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PERSPECTIVES IN RENAL MEDICINE

From secondary to primary prevention of progressive renal disease: The case for screening for albuminuria

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From secondary to primary prevention of progressive renal disease: The case for screening for albuminuria. Many subjects nowadays present with end-stage renal failure and its attendant cardiovascular complications without known prior renal damage. In this report we review the evidence available to strongly suggest that the present practice of secondary prevention in those with known prior renal disease should be extended to primary prevention for those subjects in the general population who are at risk for progressive renal failure, but who had never suffered from a primary renal disease. We show that such subjects can be detected by screening for albuminuria. Elevated urinary albumin loss is an indicator not only of poor renal, but also of poor cardiovascular prognosis. In addition to diabetic subjects who are at risk for albuminuria, we also show that hypertensive, obese, and smoking subjects are more susceptible. We suggest that therapies that have been shown to lower albumin excretion, such as ACE inhibitors, angiotensin II receptor antagonists, and statins be started early in such patients to prevent them from developing clinical renal disease and its attendant cardiovascular complications.

Historically, nephrology expanded greatly after the development of the artificial kidney and the introduction of renal transplantation. Due to the great demand for renal replacement therapy, little effort was given to primary or secondary prevention of progressive renal disease. Fortunately, however, in the last decade much has been achieved in secondary prevention in subjects who had been diagnosed with already established renal damage due to glomerular or tubulointerstitial renal diseases. This secondary prevention aimed at preventing progressive renal function loss in these patients with prior renal disease. Low-protein diets [1] (although in clinical practice difficult to achieve), and antihypertensive agents, in general [2], but angiotensin-converting enzyme (ACE) inhibitors [3, 4, 5] and angiotensin II receptor antagonists [6, 7], in particular, appeared especially effective in retarding a further progressive renal function decline. Recent, yet not thus far confirmed data suggest that the use of lipid-lowering agents [8], weight reduction [9], and cessation of smoking [10] may also be beneficial in secondary prevention. With such interventions it is possible to retard the progressive decline in renal function: the slope of glomerular filtration rate (GFR) over time becomes less steep, and the time elapsing before renal replacement therapy is started has been extended significantly. Some reports even document the reversal of prior renal function decline [11, 12].

Despite successes in slowing progression after renal injury has already occurred, we are still faced with increasing numbers of patients requiring renal replacement therapy. The increasing demand for these services is partly related to the fact that dialysis and renal transplant techniques have improved and are now extended to those who are elderly or suffer systemic diseases (i.e., diabetes and generalized atherosclerosis). Whereas diabetes now constitutes the major cause of end-stage renal disease (ESRD) in many national registries, it should be noted that the number of patients reaching ESRD without a renal diagnosis is also increasing dramatically. Besides diabetes, the importance of generalized atherosclerosis and hypertension to insidious loss of renal function, therefore, cannot be neglected [13].

In this paper we will (*1*) consider the mechanisms underlying the progressive decline in renal function observed in subjects with preexisting renal disease. Cognizant of these mechanisms, we will (*2*) examine the factors likely to be responsible for initiating loss of renal function in the general population; (*3*) review the options available to detect subjects at risk for early loss by screening for albuminuria; and (*4*) consider whether strategies that have been proven effective in secondary prevention will also be effective as primary prevention, that is, prevention of progressive renal function loss in those not known to have prior renal disease, and at a time when

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renal function loss is not yet manifest. Such preventive efforts should ultimately improve long-term health and greatly reduce the economic burden related to renal replacement therapy. Considering the evidence available, we believe it is essential for large ongoing and future epidemiologic studies that focus on risk factors for, and treatment of, cardiovascular disease to add albuminuria measurements to their protocol. Additionally, it would be of great benefit for optimizing cardio- and renoprotective therapies in primary health care to include albuminuria measurements in the routine follow-up of patients.

MECHANISMS UNDERLYING PROGRESSIVE LOSS OF RENAL FUNCTION

At present, much is known about the mechanisms underlying the progressive decline in renal function in patients with known renal disease. It has been well documented that the hemodynamic adaptations of glomerular hypertension and hyperfiltration in remnant nephrons (i.e., those nephrons not damaged by the initiating renal disease) ultimately prove detrimental. They suffer progressive glomerulosclerosis, a process that sets into motion a vicious cycle of nephron loss. The more initial nephrons lost, the more the hemodynamic burden to the remaining ones [14]. The ensuing protein leakage through these affected glomeruli results in enhanced tubule protein reabsorption, which initiates progressive tubule atrophy and interstitial fibrosis [15]. Clinically, the most important factors promoting this final common pathway of progressive nephron loss are hypertension [16], proteinuria [17], hyperlipidemia [18], and genetic factors, such as race [19] and ACE gene polymorphism [20]. Other factors such as obesity [21], smoking [22], low birth weight [23], male gender [24], and high salt intake [25] are also likely to be associated with a worse outcome in subjects with preexisting renal disease.

DOES HYPERFILTRATION ALSO OCCUR IN HEALTHY KIDNEYS, AND WHAT IS THE CONSEQUENCE?

The potential for hyperfiltration also occurs in other "physiologic" circumstances, such as congenital reduction in nephron number, sickle cell anemia, and following uninephrectomy (i.e., after kidney donation). Does glomerular hyperfiltration also explain the GFR decline in normal aging? In the normal population, GFR decreases from the age of 30 by about 0.8 mL/min/year [26]. Assuming that a 30-year-old subject has a normal GFR of about 120 mL/min, his/her GFR will be about 70 mL/min at the age of 80. A renal biopsy in a kidney from that 80-year-old person will typically reveal some atrophic glomeruli with tubule atrophy, other glomeruli showing signs of glomerulosclerosis, and still others showing glomerular enlargement and hypertrophy. It has been shown that the age-related decline in renal function, as well as in renal cortical thickness is accelerated in cases of generalized atherosclerosis [27]. If an elevated GFR by itself bears the risk of later progressive renal function loss, we should question whether screening for hyperfiltration would be of help to detect subjects at risk. Screening for glomerular hyperfiltration with accurate renal function studies is, however, not feasible in population studies. Measuring creatinine clearance is also difficult to perform in population studies, and an elevated creatinine clearance in a single subject does not allow investigators to conclude that hyperfiltration exists in that subject because of possible inaccuracies in 24-hour urine collections. Finally, indirect GFR estimates such as the Modification of Diet in Renal Disease (MDRD) formula or the Cockroft-Gault formula have never been tested in the range of normal to elevated GFRs. Thus, the detection of glomerular hyperfiltration in population studies is difficult to achieve.

With regard to the relationship between initial glomerular hyperfiltration and subsequent loss of renal function, we should learn from the experience in diabetes mellitus, especially type 1 diabetes. This is the condition in which the course of GFR in the long run is best studied, and in which the relation between hyperfiltration and albuminuria has been well established. If such an association also holds true for the general population, the screening for microalbuminuria may be appropriate.

ALBUMINURIA AS AN INDICATOR OF GLOMERULAR HYPERFILTRATION

It is well known that glomerular hyperfiltration exists in the initial years after onset of hyperglycemia both in type 1 [28, 29] and type 2 diabetes [30, 31]. This increase in GFR is related to both a rise in renal plasma flow and in filtration fraction, caused by afferent, but not efferent, vasodilatation and increased glomerular capillary pressure. Without treatment, this phase continues for about a decade before urinary albumin loss commences and rises to the level of microalbuminuria (defined as urinary albumin excretion of 20–200 μg/min or 30–300 mg/day). At this time, GFR declines to normal and then subnormal levels, and ultimately progresses to end-stage renal failure. This latter phase coincides with a further increase in albuminuria, often to more than 2 g/day. This longitudinal pattern of changes in GFR and albuminuria in type 1 diabetes is illustrated in Figure 1 [32]. Data on the time course of GFR and albuminuria in type 2 diabetes are sparse. It has been shown that GFR increases during follow-up in Pima Indians with impaired glucose tolerance and recently detected type 2 diabetes (at the time where there is not yet albuminuria), whereas GFR is

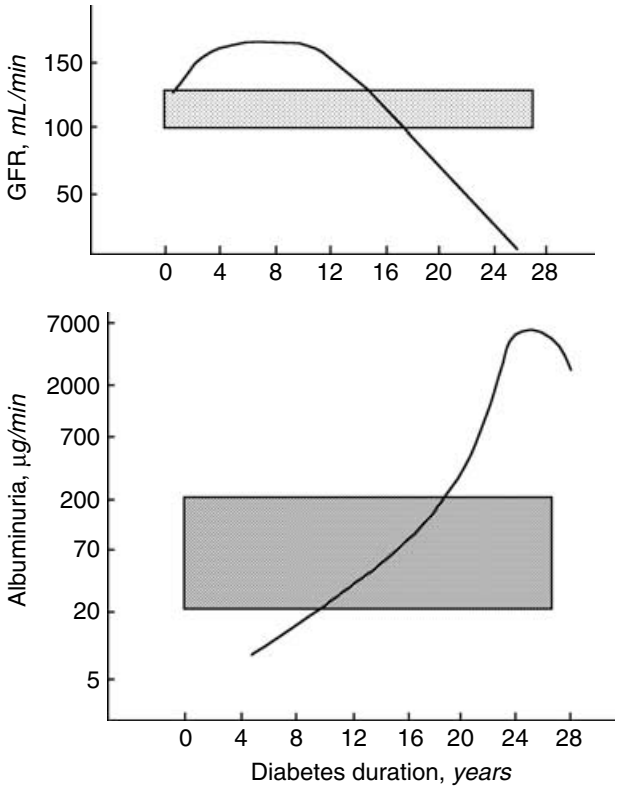

Fig. 1. The longitudinal data on glomerular filtration rate (GFR) and urinary albumin excretion in type 1 diabetes, showing that initially hyperfiltration is present. Next, in time, albumin excretion starts to rise. At that time, GFR starts to drop, to ultimately reach the level of end-stage renal failure and macroproteinuria (derived from [32]). The stippled area in the GFR plot indicates the normal value; the hatched area in the albuminuria plot refers to the microalbuminuria range.

stable during the period of microalbuminuria and diminishes as macroproteinuria develops [33].

The experience in diabetes can be used as a model to study the impact of an increased albumin excretion in nondiabetic subjects, as well. Indeed, a similar association between albuminuria and creatinine clearance was observed in a large cohort of about 8000 nondiabetic subjects of the general population. The presence of albuminuria in the high normal range (15–30 mg albumin per day), or the so-called "micro" albuminuria range (30–300 mg per day) was associated with glomerular hyperfiltration [34]. In contrast, the subjects with macroproteinuria (>300 mg per day) showed an impaired GFR. These data indicate that the presence of an elevated albumin excretion can be used to identify subjects with glomerular hyperfiltration. Although these latter data are cross-sectional, they are in agreement with the longitudinal data shown in Figure 1. The emphasis we give to the relation between glomerular hyperfiltration and an increased urinary albumin excretion does not imply that hyperfiltration is the only mechanism of albuminuria. The scope of this review, however, is not to extensively review the various pathohysiologic mechanisms underlying glomerular albumin leakage and tubular handling of proteins, which are well studied in primary glomerular diseases. To that purpose, we refer to extensive in-depth reviews that have been published recently [35, 36].

Table 1. Risk factors associated with elevated albuminuria

Nonmodifiable	Modifiable	
	Well documented	Likely
Race/ethnicity	Diabetes	Hyperlipidemia
Male gender	Hypertension	High salt (and protein) diet
Older age	Obesity	Oral contraceptives
Low birth weight	Smoking	Hormone replacement therapy

In diabetes, prevention of microalbuminuria to macroalbuminuria is considered as secondary prevention, and prevention of normoalbuminuria to microalbuminuria can be considered as primary prevention. In line with the pattern observed in Figure 1, it could thus be argued that the detection of a subject with glomerular hyperfiltration (with a shift from normo via "high-normal" to microalbuminuria) makes him/her suitable for primary prevention. In contrast, detecting him/her at the time when glomerular hyperfiltration is no longer manifest (that is, when microalbuminuria shifts to macroalbuminuria) makes him/her suitable only for secondary prevention. What conditions then, besides diabetes, are associated with increased urinary albumin excretion, and what is the evidence that these conditions are also associated with glomerular hyperfiltration?

FACTORS ASSOCIATED WITH ELEVATED URINARY ALBUMIN EXCRETION

Table 1 summarizes the various risk factors associated with albuminuria. They are grouped as either *nonmodifiable* or *modifiable* by therapeutic approaches, and further subdivided as to whether the risk has been well documented or is likely, when adequately studied, to prove to be associated. It is evident that many of the reported risk factors overlap with those already known to be associated with progression of established renal disease. Indeed, most of the factors mentioned have also been shown in diabetes to favor the development of microalbuminuria. Discussed below is the available evidence that these various risk factors contribute to both hyperfiltration and albuminuria.

Nonmodifiable risk factors associated with a higher urinary albumin excretion

Various reports have documented a higher prevalence of an elevated albumin excretion in specific ethnic groups [37, 38]. Also, male gender [39, 40], older age [40, 41], and low birth weight [38, 39, 42] are associated with higher

urinary albumin loss. Although it is generally well known that elevated albumin excretion is found more frequently in men than women, this difference is age dependent. Urinary albumin excretion is significantly higher in men than women, especially at older age [43]. In line with a difference in albumin excretion between men and women, GFR is also higher in men than women. With respect to low birth weight, an inverse association between microalbuminuria and height was found, arguing that factors operating in utero or early childhood influence urinary albumin excretion in later life.

Modifiable factors that have been well documented in relation to albuminuria

Diabetes. Both glomerular hyperfiltration and a slightly elevated albumin excretion rate have been found to predict progressive renal failure in both type 1 [44–47] and type 2 diabetes [48]. Interestingly, an elevated albumin excretion not only indicates an increased risk for renal failure, but also for cardiovascular disease. Indeed, albuminuria in both type 1 [49] and type 2 [50] diabetes is associated with widespread endothelial dysfunction, manifest not only in the glomerular vasculature, but in other vascular beds as well. The prevalence of microalbuminuria in diabetes has been found to vary from 15% to 30%, depending on the group of subjects studied. In addition, it has been shown that diabetic nephropathy progresses more rapidly in men than in women and in those of low birth weight [51].

Hypertension. Increased urinary albumin loss has also been linked to essential hypertension [52, 53], with prevalences ranging from 10% to 20%. Just as in diabetes, microalbuminuria in essential hypertension has been taken to reflect widespread endothelial dysfunction [54]. Albuminuria in essential hypertension is associated not only with left ventricular hypertrophy, but also with glomerular hyperfiltration [55]. Because microalbuminuric hypertensive subjects did not show renal vasodilatation in response to captopril as did normoalbuminuric controls, microalbuminuria may serve as a marker of early intrarenal vascular dysfunction [56]. In essential hypertension, just as in diabetes, albuminuria predicts both cardiovascular events and a decline in GFR. Indeed, essential hypertensive subjects with microalbuminuria have a greater fall in GFR over a 7-year follow-up than do hypertensive subjects without microalbuminuria [57].

Obesity. Elevated albumin excretion is frequently found in nondiabetic obese subjects [37, 58, 59]. In a group of more than 200 subjects with a body mass index of >27 kg/m^2, microalbuminuria was found in 12% compared to 3% of a control lean group. The percentage was even higher (19.2%) when hypertension coexisted with obesity [58]. In obese subjects, the risk for glomerular hyperfiltration [58, 59] and hyperperfusion [60] is also enhanced. This risk for glomerular hyperfiltration seems to be especially evident in cases of abdominal obesity [58, 48]. The time course of the renal function changes in obesity has thus far only been documented in animal experiments. In a rat model with genetic obesity, an increased GFR was found. Later in the course, GFR tended to normalize and, subsequently, to decrease together with the development of progressive albuminuria and glomerulosclerosis [61]. In this respect, it is of interest that the risk for having an impaired GFR is also especially enhanced in central obesity: there exists a dose-dependent relation between waist-to-hip ratio and the risk for an impaired glomerular filtration rate [59]. The renal consequences of obesity have drawn the attention of clinicians as obesity-related glomerulopathy [62].

Smoking. Smoking is also associated with an increased risk for albuminuria, both in diabetic [63] and nondiabetic [37, 64, 65] subjects. The PREVEND study data showed that heavy smoking is independently and equally strongly associated with an increased risk for microalbuminuria (30–300 mg/day) and for a high normal albumin excretion (15–30 mg/day) compared to the control group with an albumin excretion of 0 to 15 mg/day [65]. This finding supports that smoking may be one of the initial triggers for subsequent albuminuria, but which needs further amplifying factors, such as diabetes, hypertension, and/or obesity.

It has also been documented that smoking may result in glomerular hyperfiltration, both in diabetic [66] and nondiabetic subjects [65, 67], although glomerular hyperfiltration was not found in other epidemiologic studies [68]. It may well be that initially hyperfiltration exists, but with a longer duration of the smoking habit, GFR declines. Indeed, it was shown that smoking is associated with an increased risk for both hyperfiltration and impaired filtration [65]. Lifetime tobacco exposure, but not current level of smoking, is associated with renal function impairment and proteinuria [69].

Association between microalbuminuria and the insulin resistance syndrome. Microalbuminuria in nondiabetic subjects has been argued to be part of the insulin resistance syndrome [70, 71]. As described above, the various factors known to be associated with microalbuminuria, that is, hypertension, hyperglycemia, and obesity, are well-known components of the insulin resistance syndrome. Hypertriglyceridemia, also part of the insulin resistance syndrome, similarly is independently associated with microalbuminuria [37, 70]. Taking these findings together, one could argue that insulin resistance is the underlying pathophysiologic mechanism to explain the associations between all of the above-mentioned risk factors and microalbuminuria. In a study using the hyperglycemic clamp technique to measure insulin sensitivity, however, no association was found between insulin sensitivity and microalbuminuria [72]. Of interest, is the

finding that hyperinsulinemia is associated with glomerular hyperfiltration [73].

Modifiable factors which are likely to be related to albuminuria

Hypercholesterolemia. Some studies found no independent association between hypercholesterolemia and elevated albumin excretion [37, 40]. The Gubbio Study, however, showed that the risk for elevated albumin excretion increased 2-fold for each 40 mg/dL increase in plasma cholesterol [64]. Moreover, it has been shown that hypertensive subjects with high cholesterol levels have a more rapid decline in GFR over time [74].

Dietary salt intake. A higher salt intake is independently associated with a higher urinary albumin excretion [75]. Interestingly, a higher salt intake has also been associated with an increase in GFR, both in normotensive and hypertensive subjects [76]. The finding that salt intake may influence albumin excretion independently of salt-induced effects on blood pressure is in line with recent data that a high salt intake independently predicts mortality and the risk for coronary disease [77].

Oral contraceptives and hormone replacement therapy. The use of oral contraceptives [78, 79] and hormone replacement therapy [78] is also associated with an enhanced urinary albumin excretion. Interestingly, the subjects using such agents also had an elevated creatinine clearance [78]. Users of oral contraceptives had an increased renal vascular resistance and filtration fraction [80].

DETECTION OF SUBJECTS AT RISK FOR PROGRESSIVE RENAL FUNCTION LOSS

We have thus shown that not only diabetes and hypertension, but also other factors, such as obesity and smoking, as well as dietary salt and protein, may induce glomerular hyperfiltration and enhanced urinary albumin excretion in otherwise healthy subjects, and may thus be related to future progressive renal function loss. We next should question the magnitude of the problem. In the previous paragraphs we showed that the prevalence of microalbuminuria in relation to various risk factors is more or less comparable to that seen in diabetes and hypertension. How many subjects, however, have an elevated urinary albumin loss that is not due to diabetes or hypertension? In a study in more than 40,619 Caucasian subjects, Hillege found 3200 subjects with an albumin excretion in the microalbuminuric or macroproteinuric range (=7.9%). Of this group with albuminuria, 2311 (72.2%) were not known to have diabetes or hypertension. In other words, they, in fact, had unexplained albuminuria [40]. These figures are comparable to those of the CARDIA study, which also showed that 70% of persons with increased albumin excretion are both normoglycemic and normotensive [81].

Table 2. Values representing suspected and elevated levels of albuminuria

	Unit	Gender	Suspected	Elevated
24-hour UAE[a]	mg alb/24hr	Both	15–30	>30
Timed overnight sample	µg alb/min	Both	10–20	>20
Spot morning AC ratio[b]	mg alb/g creat	Male	10–17	>17
		Female	15–25	>25

[a]UAE, urinary albumin excretion in mg/day; no difference for values between men and women.
[b]AC ratio, the ratio between albumin (mg/L) and creatinine (g/L) concentration in the urine.

Does this imply that we will have to screen the entire population for the presence of albuminuria? One approach might be to simply do first a dipstick test for albuminuria on a morning spot urine sample. It has the advantage of being simple and relatively inexpensive. Because it may have excess of false positive, but not of false negative results, it may limit further testing to only those with a positive test result. In those who screened positive, further more precise measurements are required. Although the gold standard for defining whether there is an elevated urinary albumin excretion remains one (or preferably more) 24-hour urine sample(s), in daily practice a spot morning urine sample for measurement of albumin and creatinine excretion is frequently used. Recently, an accurate and immediately available quantitative determination of the urinary albumin-to-creatinine ratio has been introduced [82]. Although simple to obtain, this test has the disadvantage that the resulting albumin/creatinine ratio may incorrectly suggest elevated albumin excretion merely because the subject has a low creatinine excretion due to reduced muscle mass, as is the case in women or elderly. If 24-hour urine sampling is not possible, a timed overnight urine sample may also be preferable to a spot morning sample. A timed sample is not especially cumbersome, as it only requires denoting the time of the actual and previous voiding, and has the advantage over the spot sample of allowing estimation of the rate of albumin excretion. Table 2 indicates the generally accepted cut-off values for the definitions of microalbuminuria. Since there is no precise lower cut-off below which there is no increased risk [83, 84], and since there is also no known upper limit above which the risk ceases to exponentially rise, we prefer not to categorize according to the magnitude of albuminuria (that is, micro- vs. macroalbuminuria), but simply to screen for detection and quantification.

It could be questioned whether screening of the entire population is worth the effort because albuminuria will be found only in 2.2% to 10.2% of the general population, depending on the population screened, the age of the subjects, etc. Perhaps better than screening the entire population, it could be advocated to screen those subjects aged

25 or older, with any of the cited risk factors: male gender, low birth weight, diabetes, hypertension, obesity, smoking, and high salt and protein intake. By doing so, we will be able to identify subjects having not only cardiovascular and renal risk factors, but those suffering from actual vascular damage. Indeed, as in diabetes and essential hypertension, an elevated albumin excretion indicates not only progressive renal [85], but also cardiovascular damage in the general population [41, 83, 84, 87, 88]. Comparing the various publications, it is of interest to realize that the impact of microalbuminuria in predicting future renal and cardiovascular morbidity in these various cohorts is similar to that seen in subjects with overt diabetes [89] or hypertension. In all conditions, those with albuminuria have an approximately 2-fold increased risk; this risk in an absolute way is, however, less pronounced in nondiabetics compared to diabetics. Of interest is the study of Borch-Johnsen et al [87], which showed that the presence of albuminuria more than doubled the predictive effect of the conventional atherosclerotic risk factors, be it male gender, smoking, hypertension, or hypercholesterolemia. This better prediction of cardiovascular morbidity and mortality using albuminuria is probably related to the fact that the albumin leakage in the glomerular vessels is really an expression of generalized vascular damage [90]. In this way, an elevated urinary albumin excretion may thus be considered the reflection of early atherosclerosis.

WHAT THERAPY SHOULD BE INSTITUTED FOR PRIMARY PREVENTION OF RENAL DISEASE?

As already indicated, *secondary prevention* of progressive renal function loss in those with preexisting renal disease currently involves such therapies as dietary protein and salt restriction, and intervention in the renin-angiotensin-angiotensinogen system (RAAS) with either ACE inhibitors or angiotensin II receptor antagonists, along with other antihypertensives, if needed. The efficacy of various approaches in *primary prevention* of both development and progression of albuminuria is less well defined. Although there are some studies that report that progression of microalbuminuria can be halted in diabetic subjects with strict control of plasma glucose levels [91, 92], ACE inhibition [93, 94], and angiotensin II receptor antagonism [94–97], real primary prevention trials showing that the progression of normoalbuminuria to microalbuminuria can be prevented are even more scarce. Strict glucose control has been shown both in type 1 [98] and type 2 [99] diabetics to slow the increase in the level of albuminuria, and to postpone the occurrence of overt diabetic nehropathy. Of special interest are the data of the DCCT trial [98], which showed that intensive insulin treatment prevented the development of microalbuminuria both in the primary prevention and the secondary intervention cohort to approximately similar extent (e.g., by 34% and 43%, respectively).

Ravid et al [100] studied the effect of ACE inhibitors to prevent the rise in albuminuria and the fall in GFR in normotensive normoalbuminuric type 2 diabetics. They showed that enalapril reduced the transition from normo- to microalbuminuria from 19% on placebo to 6.5% on enalapril during a 6-year follow-up in type 2 diabetics. The fall in creatinine clearance was less marked in the enalapril-treated patients. The Euclid study group showed that an ACE inhibitor prevented the rise in albuminuria more effectively than placebo, although this beneficial effect was more pronounced (49.7%) in the subjects with microalbuminuria at baseline than in the subjects with an albumin excretion in the high-normal (5–10 or 10–20 μg/min) range (e.g., 21.3% and 18.8%, respectively) [101]. Also encouraging are studies showing regression of microalbuminuria both in type 1 [102] and type 2 [95, 96] diabetic patients.

Some data have been have published on the effects of lipid-lowering drugs on urinary albumin loss and renoprotection in diabetes. Although a review of older studies questioned the efficacy of statins to confer renoprotection [103], more recent reports favor some optimism, since statins have been found to lower albuminuria both in normotensive [104] and hypertensive [105] dyslipidemic type 2 diabetic subjects, as well as in patients with familial hypercholesterolemia [106]. This reduction of albumin loss seems in large part to be independent of the reduction of low-density lipoprotein (LDL) cholesterol. It has similarly been shown that lowering of plasma triglycerides with gemfibrozil in type 2 diabetic subjects improves urinary albumin excretion [107].

Also of interest are recent data showing that the oral glycosaminoglycan sulodexide improves albuminuria both in type 1 [108, 109] and type 2 [109] diabetes. The effect was also manifest in patients who were already on ACE inhibitors, which suggests an additive effect. Studies designed to evaluate the long-term effects of statins, fibrates, or sulodexide on progression of normo- to albuminuria have, however, yet to be reported.

Some data are available on primary prevention in essential hypertension. It has been shown that blood pressure lowering with an ACE inhibitor is more effective than a diuretic, a beta-blocking agent, or a calcium entry blocker to lower albumin excretion in essential hypertension [110]. It is more difficult to draw conclusions regarding the long-term effects of antihypertensive regimens on progression of albuminuria and on renal function decline. Aurell et al [111] found no difference in a 6-year treatment course with an ACE inhibitor or a beta-blocking agent on the change in GFR in essential hypertensive subjects with a baseline GFR of >80 mL/min. On both drugs the blood pressure treatment goal was reached, and in both groups the decline in GFR was

1 mL/min/year, which is comparable to the GFR decline observed in normal subjects. Adequate blood pressure lowering is thus probably of more importance than the type of drug used. That study unfortunately did not report on albumin excretion. Whether ACE inhibitors and statins will lower urinary albumin excretion and prevent renal function decline in albuminuric, but nonhypertensive and nonhyperlipidemic subjects, is presently under investigation in the PREVEND study [112].

Some studies report on the effects of weight reduction on urinary albumin loss in obese subjects. It was shown that a diet low in calories improves urinary albumin loss and GFR in obese diabetic [113] and hypertensive [114] subjects.

Although a cross-sectional study showed subjects who quit smoking to have a lower albumin loss than those that were still smoking [65], a prospective study could not demonstrate a beneficial effect of smoking cessation on albumin excretion, at least not in subjects with an albumin excretion in the normal range [115].

CONCLUSION

In recent years, more and more subjects present with end-stage renal failure without known prior renal disease. Such subjects could undoubtedly be detected in an earlier phase by screening for albuminuria. Urinary albumin loss is an indicator of poor renal, as well as poor cardiovascular, prognosis. Not only are diabetic subjects at risk for albuminuria, but also hypertensive, obese, and smoking subjects. Men at older age, and with a low birth weight, are especially at risk, while such exogenous factors as high salt and protein intake, as well as hormone replacement therapy in women, also enhance the risk. Therapies that have been shown to lower albumin excretion, such as ACE inhibitors, angiotensin II receptor antagonists, and statins should be started early in such patients to prevent them from reaching end-stage renal failure. In this way, we believe the present practice of secondary prevention in those with known prior renal disease should be extended to primary prevention for those subjects in the general population who are at risk for progressive renal failure, including those with high-normal albumin excretion rates.

In carrying out this early attempt to marshal evidence in support of a screening initiative based on albuminuria, the authors recognize that many areas relating to preventive therapy will require far more outcomes-based evidence than now exists. Indeed, our goal has been to draw attention not only to these relatively few modalities of therapy that may already be regarded as proven, but to identify the more numerous areas where definitive evidence of efficacy and safety is still lacking. We recognize, too, that any fruitful discussion relating to primary prevention must also consider such important factors as health manpower resources, other competing public health priorities, economics and cost-effectiveness issues, and the general applicability of the present discussion to first versus third world health care systems [116]. It is hoped that this review will spur others to augment the level of dialogue, and to carry out epidemiologic and clinical outcome studies needed to permit a forward thrust in this heretofore-neglected area of chronic disease prevention.

NOTE ADDED IN PROOF

After acceptance of this manuscript, the results of the PREVEND intervention trial have been published. Treatment with an ACE inhibitor, but not a statin, lowered albuminuria persistently over a 4-year period in subjects with an elevated albuminuria but relatively normal blood pressure and serum cholesterol levels. The lowering of albuminuria on the ACE inhibitor was associated with fewer cardiovascular events [117].

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The data for this seminar were identified by computer-aided searches of PubMed, using key words relevant to the various sections apart from the above-mentioned key words, namely: diabetes, hypertension, obesity, smoking, hyperlipidemia, dietary protein intake, dietary salt intake, oral contraceptives, hormone replacement therapy. We reviewed the standard textbooks and journal reference lists. We selected reports that, in our view, have contributed substantially to the current knowledge base, and that are of interest for further reading.

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