of the study (18). However, risk for progression of this subgroup to P remains unknown.

## DN Risk in Patients with Type 2 Diabetes

Despite that at least 85% of ESRD that is caused by DN occurs in patients with type 2 diabetes, the natural history of DN in these patients is, as yet, relatively poorly defined. We previously reviewed the literature on this topic and estimated that, during a follow-up of 6 to 9 yr, the incidence of progression from NA to MA and P was 20 to 30% (14). The overall risk for progression from NA to P in patients with type 2 diabetes is similar to that seen in patients with type 1 diabetes (approximately 10% in 10 yr). Assuming the risk for progression from MA to P in patients with type 2 diabetes to be approximately 40% (see below), the risk for developing P over the next 10 to 15 yr in patients with NA and type 2 diabetes would be approximately 12%. Also, as with patients with type 1 diabetes, approximately 70% of screened patients with type 2 diabetes have NA (23). It then can be estimated that approximately 40% of the dipstick-negative patients who have type 2 diabetes and are ultimately destined to develop P will have NA at initial screening, whereas approximately 60% will have MA. Thus, despite that the risk for developing P is approximately 3.3 times greater in the MA group than the NA group, a large percentage of patients who have type 2 diabetes and ultimately are at risk for P will have NA at initial screening.

The regularity with which patients with type 2 diabetes and P progress to ESRD is less well known than for patients with type 1 diabetes. Nelson *et al.* (24) suggested that the rate of decline of GFR among Pima Indians with type 2 diabetes is similar to that of white individuals with type 1 diabetes, but whether Pima Indian patients with their younger age of onset and racial specificity are fully representative of the larger body of patients with type 2 diabetes is not yet established.

Patients with NA type 2 diabetes, as a group, have diabetic glomerular lesions, but their rate of development is less clear, because, with the exception of the Pima Indian studies, duration is usually not precisely established in type 2 diabetes. Whether patients with NA and type 2 diabetes with more advanced diabetic renal lesions are at greater risk for progression needs to be determined.

Mogensen (25) was the first to explore the prognostic value of AER in patients with type 2 diabetes. MA, in this 10-yr retrospective study, was defined as urinary albumin concentration of 30 to 140 $\mu$g/ml. The 76 patients with MA and type 2 diabetes in this study experienced a 77.6% 10-yr mortality mostly from cardiovascular disease, whereas 22% progressed to P (25). Subsequently, three prospective studies with much lower mortality rates among patients with MA and type 2 diabetes have been published. These studies included a total of 152 patients who had MA and were followed for 5 to 6 yr and had an average risk for progression to P of approximately 40%. In one of these studies (26), no patients had NA at follow-up, whereas the other two studies (27,28) did not provide these

data. Other studies described progression rates from MA to P from 33 to 40% (29–31). In one report with 21 patients, none progressed to P, whereas 43% reverted to NA (32).

The United Kingdom Prospective Diabetes Study (UKPDS) (33), using data from >5000 patients who were followed from the diagnosis of type 2 diabetes, found that progression from NA to MA occurred at a rate of 2.0% per year, from MA to P at 2.8% per year, and from P to increased serum creatinine (>175 μmol/L) or RRT at 2.3% per year. Cardiovascular death increased from an annual rate of 0.7% in NA to 2.0% in MA, 3.5% in P, and 12.1% in patients with increased serum creatinine or RRT. This very important analysis unfortunately did not provide any information on the risk factors associated with DN progression.

The Steno-2 study (34) evaluated the effects of multifactorial intervention on micro- and macrovascular events in 151 patients with type 2 diabetes and MA during 7.8 yr of follow-up. When all 151 patients were pooled, 46 (31%) patients reverted to NA, 58 (38%) still had MA, and 47 (31%) progressed to P (34). Baseline predictors of reversion and progression were AER levels and retinopathy status; predictors during follow-up were glycated hemoglobin ($HbA_{1c}$), start of antihypertensive therapy, and start of RAS blockade (34) (see below). It is interesting that patients who reverted to NA had a GFR decline of 2.3 ml/min per yr, those who still had MA lost 3.7 ml/min per yr, and those who progressed to P lost 5.4 ml/min per yr (34). Recently, Araki *et al.* (35) reported that return to NA was frequent among Japanese patients with MA and type 2 diabetes. Indeed, among 216 patients with MA, during a follow-up of up to 6 yr, the prevalence of NA was observed to be 22, 33, and 23% at each successive 2-yr follow-up period; the prevalence of P was 9, 13, and 19% at the same time intervals (35). The factors that were associated with reversal to NA were short duration of MA, use of RAS-blocking drugs, and lower $HbA_{1c}$ and systolic BP (SBP) values (see below). Thus, also in type 2 diabetes, a significant proportion of patients with MA may return to NA.

In summary, AER remains the strongest indicator of DN risk in patients with type 1 diabetes and type 2 diabetes, and patients with MA have 200 to 400% higher risk for progression to P than patients with NA. Nonetheless, MA is not as strong a predictor of P as initially considered and a high proportion of patients who are at risk for severe DN will have NA at initial evaluation. For these reasons, it is important to consider other variables that could augment the predictive power of AER.

## Family History

As is reviewed elsewhere in this issue (36), it is now clear that there is a strong genetic familial predisposition to DN. Among patients with type 2 diabetes, race is a strong independent risk factor, with DN rates being much higher in black, American Indian, and Hispanic compared with white populations (1,37–39). The marked concordance (300 to 800%) for DN risk between sibling pairs with type 1 diabetes (40–42) and type 2 diabetes (43–46) would provide strong predictive value when siblings are concordant for diabetes and the DN risk of the proband is known. Higher parental BP values (47) and the presence of hypertension (48,49) among parents without diabetes predicts greater (1.5- to 2.0-fold) DN risk among their offspring with type 1 diabetes. Similarly, parental hypertension predicts increased P risk in Pima Indians with type 2 diabetes (50). Also, cardiovascular morbidity and mortality in parents without diabetes predicts a greater (approximately two-fold) DN risk in their offspring with type 1 diabetes (51). Finally, AER and BP are heritable and are linked in white families with type 2 diabetes (52). These studies suggest that taking thorough family histories and, perhaps, careful study of the relatives of patients with diabetes could help to refine DN risk predictions.

## Glycemia

Perhaps the clearest indication that glycemia is a risk factor for progression to MA among patients with type 1 diabetes comes from the controlled trial design of the DCCT, in which patients who had NA and were randomly assigned to strict glycemic control had lower likelihood of MA at the end of this 6.5-yr study (3). Perhaps even more interesting are the findings of the DCCT follow-up study (Epidemiology of Diabetes Interventions and Complications). Despite that the differences in glycemia ($HbA_{1c}$) between the DCCT intensive and standard control groups disappeared shortly after the DCCT study terminated, 7 to 8 yr, later there were fewer new cases of MA (6.8%) in patients who were randomly assigned to intensive compared with 15.8% in the standard treatment, *i.e.*, a 59% risk reduction ($P < 0.001$) (53). This suggested a "memory" effect of glycemic control on DN risk. In the Steno cohort study, $HbA_{1c}$ was similar in patients 6 mo after type 1 diabetes onset but was higher at follow-up before MA developed (18). Although the large UKPDS observational study found that intensive glucose control reduced the risk for MA development (54), the benefits of strict control (approximately 25% risk reduction; see UKPDS web site) were less than in the DCCT, in part perhaps because the difference in $HbA_{1c}$ between groups was only 0.9% in the UKPDS *versus* 1.5% in the DCCT. Also, UKPDS patients with lower fasting plasma glucose levels at diagnosis of type 2 diabetes were less likely to have developed MA after 12 yr of follow-up (33).

As discussed above, a significant proportion of patients with MA revert to NA. In the Joslin Clinic Study, patients who had type 1 diabetes and MA and reverted to NA had lower $HbA_{1c}$ levels (8.8 ± 1.5%) than the nonregressors (9.3 ± 1.6%; $P < 0.001$), and, compared with a $HbA_{1c}$ reference value of ≥10.0%, the likelihood of regression increased with each 1% decrease in the $HbA_{1c}$ value (21). Thus, in patients with $HbA_{1c}$ <8.0%, the adjusted hazard ratio was reduced by 1.9-fold (1.2- to 2.9-fold) *versus* the reference group (21). A similar trend was seen in the smaller Steno cohort study ($P = 0.09$) (18). Although there was no $HbA_{1c}$ difference in patients who had type 1 diabetes and still had MA *versus* those who reverted to NA in the EURODIAB Study (22), patients who had MA that progressed to P had higher $HbA_{1c}$ levels. $HbA_{1c}$ values during follow-up in the Steno type 2 diabetes study were predictive of return to NA (34). Similarly, $HbA_{1c}$ values <6.95% were associated with more frequent reversal to NA in Japanese patients with type 2 diabetes (35). Taken together, these studies support the view that measures of glycemia provide added information to AER

in the estimate of DN risk for development and progression and on the potential for reversal.

## BP

Several lines of evidence suggest that higher BP levels, even within the "normal range," are predictive of DN risk. Conversely, low BP values may be predictive of low DN risk (55). Patients with type 1 diabetes and advanced DN had higher mean arterial BP during adolescence (49), whereas prediabetic BP predicted subsequent AER among Pima Indians with type 2 diabetes (56). Ambulatory BP (ABP) measures and dipper status are related to AER within the NA range (57), and, as outlined below, higher AER values in the NA range, in turn, are predictive of progression to MA. ABP measurement, especially nocturnal values and dipper status, predicted subsequent MA risk among adolescents with NA and type 1 diabetes, even though these patients were normotensive by standard criteria (58). Importantly, office BP values did not differentiate among those who still had NA and those who progressed to MA (58). ABP values, especially nocturnal values, also predicted underlying DN lesions among young patients with NA and type 1 diabetes, although increased pulse rate caused the ABP variables to drop out of the multiple regression models in this study (59). In the Steno inception cohort study of patients with adult-onset type 1 diabetes (average age at onset approximately 27 yr), systolic BP and diastolic BP were higher within 6 mo of type 1 diabetes diagnosis using clinic BP methods despite that these patients were normotensive by standard criteria (18). This was confirmed by follow-up study measurements in this cohort. Thus, before MA developed, 62% of those who later developed MA *versus* 14% of those who still had NA were receiving antihypertensive therapy.

As already noted, reversion from MA to NA is much more common than initially anticipated. However, clinic BP values did not predict which patients with MA and type 1 diabetes would have NA on subsequent follow-up in the EURODIAB Study (22); SBP <115 mmHg was associated with a 1.4-fold (1.0- to 1.9-fold) likelihood of return to NA in another study of patients with type 1 diabetes (21), and this was strongly confirmed in the Steno type 1 diabetes cohort study (18). Moreover, return from MA to NA was more common in Japanese patients with type 2 diabetes and SBP <129 mmHg (35). In the Steno 2 study, initiation of antihypertensive therapy during follow-up was one of the significant predictors of reversion to NA in patients with type 2 diabetes (34). Taken together, these studies support the careful measure of systemic BP in patients with type 1 diabetes and type 2 diabetes, perhaps especially if normotensive by current standards. It is reasonable to recommend annual 24-h ABP measures for these "normotensive" patients to assist in the assessment to DN risk.

## Albuminuria

AER, clearly a continuous variable, has been categorized, for the sake of risk assessment and diagnosis, into NA, MA, and macroalbuminuria or P. The most widely currently used MA definition (AER 20 to 200 $\mu$g/min [equivalent to an albumin-to-creatinine ratio (ACR) of 30 to 300 mg/g]) was adopted at a convention (13) aimed at imposing uniformity on the disparate criteria published to that point. Although MA has less predictive precision for the development of P than initially considered, persistent MA nonetheless defines a group of patients with type 1 diabetes and type 2 diabetes and a 200 to 400% or greater risk for progression to P than patients who have long-term diabetes and still persistently have NA (see above). It is therefore of interest to consider whether, along the continuum of this variable, higher levels of AER within the so-called NA range are predictors of progression to MA or P. In this regard, it should be noted that the upper limits of normal (95th percentile) for AER in our laboratory is in fact 13 $\mu$g/min (60). In another study in completely healthy individuals, there was no clear correlation between AER and age up to approximately 70 yr, and the mean AER was approximately 5 $\mu$g/min and rarely exceeded 15 $\mu$g/min (61). Thus, values between approximately 13 to 15 and 20 $\mu$g/min are abnormal, and in this range, "normoalbuminuria" is, in fact, a misnomer. Moreover, there are unsolved conceptual problems in regard to the gender standardization for urine ACR. Women, with less muscle mass, normally have higher values for ACR than men. In one study, the 95th percentile of the respective normal distribution was 17 $\mu$g/mg in men and 25 $\mu$g/mg in women. This was reported to be equivalent to AER of 30 and 31 $\mu$g/min, respectively (62), but this is much higher than the upper limit of normal values for AER cited above. Moreover, considered in terms of equivalent permselectivity (63), normal men should have higher AER than women, as raw GFR is higher in men.

In a small study of 75 adolescents with type 1 diabetes, Lurbe *et al.* (58) found no predictive value of AER in the "normoalbuminuric" range. However, in a large study of 170 children, adolescents, and young adults with an average of approximately 9 yr of type 1 diabetes, we found that baseline AER within the NA range was higher in those who had MA *versus* those who had NA at the end of this 5-yr natural history study (64). Moreover, the group with persistent MA during the study (*i.e.*, at least two of three consecutive values between 20 and 200 $\mu$g/min), whether they reverted to NA by the end of the study or not, had greater glomerular basement membrane (GBM) width at baseline. This indicated that higher AER within the NA range was associated with worse underlying DN lesions (64). Hovind *et al.* (18), in the Steno inception cohort study, found that AER was higher at the first assessment, 6 mo after onset of type 1 diabetes, in those who progressed to MA than in those who still had NA through a median of 18 yr (1.0 to 21.5 yr) of follow-up. The gap in AER values between the progressors and nonprogressors increased during follow-up studies before MA developed (18). In fact, those who progressed to MA had AER values that tended to increase, whereas those who still had NA had stable AER follow-up values (18). Larger epidemiologic studies in 1201 patients with type 1 diabetes also showed that baseline urinary albumin concentration above the normal range predicted the risk for progression to overt nephropathy in the subsequent 4 yr (2.5 to 5.5 yr) (65). Higher baseline AER in the NA range was also a predictor of progression to MA in patients with type 2 diabetes (66).

The absolute values of AER in the MA range were also

evaluated as a risk predictor. These levels were nearly identical in patients who had type 1 diabetes and did or did not revert to NA in the study of Perkins *et al.* (21). Conversely, the cohort study of Hovind *et al.* (18) found lower AER values at final detection of MA in those who reverted to NA (29 $\mu$g/min [24 to 44 $\mu$g/min]) than in those who still had MA or progressed to P (41 $\mu$g/min [29 to 86 $\mu$g/min]; $P = 0.01$). Also the EURODIAB Progressive Complications Study found lower values for baseline AER in patients who had MA and type 1 diabetes and reverted to NA *versus* those who progressed to P, and this was an independent risk factor in multivariate analysis (22). Similarly, in patients with type 2 diabetes and MA, baseline AER values were predictive of the subsequent return to NA and progression to P (34).

These data are consonant with the idea that there is more to be gleaned from AER measurements than achieved by simple categorization and that absolute values and time trends within categories can provide additional prognostic precision. Given the approximately 40% day-to-day coefficient of variation in AER (67), these studies also suggest that this test should be done more frequently, and quarterly measures of AER are probably warranted.

The predictive value of AER studies in patients who are taking drugs that block the RAS system is unclear. Patients with MA and type 1 diabetes after 8 yr of angiotensin-converting enzyme inhibitor treatment had less increase in AER and less progression to P than patients who were given placebo (68). However, AER increased rapidly to above baseline values and, in several patients, into the P range within 2 mo of cessation of treatment (69). This suggested that progression in AER might have been masked by angiotensin-converting enzyme inhibitor treatment. In patients who had type 2 diabetes and MA and were treated with angiotensin receptor blocker (ARB) for 2 yr, a 1-mo hiatus in ARB therapy resulted in a disappearance in the AER-lowering effect of the lower dose of the ARB (150 mg/d irbesartan) and some loss of the effect of the 300 mg/d dose, albeit the significant difference from placebo remained at this higher dose (70). The BENEDICT trial (9) suggested a lower rate of MA development in patients who had NA and type 2 diabetes and were randomly assigned to ARB treatment, but the possibility of "masking" of AER increase by ARB therapy was not explored (9). RAS blockade did not increase the rate of remission from MA to NA in the type 1 diabetes study of Perkins *et al.* (21) but did so in the type 2 diabetes study of Araki *et al.* (35). In summary, it is possible that the prognostic value of AER levels may be influenced by treatment, but too little is known and much longer follow-up studies are critical. These factors should be kept in mind when interpreting AER values.

## Total Intact and Immuno-Unreactive Albumin

The concentration of albumin in the urine has traditionally been measured by quantitative immunochemical methods such as immunonephelometry, immunoturbidimetry, and RIA. Until recently, urinary albumin that was not reabsorbed by the proximal tubular cells was assumed to be excreted as intact albumin. It is now known that the nature of urinary albumin is complex: Indeed, albumin is excreted as a mixture of intact albumin (immunoreactive), detected by routine tests, albumin-derived peptides that are not detected by routine antibody-based tests, and a species of intact albumin (immuno-unreactive albumin), also not detected by antibody-based tests (71). A new test, based on HPLC, identifies all of the immunoreactive and immuno-unreactive intact albumin (total intact albumin) in the urine (71). The underestimation of total intact urinary albumin by conventional methods is especially relevant for low AER ($<20$ $\mu$g/min by current methods); in contrast, in presence of macroalbuminuria, HPLC and antibody-based methods provide comparable values for albumin concentration (72). It has been shown that the HPLC method detects patients with AER $>20$ $\mu$g/min 3.9 and 2.4 yr before conventional methods in type 1 diabetes and type 2 diabetes, respectively (73). The advantage in the use of HPLC over conventional methods for detecting MA is that false-negative results may be reduced and a relatively earlier detection of patients who are at increased risk for DN could be achieved. Despite these encouraging early findings, it remains to be established whether the measurement of total intact urinary albumin is a clinically useful addition to current methods and adds to the precision of standard AER measures for prediction of DN risk. It should be kept in mind that the usefulness of MA as predictor of overt nephropathy was based on studies in which immunoreactive albumin (antibody-based tests) was measured; for total albumin (HPLC), the predictive values still need to be established.

## Retinopathy

It is a generally accepted concept that, with long enough diabetes duration, diabetic retinopathy (DR) will develop in almost all patients with diabetes, whereas DN develops only in a subset of approximately 25% of patients. This concept is substantially incorrect. This idea stems from the fact that DR is diagnosed by direct evaluation of retinal lesions through funduscopy. DR changes thus are describable in their early stages long before there are functional consequences to the eye. In fact, most patients with background DR do not progress to visual loss (74). DN diagnosis, however, has been almost entirely based on renal functional disturbances that manifest as increased albuminuria, hypertension, and GFR decline. Indeed, in studies in which research renal biopsies were compared in identical twins who were discordant for type 1 diabetes (75), it was concluded that, compared with their twins without diabetes, all patients with type 1 diabetes are developing DN lesions. This could be deduced even though measured values for renal structural parameters among some patients with type 1 diabetes may still have been within the "normal" range and their renal function was entirely normal (75). Thus, like DR, DN renal structural changes seem to develop in virtually all patients with long-standing diabetes, but in most, this occurs so slowly or minimally that functional consequences do not manifest.

Given this background, it is not surprising that much stronger relationships between DN and DR than previously appreciated were found when patients with a broad spectrum of DN and DR were compared directly as to severity of respective eye

and kidney lesions (60). Although serious DR lesions could occur in a subset of patients without clear DN lesions, this and the converse were, in fact, distinctly unusual (60). More recently, this research approach was applied to a cohort of 252 normotensive and normo- or hyperfiltering patients with NA and 12 ± 5 yr of type 1 diabetes duration (76). Eighty-nine patients had no DR, 136 had early nonproliferative DR, and 27 had moderate to severe nonproliferative DR or proliferative DR (76). The presence and the severity of DR lesions were strongly associated with DN glomerular lesions in these patients who had no renal functional abnormalities (76). Of interest, ABP parameters, which, as already noted, are related to underlying renal structure, were also related to DR in these patients with type 1 diabetes (Klein R, Mauer M, unpublished results).

The Steno cohort study found that the presence of simplex (77%) or proliferative (18%) DR antedated MA, whereas only 5% of the 79 patients who had NA and type 1 diabetes and progressed to MA had no DR (18). Conversely, of 198 patients who still had NA, 40% had no DR, 58% had simplex DR, and only 2% had proliferative DR (18). Patients with NA and proliferative DR had a nine-fold risk for MA; this risk was 1.3-fold in patients who had type 1 diabetes, NA, and simplex DR (18). The risk for MA was eight-fold less in those without DR (18). Whether DR status predicted subsequent reversion from MA to NA was not commented on in this paper (18) or in that of Perkins *et al.* (21). These studies in patients with type 1 diabetes suggest some common pathogenetic pathways for DR and DN and support the idea that the eye is a window on the kidney in type 1 diabetes.

The relationships between DR and DN are less well understood in patients with type 2 diabetes. Østerby *et al.* (77) found a correlation between diabetic glomerulopathy and DR lesions in patients with P and type 2 diabetes. However, discordance between DR and renal structure has been described in Japanese patients with type 2 diabetes (78). Mathian *et al.* (79) also showed that several patients with P and type 2 diabetes had normal fundi despite DN that was proved by kidney biopsy and that, when present, DR was predictive of nodular glomerulosclerosis, whereas the absence of DR was predictive of diffuse mesangial expansion lesions. We and others (80,81) reported that approximately 40% of patients with type 2 diabetes and MA or P had typical diabetic glomerulopathy, whereas the remaining patients had minimal structural changes or tubular, interstitial, vascular, and/or global glomerulosclerosis lesions that are advanced relative to the severity of DN glomerular lesions. When only those with diabetic glomerulopathy were considered, almost all patients in our cohort had DR. All patients with proliferative DR had typical diabetic glomerulopathy. The proportion of patients with type 2 diabetes and without DR was 44% among patients with MA and 25% among patients with P (Fioretto P, unpublished data). Thus, there is considerable discordance between DR and DN in type 2 diabetes when retinal structural abnormalities are compared with renal functional parameters. However, when key structural parameters of diabetic glomerulopathy (mesangial expansion and GBM thickening) were considered, we found a strong concordance between DR and DN lesions in patients with type 2 diabetes. The proportion of patients with DR was 81% in the group of patients with mesangial expansion, whereas it was only 38% in patients without mesangial expansion (Fioretto P, unpublished data). Longitudinal studies on the prognostic impact of DR on risk for progression of DN in patients with NA and MA and type 2 diabetes are lacking; it is known, however, that the presence of DR is associated with an increased risk of overt nephropathy in patients with type 2 diabetes and MA (34), and that the presence of DR predicts a faster loss of renal function in patients with type 2 diabetes and P (82). It therefore is likely that patients with DR are at higher risk to progress to overt nephropathy and that, as for type 1 diabetes, the eye is a window on the kidney in patients with type 2 diabetes.

## Cigarette Smoking

It is now well established that cigarette smoking is an independent risk factor for MA and for progression to P and ESRD in patients with diabetes (83–86). A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of MA in type 1 diabetes with the steeper slope for $HbA_{1c}$ >8% magnified among current smokers (83). We have reported, in a large group of patients with type 2 diabetes, most of whom had MA, that cigarette smoking was an independent determinant of increased GBM width (87), providing a possible explanation for the link between smoking and abnormal AER. Thus, smoking habits should be considered in the evaluation of the risk for development and progression of DN.

## GFR

Hyperfiltration predicted DN lesions or risk in some type 1 diabetes studies (15,16,25,88). Mogensen and Christensen (10), in a study of 12 patients who had type 1 diabetes and were followed for 14 yr, found GFR higher in those who progressed to MA or P. Chiarelli *et al.* (16) found that a GFR of >140 ml/min per 1.73 $m^2$ had a positive predictive value of 63% and a GFR <140 ml/min a negative predictive value of 94% for the subsequent development of MA among children who had type 1 diabetes and were aged 9 to 15 yr. Similar results were seen in a nearly 30-yr follow-up study of 75 children (89). Conversely, in a smaller study of 29 patients who had type 1 diabetes and were followed for 18 yr, Lervang *et al.* (90) did not find higher GFR in those who progressed to MA. Similarly, Yip *et al.* (91), in a 10-yr prospective case-control study, did not find a greater risk for MA in those with GFR >135 ml/min per 1.73 $m^2$. Using similar criteria, we did not find differences in underlying renal lesions in 158 hyperfiltering patients with type 1 diabetes (65% of the total cohort of 243 patients with type 1 diabetes in the DN Natural History Study) compared with the 85 subjects (35%) with normal GFR. Whether GFR will be an independent predictor of lesion progression in the Natural History Study remains to be determined.

Cross-sectional studies of Danish patients with type 2 diabetes found higher mean GFR values and frequency of hyperfiltration in patients with MA (92). However, in a longitudinal study of black patients with type 2 diabetes, in which the baseline prevalence of hyperfiltration was 15%, hyperfiltration did not predict deterioration of renal function (93). Silveiro *et al.*

(66) found that increased GFR did not predict the subsequent development of MA in patients with type 2 diabetes, but patients with hyperfiltration had an increased GFR loss over the 5 yr of the study. This could have represented regression to the mean. In summary, the literature to date is mixed, and hyperfiltration does not consistently emerge as a strong predictor of progression from NA to MA or P, independent of glycemia and BP.

Reduced GFR may be a useful predictor of DN risk. The typical sequence for functional consequences of DN in type 1 diabetes is increasing AER and ABP values within the normal range followed by MA and overt hypertension. Proteinuria typically ushers in acceleration of GFR loss, culminating in uremia. The sequence in type 2 diabetes is more complex, with many patients already hypertensive at type 2 diabetes diagnosis and with a subset manifesting increases in AER without significant DN lesions (81). However, not all patients follow these patterns. We initially described a subset of patients, all women, who had type 1 diabetes patients and low GFR (<90 ml/min per 1.73 $m^2$) despite NA (94). These patients had significantly worse DN lesions than women with NA and similar type 1 diabetes duration and normal to high GFR. It is interesting that most of these patients with low GFR and type 1 diabetes had self-selected a relatively low-protein diet (94). More recently, we confirmed these observations in a larger cohort of 105 patients with NA and type 1 diabetes, 23 (19 women, four men) of whom had GFR <90 ml/min per 1.73 $m^2$ (95). These patients with low GFR much more often were female and had a higher incidence of hypertension and more severe DR than the normal or high GFR group and had significantly worse diabetic glomerulopathy lesions (95). These findings were independent of the use of RAS-blocking drugs.

Reduced GFR has also been described in patients with NA and type 2 diabetes (96). Using a GFR cutoff of 60 ml/min per 1.73 $m^2$ in an older cohort of patients with type 2 diabetes (mean age 73 yr), the prevalence of low GFR among patients with NA was 23% (96). Also, the prevalence of NA was high (39%) among these patients with type 2 diabetes and reduced GFR (96). Compared with patients with P and similarly reduced GFR, patients with NA were older and more frequently female (58% in NA *versus* 18% in P) (96). These group differences for age and female gender remained significant after patients who did not have NA before RAS inhibitor therapy were excluded. So configured, 23% of patients with NA and long-term type 2 diabetes had low GFR, 65% of whom were female (96). This compared with 22% of patients with long-standing NA and type 1 diabetes, 83% of whom were female (95). In one report, 24% of the patients with NA, low GFR, and type 2 diabetes had AER values >20 $\mu$g/min when both immunoreactive and immuno-unreactive albumin were measured (97).

Given that GFR estimates from the application of serum creatinine formulas to patients with diabetes are, at best, imprecise and, at worst, misleading (98), other means of estimating GFR need to be considered. Serum cystatin C levels were found to be a better approximation of formal GFR measures than serum creatinine values in several studies (99–103) in patients with type 1 diabetes and type 2 diabetes. Alternatively, plasma clearance of $^{51}$Cr-EDTA or iohexol (104,105) may be more convenient as direct measures of GFR than methods that involve timed urine collections. The important point here is that there are many exceptions to the concept that clinical manifestations of DN are lock step, increased AER followed by hypertension, and then GFR decline. Given the magnitude of the clinical problem of DN and high risks that patients with DN face, we are no longer justified in using inadequate GFR estimates in these patients, especially in certain subsets, such as women with NA, long-standing diabetes, retinopathy, and/or hypertension. The time and money required for more precise GFR estimates, in our view, is warranted. Otherwise, to take the analogy to DR one step further, not only are we using renal functional tests to diagnose and follow DN while ophthalmologists follow retinal structure, but we also are using poor renal function tests, such as inaccurate GFR estimates, limited value clinic BP, and AER with all of its inherent problems as discussed above.

## Renal Biopsy

### *Electron Microscopy*

It is known that greater GBM width is a predictor of the subsequent development of MA in patients with NA and type 1 diabetes (64). We have also shown that greater GBM width in patients with NA and type 1 diabetes predicts progression to P and increased mortality in a 14-yr follow-up study (Caramori ML, Mauer M, unpublished data). AER in patients with type 1 diabetes and MA after 8 yr of follow-up was predicted by the baseline GBM width and mesangial matrix fractional volume [Vv(MM/glom)], whereas baseline mesangial fractional volume [Vv(Mes/glom)] predicted GFR change (106).

No studies have identified structural predictors of progression from NA to MA in patients with type 2 diabetes. However, studies in Pima Indians with MA and type 2 diabetes found that reduced baseline podocyte number predicted greater increase in AER after 4 yr of follow-up ($r = 0.57$, $P = 0.02$) (107). Baseline Vv(Mes/glom) had a similar predictive value ($r = 0.48$, $P = 0.06$) for the AER increase over this time (107). The odds ratio for having progressive GFR loss in white patients with type 2 diabetes and abnormal AER increased across the quartiles of electron microscopy (EM) morphometrically measured GBM width and Vv(Mes/glom) (108). Baseline AER levels did not predict subsequent changes in GFR in this study (108), perhaps because several patients had MA without significant DN glomerular lesions.

### *Light Microscopy*

Although the above discussion focuses on quantitative EM data, it should be noted that the experienced reader of light microscopy (LM) can develop semiquantitative estimates of mesangial (109) and interstitial (110) expansion, which closely approach unbiased morphometric measurements of these parameters. Also, severity of arteriolar hyalinosis lesions and global glomerulosclerosis are closely related, and the latter is associated with GFR loss (111). Given the greater heterogeneity of lesions in type 2 diabetes *versus* type 1 diabetes (see the

*Table 1.* Variables that are associated with increased likelihood of progression from MA to P or risk for P in type 1 diabetes[a]

| Variable (in Alphabetical Order) | Reference | Mean Values for Patients Who Still Had MA | Mean Values for Patients Who Progressed to P | Threshold | OR |
|---|---|---|---|---|---|
| AER ($\mu$g/min) | (22) | 44.9 | 64.4 | NP | 1.9 |
| $HbA_{1c}$ (%) | (22) | 6.8 | 7.9 | NP | 2.1 |
| Mean BP (mmHg) | (49) | 83 | 85 | >81.1 | 3.1 |
| Parental history of CV disease[b] | (51) | — | — | Present | 3.2 |
| Parental history of hypertension[b] | (48) | — | — | Present | 3.7 |
| | (49) | — | — | Present | 3.8 |
| Smoking | (84) | — | — | Present | 2.8 |
| Weight (kg) | (22) | 68 | 70 | NP | 1.5 |

[a]AER, albumin excretion rate; CV, cardiovascular; $HbA_{1c}$, glycated hemoglobin; MA, microalbuminuria, NP, not provided; OR, odds ratio; P, proteinuria.
[b]Risk for P.

*Table 2.* Variables associated with increased likelihood of progression from MA to P or risk for P in type 2 diabetes[a]

| Variable (in Alphabetical Order) | Reference | Mean Value for Patients Who Still Had MA | Mean Value for Patients Who Progressed to P | Threshold | OR |
|---|---|---|---|---|---|
| AER (mg/24 h) | (34) | 75 | 101 | NP | 2.68 (OR per doubling of log AER) |
| $HbA_{1c}$ (change during follow-up) | (34) | 8.8 | 8.6 | NP | 1.43 (OR per % $HbA_{1c}$ increase) |
| Parental history of hypertension (both parents)[b] | (50) | — | — | Present | 2.2 |
| Retinopathy | (34) | — | — | Present | 2.93 |
| Start of antihypertensive agent (during follow-up) | (34) | — | — | Present | 0.20 |
| Start of RAS blockade (during follow-up) | (34) | — | — | Present | 0.16 |

[a]RAS, renin-angiotensin system.
[b]Risk for P.

Retinopathy section), LM evaluations in type 2 diabetes can be very helpful in predicting outcomes. Thus, patients with typical diabetic nephropathology (balanced severity of glomerular, tubular, interstitial, global glomerulosclerosis, and vascular lesions) have more rapid GFR decline than the patients with less advanced diabetic glomerulopathy relative to other renal lesions (Fioretto P, unpublished observations). LM can also be helpful in diagnosing diseases other than or in addition to DN. However, at the earlier stages of DN, when LM may look normal, there are, unfortunately, no substitutes for unbiased EM morphometric studies.

In summary, renal biopsies that are done strictly for research purposes, given adequate diabetes duration, are renal functional outcome predictors in both type 1 diabetes and type 2 diabetes. It should be emphasized, however, that studies of patients who undergo biopsy for clinical indications (*i.e.*, because these patients were following what was considered to be an atypical clinical course) have not been included here because of the strong possibility of selection bias.

## Lipids

Plasma lipid levels have emerged as potentially important predictors of DN risk. It is worth stating again that macrovascular disease in parents without diabetes is a strong predictor of DN in their offspring with diabetes (see above). Although not differentially expressed at baseline in the Steno type 1 diabetes cohort study (18), serum cholesterol, later on, was statistically significantly higher before MA onset than in patients who still had NA. However, this variable was not an independent predictor of MA using Cox proportional hazard model testing after factoring for glycemia, AER, BP, male gender, and height. Relatively lower serum cholesterol levels also predicted return from MA to NA in this study (18). This was also true in the Joslin Clinic Study, in which serum cholesterol and triglyceride

*Table 3.* Variables associated with increased likelihood of return from MA to NA in type 1 diabetes[a]

| Variable (in Alphabetical Order) | Reference | Mean Value for Patients Who Still Had MA | Mean Value for Patients Who Returned to NA | Threshold | OR |
|---|---|---|---|---|---|
| Age (yr) | (21) | 31 | 29 | ≤26 | 1.6 |
| AER | (18) | 59 mg/24 h | 42 mg/24 h | NP | NP |
| | (22) | 44.9 μg/min | 37.2 μg/min | NP | 0.7[b] |
| DBP (mmHg) | (18) | 84 | 79 | NP | NP |
| SBP (mmHg) | (18) | 140 | 127 | NP | NP |
| | (21) | 124 | 121 | <115 | 1.4 |
| Diabetes duration (yr) | (22) | 18 | 15 | NP | 0.8[b] |
| $HbA_{1c}$ (%) | (21) | 9.3 | 8.8 | <8.0 | 1.9 |
| Lipids | | | | | |
| cholesterol (mg/dl) | (18) | 208 | 185 | NP | NP |
| | (21) | 203 | 193 | <198 | 1.9 |
| triglycerides (mg/dl) | (21) | 146 | 109 | <145 | 2.1 |
| | (22) | 90 | 84 | NP | NP |
| triglycerides (mg/dl) and cholesterol (mg/dl) | (21) | — | — | Triglycerides <145 and cholesterol <198 | 2.4 |
| Peripheral neuropathy | (22) | — | — | Absence | 0.6[b] |
| Waist-to-hip ratio | (22) | 0.86 | 0.83 | NP | 0.8[b] |

[a]DBP, diastolic BP; NA, normoalbuminuria; SBP, systolic BP.
[b]Standardized estimates of relative risk.

levels were independent predictors of return from MA to NA after 6 yr of follow-up (21). Fasting triglycerides but not total HDL or LDL cholesterol also predicted reversion to NA or progression to P in the patients with MA and type 1 diabetes in the EURODIAB Study (22). It is interesting and perhaps related to lipid levels that lower waist-to-hip ratio was associated with greater likelihood of reversion from MA to NA in this study (22).

In summary, the measurement of plasma lipid levels adds to the prognostic value of AER measures, and this association is consistent with a role for lipid abnormalities in DN pathogenesis.

## Conclusion

This article began with the assertion that the problem of DN is far from solved. Although some might take comfort that the growth in the annual incidence of DN has leveled off somewhat (1), this is hardly a victory considering that the current incidence rate is double that of a decade ago. Although the concept of MA was a major advance in this field, it is also clear that the predictive precision of this test alone is not adequate for a disease of such dire consequences. Whether this predictive imprecision derives in part from treatments that have altered the natural history of DN is a moot point. What is argued here is that we can do better in estimating DN risk by looking at the whole patient, not just their AER measurements. We have suggested that a more complete view of individual patients with type 1 diabetes and type 2 diabetes than what is obtainable by AER alone could be helpful. Selected publications with data supportive of these ideas are summarized in Tables 1 through 4 and Figure 1.

*Table 4.* Variables associated with increased likelihood of return from MA to NA in type 2 diabetes

| Variable (in Alphabetical Order) | Reference | Mean Value for Patients Who Still Had MA | Mean Value for Patients Who Returned to NA | Threshold | OR |
|---|---|---|---|---|---|
| AER (mg/24 h) | (34) | 75 | 56 | NP | 2.27 (reduce log AER in half) |
| $HbA_{1c}$ (%) | (34) | NP | NP | NP | 1.48 per % increase during follow-up |
| | (35) | 7.5 | 7.5 | <6.95% | 3.0 |
| SBP (mmHg) | (35) | 136 | 138 | <129 | 2.7 |
| Start antihypertensive treatment (during follow-up) | (34) | — | — | Present | 2.32 |
| Start RAS blockade (during follow-up) | (35) | — | — | Present | 1.9 |
| | (34) | — | — | Present | 2.94 |

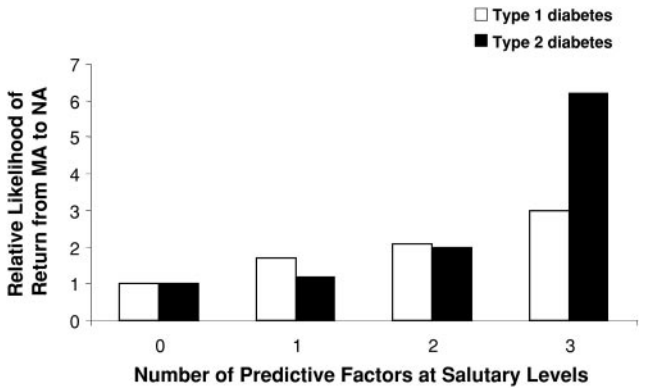


*Figure 1.* Additive effects of predictive factors on the likelihood of return from microalbuminuria (MA) to normoalbuminuria (NA) in patients with type 1 and type 2 diabetes. In patients with type 1 diabetes, salutary levels of these predictors were defined as $HbA_{1c}$ <8%, systolic BP <115 mmHg, cholesterol <198 mg/dl, and triglycerides <145 mg/dl. Salutary predictors in patients with type 2 diabetes were $HbA_{1c}$ <6.5%, BP <130/80 mmHg, cholesterol <200 mg/dl, triglycerides <150 mg/dl, and HDL >40 mmHg. Adapted from Perkins *et al.* (21) and Araki *et al.* (36)

Some of the measures discussed, such as precise GFR or ABP recordings, are cumbersome, expensive, or both, and it may be argued that the analogy to DR breaks down because we do not have the equivalent of laser therapy for the kidney. So what is the benefit of the more precise DN risk estimates that could emanate from a closer look at patients with diabetes? It is beyond the scope of this article to discuss all of the therapeutic options in detail, especially those that are still controversial, such as RAS blockade in normotensive patients with NA. At the very least, we consider that the selection of patients who are at high DN risk for intensive glycemia management is warranted (3,54). Also, focus on BP control, smoking cessation, and normalization of lipid levels seems sensible.

Although AER is important and should be measured more frequently, there are gains to be made in predictive precision in considering family history, smoking habits, glycemia, retinopathy status, GFR, BP including ABP recordings, lipid levels, and the possible influences of treatment on AER. We also recognize that current information is inadequate for the appropriate weighting of these additional DN parameters for risk assessment algorithms to be developed. It is hoped, in fact, that this discussion will stimulate cooperative merging of appropriate longitudinal databases to facilitate the emergence of such clinical tools that, we predict, would improve patient outcomes and clinical trial design. In the mean time, the clinician will need to apply a more qualitative thought process to integrate these predictive variables.

We also recognize that we need better biomarkers and risk predictors. Cystatin C as a surrogate measure of GFR and total intact urinary albumin as an early marker of altered permselectivity and increased risk deserve further exploration. Also promising are inflammatory markers; urinary proteomics; and the genetic, molecular, and cellular approaches outlined elsewhere in this issue (112). Although these newer approaches may improve DN risk prediction, the application of the integrated approach outlined here will, we believe, remain valuable.

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# Errata

## Correction

Rowshani *et al.*: No Difference in Degree of Interstitial Sirius Red–Stained Area in Serial Biopsies from Area under Concentration-over-Time Curves–Guided Cyclosporine *versus* Tacrolimus-Treated Renal Transplant Recipients at One Year. *J Am Soc Nephrol* 17: 305–312, 2006.

There is an error in the name of one of the article's authors. The sixth author of this article is Marian C. Roos-van Groningen. The authors and publisher regret this error.

## Correction

Caramori *et al.*: Enhancing the Predictive Value of Urinary Albumin for Diabetic Nephropathy. *J Am Soc Nephrol* 17: 339–352, 2006.

In this article, the authors regretfully report an error in Table 4 (on page 347). The odds ratio (OR) for returning from macroalbuminuria (MA) to normoalbuminuria (NA) should be presented as 1.48 per % **decrease** (not increase) in glycated hemoglobin ($HbA_{1c}$) during follow-up.


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## Correction

Morgenstern *et al.*: Anthropometric Prediction of Total Body Water in Children Who Are on Pediatric Peritoneal Dialysis. *J Am Soc Nephrol* 17: 285–293, 2006.

The authors regretfully report a number of erroneous values in the tables that appeared as an Appendix to their article. The corrected tables are shown here:

*Male TBW nomogram*

a

| Weight (kg) \ Height (cm) | 50 | 54 | 58 | 62 | 66 | 70 | 74 | 78 | 82 | 86 | 90 | 94 | 98 | 102 | 106 | 110 | 114 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 1.6 | 1.7 | 1.8 | 1.9 | | | | | | | | | | | | | |
| 3 | 1.9 | 2.1 | 2.2 | 2.4 | | | | | | | | | | | | | |
| 4 | 2.2 | 2.4 | 2.6 | 2.8 | 3.0 | | | | | | | | | | | | |
| 5 | 2.4 | 2.7 | 2.9 | 3.1 | 3.3 | | | | | | | | | | | | |
| 6 | 2.6 | 2.9 | 3.1 | 3.4 | 3.6 | 3.9 | 4.1 | | | | | | | | | | |
| 7 | 2.8 | 3.1 | 3.4 | 3.6 | 3.9 | 4.2 | 4.4 | 4.7 | 4.9 | | | | | | | | |
| 8 | 2.9 | 3.2 | 3.5 | 3.9 | 4.1 | 4.4 | 4.7 | 5.0 | 5.3 | 5.5 | 5.8 | | | | | | |
| 9 | | | | 4.0 | 4.4 | 4.7 | 5.0 | 5.3 | 5.6 | 5.9 | 6.2 | 6.5 | 6.7 | | | | |
| 10 | | | | 4.2 | 4.6 | 4.9 | 5.2 | 5.6 | 5.9 | 6.2 | 6.5 | 6.8 | 7.1 | 7.4 | 7.7 | | |
| 11 | | | | 4.4 | 4.8 | 5.1 | 5.5 | 5.8 | 6.2 | 6.5 | 6.8 | 7.1 | 7.5 | 7.8 | 8.1 | 8.4 | 8.7 |
| 12 | | | | 4.5 | 4.9 | 5.3 | 5.7 | 6.0 | 6.4 | 6.8 | 7.1 | 7.5 | 7.8 | 8.1 | 8.5 | 8.8 | 9.1 |
| 13 | | | | | | | | 6.3 | 6.6 | 7.0 | 7.4 | 7.8 | 8.1 | 8.5 | 8.8 | 9.2 | 9.5 |
| 14 | | | | | | | | 6.5 | 6.9 | 7.3 | 7.7 | 8.0 | 8.4 | 8.8 | 9.2 | 9.5 | 9.9 |
| 15 | | | | | | | | 6.7 | 7.1 | 7.5 | 7.9 | 8.3 | 8.7 | 9.1 | 9.5 | 9.9 | 10.2 |
| 16 | | | | | | | | 6.8 | 7.3 | 7.7 | 8.1 | 8.6 | 9.0 | 9.4 | 9.8 | 10.2 | 10.6 |
| 17 | | | | | | | | | | | 8.4 | 8.8 | 9.2 | 9.7 | 10.1 | 10.5 | 10.9 |
| 18 | | | | | | | | | | | 8.6 | 9.0 | 9.5 | 9.9 | 10.4 | 10.8 | 11.2 |
| 19 | | | | | | | | | | | 8.8 | 9.3 | 9.7 | 10.2 | 10.6 | 11.1 | 11.5 |
| 20 | | | | | | | | | | | 9.0 | 9.4 | 9.9 | 10.4 | 10.9 | 11.3 | 11.8 |

b

| Weight (kg) \ Height (cm) | 106 | 110 | 114 | 118 | 122 | 126 | 130 | 134 | 138 | 142 | 146 | 150 | 154 | 158 | 162 | 166 | 170 | 174 | 178 | 182 | 186 | 190 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 10.9 | 11.3 | 11.8 | 12.3 | 12.7 | 13.2 | 13.6 | 14.0 | 14.5 | 14.9 | 15.3 | 15.7 | | | | | | | | | | |
| 22 | 11.4 | 11.9 | 12.4 | 12.8 | 13.3 | 13.8 | 14.3 | 14.7 | 15.2 | 15.7 | 16.1 | 16.6 | | | | | | | | | | |
| 24 | 11.8 | 12.3 | 12.9 | 13.4 | 13.9 | 14.4 | 14.9 | 15.4 | 15.9 | 16.4 | 16.8 | 17.3 | 17.8 | 18.3 | 18.7 | | | | | | | |
| 26 | 12.2 | 12.8 | 13.3 | 13.9 | 14.4 | 15.0 | 15.5 | 16.0 | 16.5 | 17.0 | 17.5 | 18.0 | 18.5 | 19.0 | 19.5 | | | | | | | |
| 28 | 12.6 | 13.2 | 13.8 | 14.4 | 14.9 | 15.5 | 16.0 | 16.6 | 17.1 | 17.7 | 18.2 | 18.7 | 19.3 | 19.8 | 20.3 | 20.8 | 21.3 | | | | | |
| 30 | 13.0 | 13.6 | 14.2 | 14.8 | 15.4 | 16.0 | 16.6 | 17.1 | 17.7 | 18.3 | 18.8 | 19.4 | 19.9 | 20.5 | 21.0 | 21.6 | 22.1 | | | | | |
| 32 | 13.3 | 14.0 | 14.6 | 15.2 | 15.8 | 16.5 | 17.1 | 17.7 | 18.3 | 18.8 | 19.4 | 20.0 | 20.6 | 21.2 | 21.7 | 22.3 | 22.9 | 23.4 | 24.0 | | | |
| 34 | 13.6 | 14.3 | 15.0 | 15.6 | 16.3 | 16.9 | 17.5 | 18.2 | 18.8 | 19.4 | 20.0 | 20.6 | 21.2 | 21.8 | 22.4 | 23.0 | 23.6 | 24.2 | 24.7 | | | |
| 36 | 13.9 | 14.6 | 15.3 | 16.0 | 16.7 | 17.3 | 18.0 | 18.7 | 19.3 | 19.9 | 20.6 | 21.2 | 21.8 | 22.4 | 23.1 | 23.7 | 24.3 | 24.9 | 25.5 | 26.1 | 26.6 | |
| 38 | 14.2 | 14.9 | 15.7 | 16.4 | 17.1 | 17.8 | 18.4 | 19.1 | 19.8 | 20.4 | 21.1 | 21.8 | 22.4 | 23.0 | 23.7 | 24.3 | 24.9 | 25.6 | 26.2 | 26.8 | 27.4 | |
| 40 | | | 16.0 | 16.7 | 17.4 | 18.1 | 18.8 | 19.5 | 20.2 | 20.9 | 21.6 | 22.3 | 23.0 | 23.6 | 24.3 | 24.9 | 25.6 | 26.2 | 26.9 | 27.5 | 28.1 | 28.8 |
| 42 | | | 16.3 | 17.0 | 17.8 | 18.5 | 19.2 | 20.0 | 20.7 | 21.4 | 22.1 | 22.8 | 23.5 | 24.2 | 24.9 | 25.5 | 26.2 | 26.9 | 27.5 | 28.2 | 28.8 | 29.5 |
| 44 | | | 16.6 | 17.3 | 18.1 | 18.9 | 19.6 | 20.4 | 21.1 | 21.8 | 22.6 | 23.3 | 24.0 | 24.7 | 25.4 | 26.1 | 26.8 | 27.5 | 28.2 | 28.8 | 29.5 | 30.2 |
| 46 | | | 16.8 | 17.6 | 18.4 | 19.2 | 20.0 | 20.8 | 21.5 | 22.3 | 23.0 | 23.8 | 24.5 | 25.2 | 26.0 | 26.7 | 27.4 | 28.1 | 28.8 | 29.5 | 30.2 | 30.9 |
| 48 | | | 17.1 | 17.9 | 18.7 | 19.5 | 20.3 | 21.1 | 21.9 | 22.7 | 23.5 | 24.2 | 25.0 | 25.7 | 26.5 | 27.2 | 27.9 | 28.7 | 29.4 | 30.1 | 30.8 | 31.5 |
| 50 | | | 17.3 | 18.2 | 19.0 | 19.8 | 20.7 | 21.5 | 22.3 | 23.1 | 23.9 | 24.7 | 25.4 | 26.2 | 27.0 | 27.7 | 28.5 | 29.2 | 30.0 | 30.7 | 31.5 | 32.2 |
| 52 | | | | | | 20.1 | 21.0 | 21.8 | 22.6 | 23.5 | 24.3 | 25.1 | 25.9 | 26.7 | 27.5 | 28.2 | 29.0 | 29.8 | 30.6 | 31.3 | 32.1 | 32.8 |
| 54 | | | | | | 20.4 | 21.3 | 22.1 | 23.0 | 23.8 | 24.7 | 25.5 | 26.3 | 27.1 | 27.9 | 28.7 | 29.5 | 30.3 | 31.1 | 31.9 | 32.7 | 33.4 |
| 56 | | | | | | 20.7 | 21.6 | 22.5 | 23.3 | 24.2 | 25.0 | 25.9 | 26.7 | 27.6 | 28.4 | 29.2 | 30.0 | 30.8 | 31.7 | 32.4 | 33.2 | 34.0 |
| 58 | | | | | | 20.9 | 21.8 | 22.8 | 23.7 | 24.5 | 25.4 | 26.3 | 27.1 | 28.0 | 28.8 | 29.7 | 30.5 | 31.4 | 32.2 | 33.0 | 33.8 | 34.6 |
| 60 | | | | | | 21.2 | 22.1 | 23.1 | 24.0 | 24.9 | 25.8 | 26.7 | 27.5 | 28.4 | 29.3 | 30.1 | 31.0 | 31.8 | 32.7 | 33.5 | 34.4 | 35.2 |
| 62 | | | | | | 21.4 | 22.4 | 23.3 | 24.3 | 25.2 | 26.1 | 27.0 | 27.9 | 28.8 | 29.7 | 30.6 | 31.5 | 32.3 | 33.2 | 34.0 | 34.9 | 35.7 |
| 64 | | | | | | 21.7 | 22.6 | 23.6 | 24.6 | 25.5 | 26.4 | 27.4 | 28.3 | 29.2 | 30.1 | 31.0 | 31.9 | 32.8 | 33.7 | 34.5 | 35.4 | 36.3 |
| 66 | | | | | | | | | 24.8 | 25.8 | 26.8 | 27.7 | 28.6 | 29.6 | 30.5 | 31.4 | 32.3 | 33.2 | 34.1 | 35.0 | 35.9 | 36.8 |
| 68 | | | | | | | | | 25.1 | 26.1 | 27.1 | 28.0 | 29.0 | 30.0 | 30.9 | 31.8 | 32.8 | 33.7 | 34.6 | 35.5 | 36.4 | 37.3 |
| 70 | | | | | | | | | 25.4 | 26.4 | 27.4 | 28.4 | 29.3 | 30.3 | 31.3 | 32.2 | 33.2 | 34.1 | 35.1 | 36.0 | 36.9 | 37.8 |
| 72 | | | | | | | | | 25.6 | 26.6 | 27.7 | 28.7 | 29.7 | 30.7 | 31.6 | 32.6 | 33.6 | 34.5 | 35.5 | 36.4 | 37.4 | 38.3 |
| 74 | | | | | | | | | 25.9 | 26.9 | 27.9 | 29.0 | 30.0 | 31.0 | 32.0 | 33.0 | 34.0 | 34.9 | 35.9 | 36.9 | 37.8 | 38.8 |
| 76 | | | | | | | | | 26.1 | 27.2 | 28.2 | 29.3 | 30.3 | 31.3 | 32.3 | 33.3 | 34.4 | 35.3 | 36.3 | 37.3 | 38.3 | 39.3 |
| 78 | | | | | | | | | 26.3 | 27.4 | 28.5 | 29.5 | 30.6 | 31.6 | 32.7 | 33.7 | 34.7 | 35.7 | 36.7 | 37.7 | 38.7 | 39.7 |
| 80 | | | | | | | | | 26.5 | 27.6 | 28.7 | 29.8 | 30.9 | 31.9 | 33.0 | 34.1 | 35.1 | 36.1 | 37.1 | 38.2 | 39.2 | 40.2 |

*Female TBW nomogram*

a

| Weight (kg) \ Height (cm) | 50 | 54 | 58 | 62 | 66 | 70 | 74 | 78 | 82 | 86 | 90 | 94 | 98 | 102 | 106 | 110 | 114 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 2.0 | 2.1 | 2.2 | 2.4 | | | | | | | | | | | | | |
| 3 | 2.4 | 2.6 | 2.8 | 2.9 | | | | | | | | | | | | | |
| 4 | 2.8 | 3.0 | 3.2 | 3.4 | 3.6 | | | | | | | | | | | | |
| 5 | 3.1 | 3.3 | 3.5 | 3.8 | 4.0 | | | | | | | | | | | | |
| 6 | 3.3 | 3.6 | 3.8 | 4.1 | 4.3 | 4.6 | 4.8 | | | | | | | | | | |
| 7 | 3.5 | 3.8 | 4.1 | 4.4 | 4.8 | 4.9 | 5.2 | 5.5 | 5.7 | | | | | | | | |
| 8 | 3.7 | 4.0 | 4.3 | 4.6 | 4.9 | 5.2 | 5.5 | 5.8 | 6.1 | 6.4 | 6.6 | | | | | | |
| 9 | | | | 4.9 | 5.2 | 5.5 | 5.8 | 6.1 | 6.4 | 6.7 | 7.0 | 7.3 | 7.6 | | | | |
| 10 | | | | 5.1 | 5.4 | 5.8 | 6.1 | 6.4 | 6.8 | 7.1 | 7.4 | 7.7 | 8.0 | 8.3 | 8.6 | | |
| 11 | | | | 5.3 | 5.6 | 6.0 | 6.4 | 6.7 | 7.1 | 7.4 | 7.7 | 8.1 | 8.4 | 8.7 | 9.0 | 9.3 | 9.6 |
| 12 | | | | 5.4 | 5.8 | 6.2 | 6.6 | 7.0 | 7.3 | 7.7 | 8.0 | 8.4 | 8.7 | 9.1 | 9.4 | 9.7 | 10.0 |
| 13 | | | | | | | | 7.2 | 7.6 | 8.0 | 8.3 | 8.7 | 9.1 | 9.4 | 9.8 | 10.1 | 10.4 |
| 14 | | | | | | | | 7.4 | 7.8 | 8.2 | 8.6 | 9.0 | 9.4 | 9.7 | 10.1 | 10.5 | 10.8 |
| 15 | | | | | | | | 7.6 | 8.0 | 8.5 | 8.9 | 9.3 | 9.7 | 10.0 | 10.4 | 10.8 | 11.2 |
| 16 | | | | | | | | 7.8 | 8.3 | 8.7 | 9.1 | 9.5 | 9.9 | 10.3 | 10.7 | 11.1 | 11.5 |
| 17 | | | | | | | | | | | 9.3 | 9.8 | 10.2 | 10.6 | 11.0 | 11.4 | 11.8 |
| 18 | | | | | | | | | | | 9.6 | 10.0 | 10.5 | 10.9 | 11.3 | 11.7 | 12.2 |
| 19 | | | | | | | | | | | 9.8 | 10.2 | 10.7 | 11.1 | 11.6 | 12.0 | 12.5 |
| 20 | | | | | | | | | | | 10.0 | 10.4 | 10.9 | 11.4 | 11.8 | 12.3 | 12.7 |

b

| Weight (kg) \ Height (cm) | 106 | 110 | 114 | 118 | 122 | 126 | 130 | 134 | 138 | 142 | 146 | 150 | 154 | 158 | 162 | 166 | 170 | 174 | 178 | 182 | 186 | 190 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 11.8 | 12.3 | 12.7 | 13.2 | 13.6 | 14.0 | 14.5 | 14.9 | 15.3 | 15.7 | 16.1 | 16.5 | | | | | | | | | | |
| 22 | 12.3 | 12.8 | 13.3 | 13.7 | 14.2 | 14.7 | 15.1 | 15.6 | 16.0 | 16.4 | 16.9 | 17.3 | | | | | | | | | | |
| 24 | 12.8 | 13.3 | 13.8 | 14.3 | 14.8 | 15.2 | 15.7 | 16.2 | 16.7 | 17.1 | 17.6 | 18.0 | 18.5 | 18.9 | 19.4 | | | | | | | |
| 26 | 13.2 | 13.7 | 14.2 | 14.8 | 15.3 | 15.8 | 16.3 | 16.8 | 17.3 | 17.8 | 18.3 | 18.7 | 19.2 | 19.7 | 20.1 | | | | | | | |
| 28 | 13.6 | 14.1 | 14.7 | 15.2 | 15.8 | 16.3 | 16.8 | 17.3 | 17.9 | 18.4 | 18.9 | 19.4 | 19.9 | 20.4 | 20.9 | 21.3 | 21.8 | | | | | |
| 30 | 13.9 | 14.5 | 15.1 | 15.7 | 16.2 | 16.8 | 17.3 | 17.9 | 18.4 | 18.9 | 19.5 | 20.0 | 20.5 | 21.0 | 21.5 | 22.0 | 22.5 | | | | | |
| 32 | 14.3 | 14.9 | 15.5 | 16.1 | 16.6 | 17.2 | 17.8 | 18.4 | 18.9 | 19.5 | 20.0 | 20.6 | 21.1 | 21.7 | 22.2 | 22.7 | 23.2 | 23.7 | 24.3 | | | |
| 34 | 14.6 | 15.2 | 15.8 | 16.4 | 17.0 | 17.7 | 18.2 | 18.8 | 19.4 | 20.0 | 20.6 | 21.1 | 21.7 | 22.3 | 22.8 | 23.4 | 23.9 | 24.4 | 25.0 | | | |
| 36 | 14.8 | 15.5 | 16.2 | 16.8 | 17.4 | 18.1 | 18.7 | 19.3 | 19.9 | 20.5 | 21.1 | 21.7 | 22.3 | 22.8 | 23.4 | 24.0 | 24.5 | 25.1 | 25.6 | 26.2 | 26.7 | |
| 38 | 15.1 | 15.8 | 16.5 | 17.1 | 17.8 | 18.4 | 19.1 | 19.7 | 20.3 | 21.0 | 21.6 | 22.2 | 22.8 | 23.4 | 24.0 | 24.6 | 25.1 | 25.7 | 26.3 | 26.9 | 27.4 | |
| 40 | | | 16.8 | 17.4 | 18.1 | 18.8 | 19.5 | 20.1 | 20.7 | 21.4 | 22.0 | 22.7 | 23.3 | 23.9 | 24.5 | 25.1 | 25.7 | 26.3 | 26.9 | 27.5 | 28.1 | 28.6 |
| 42 | | | 17.0 | 17.7 | 18.4 | 19.1 | 19.8 | 20.5 | 21.1 | 21.8 | 22.5 | 23.1 | 23.8 | 24.4 | 25.0 | 25.7 | 26.3 | 26.9 | 27.5 | 28.1 | 28.7 | 29.3 |
| 44 | | | 17.3 | 18.0 | 18.7 | 19.5 | 20.2 | 20.9 | 21.5 | 22.2 | 22.9 | 23.6 | 24.2 | 24.9 | 25.5 | 26.2 | 26.8 | 27.4 | 28.1 | 28.7 | 29.3 | 29.9 |
| 46 | | | 17.5 | 18.3 | 19.0 | 19.8 | 20.5 | 21.2 | 21.9 | 22.6 | 23.3 | 24.0 | 24.7 | 25.3 | 26.0 | 26.7 | 27.3 | 28.0 | 28.6 | 29.3 | 29.9 | 30.5 |
| 48 | | | 17.8 | 18.5 | 19.3 | 20.0 | 20.8 | 21.5 | 22.3 | 23.0 | 23.7 | 24.4 | 25.1 | 25.8 | 26.5 | 27.2 | 27.8 | 28.5 | 29.2 | 29.8 | 30.5 | 31.1 |
| 50 | | | 18.0 | 18.8 | 19.6 | 20.3 | 21.1 | 21.8 | 22.6 | 23.3 | 24.1 | 24.8 | 25.5 | 26.2 | 26.9 | 27.6 | 28.3 | 29.0 | 29.7 | 30.4 | 31.0 | 31.7 |
| 52 | | | | | | 20.6 | 21.4 | 22.1 | 22.9 | 23.7 | 24.4 | 25.2 | 25.9 | 26.6 | 27.4 | 28.1 | 28.8 | 29.5 | 30.2 | 30.9 | 31.6 | 32.2 |
| 54 | | | | | | 20.8 | 21.6 | 22.4 | 23.2 | 24.0 | 24.8 | 25.5 | 26.3 | 27.0 | 27.8 | 28.5 | 29.2 | 29.9 | 30.7 | 31.4 | 32.1 | 32.8 |
| 56 | | | | | | 21.1 | 21.9 | 22.7 | 23.5 | 24.3 | 25.1 | 25.9 | 26.6 | 27.4 | 28.2 | 28.9 | 29.7 | 30.4 | 31.1 | 31.9 | 32.6 | 33.3 |
| 58 | | | | | | 21.3 | 22.1 | 23.0 | 23.8 | 24.6 | 25.4 | 26.2 | 27.0 | 27.8 | 28.5 | 29.3 | 30.1 | 30.8 | 31.6 | 32.3 | 33.1 | 33.8 |
| 60 | | | | | | 21.5 | 22.4 | 23.2 | 24.1 | 24.9 | 25.7 | 26.5 | 27.3 | 28.1 | 28.9 | 29.7 | 30.5 | 31.3 | 32.0 | 32.8 | 33.5 | 34.3 |
| 62 | | | | | | 21.7 | 22.6 | 23.4 | 24.3 | 25.2 | 26.0 | 26.8 | 27.7 | 28.5 | 29.3 | 30.1 | 30.9 | 31.7 | 32.4 | 33.2 | 34.0 | 34.8 |
| 64 | | | | | | 21.9 | 22.8 | 23.7 | 24.6 | 25.4 | 26.3 | 27.1 | 28.0 | 28.8 | 29.6 | 30.4 | 31.3 | 32.1 | 32.9 | 33.6 | 34.4 | 35.2 |
| 66 | | | | | | | | | 24.8 | 25.7 | 26.5 | 27.4 | 28.3 | 29.1 | 30.0 | 30.8 | 31.6 | 32.4 | 33.2 | 34.1 | 34.9 | 35.7 |
| 68 | | | | | | | | | 25.0 | 25.9 | 26.8 | 27.7 | 28.6 | 29.4 | 30.3 | 31.1 | 32.0 | 32.8 | 33.6 | 34.5 | 35.3 | 36.1 |
| 70 | | | | | | | | | 25.2 | 26.1 | 27.0 | 27.9 | 28.8 | 29.7 | 30.6 | 31.5 | 32.3 | 33.2 | 34.0 | 34.9 | 35.7 | 36.5 |
| 72 | | | | | | | | | 25.4 | 26.4 | 27.3 | 28.2 | 29.1 | 30.0 | 30.9 | 31.8 | 32.7 | 33.5 | 34.4 | 35.2 | 36.1 | 36.9 |
| 74 | | | | | | | | | 25.6 | 26.6 | 27.5 | 28.4 | 29.4 | 30.3 | 31.2 | 32.1 | 33.0 | 33.9 | 34.7 | 35.6 | 36.5 | 37.3 |
| 76 | | | | | | | | | 25.8 | 26.8 | 27.7 | 28.7 | 29.6 | 30.6 | 31.5 | 32.4 | 33.3 | 34.2 | 35.1 | 36.0 | 36.8 | 37.7 |
| 78 | | | | | | | | | 26.0 | 27.0 | 27.9 | 28.9 | 29.9 | 30.8 | 31.7 | 32.7 | 33.6 | 34.5 | 35.4 | 36.3 | 37.2 | 38.1 |
| 80 | | | | | | | | | 26.2 | 27.2 | 28.1 | 29.1 | 30.1 | 31.1 | 32.0 | 33.0 | 33.9 | 34.8 | 35.7 | 36.7 | 37.6 | 38.5 |