Microalbuminuria in Patients With NIDDM: An Overview

AUS A. ALZAID, FRCPI

The introduction of the concept of microalbuminuria, i.e., elevated but clinically undetectable urinary albumin excretion, has unveiled new and exciting information with profound clinical implications for the care of diabetic patients. For largely historical reasons, however, progress in this area has been confined predominantly to patients with IDDM. Important issues such as definition, natural history, and clinical significance of microalbuminuria as well as merits of therapeutic intervention have been extensively addressed in the case of patients with IDDM. Far less recognition and dedication, however, has been awarded to the study of microalbuminuria in NIDDM until very recently. Emerging new facts are slowly changing the scene, gradually restoring the spotlight in favor of NIDDM. To begin with, NIDDM is ten times more common than IDDM in the community at large and its toll in terms of morbidity and mortality is disturbing. Thus, while the proportion of NIDDM patients who will ultimately develop end-stage renal failure is much smaller than that for patients with IDDM, the sheer numerical superiority of NIDDM ensures that the human and economic burden of diabetic end-stage renal disease is at least equally distributed between the two types of diabetes. Secondly, it has been demonstrated in numerous studies over the past decade that microalbuminuria is not only an independent predictor of progressive renal disease (as has been the case in patients with IDDM) but also an important marker of atherosclerotic disease and premature death in people with NIDDM. Indeed, the development of microalbuminuria in patients with NIDDM is closely related to abnormalities of hemostasis, coagulation, and glucose and lipid metabolism. Microalbuminuria may precede and even predict later onset of NIDDM. Finally, the recent revelations that microalbuminuria per se may represent an independent manifestation of the cardiometabolic disorder syndrome X have added a new dimension to the study of microalbuminuria in NIDDM. Thus, the clinical importance of microalbuminuria in patients with NIDDM cannot be overstated, and greater awareness of its significance by clinicians and health care providers should be actively reinforced. In this article, therefore, I will review the topic of microalbuminuria as it pertains to NIDDM, placing emphasis on past difficulties, recent developments, and the rationale and limitations of medical intervention.

Diabetic nephropathy is fast becoming the leading cause of end-stage renal disease (ESRD) in the industrialized world (1). Diabetic nephropathy is now the single most common cause of ESRD requiring therapy in the U.S., accounting for more than one-third of all cases of ESRD (2). In 1987 alone, approximately $1.5 billion was required to meet the costs of treating diabetic ESRD in the U.S. (3). Even more worrisome is that the trend is escalating (4). The pattern is strikingly similar in Europe, where the proportion of patients with renal failure due to diabetes accepted for renal replacement therapy has risen from <2% of all causes of renal failure in 1973 to 13% in 1990 (5). Elsewhere, diabetic nephropathy takes a significant share of renal supportive therapy programs in Japan and the Middle East (6,7). Worldwide, an estimated 100,000 diabetic patients are currently receiving renal maintenance therapy; this figure will continue to grow as more lenient policies are adopted for inclusion of elderly diabetic patients into dialysis programs (8).

Once initiated, the course of diabetic nephropathy is one of progressive and relentless decline in renal function, and once established, it is essentially irreversible and refractory to treatment. Moreover, onset of diabetic nephropathy renders the diabetic patient characteristically vulnerable to atherosclerotic disease, an affliction that continues to deny diabetic patients the prospect of a better and longer life even after the institution of renal replacement therapy. Clearly, therefore, the best and most effective strategy to prevent diabetic nephropathy should be directed toward the detection and treatment of the disease at an early stage of development, i.e., at a time when it is known to be more amenable to treatment.

Proteinuria is the hallmark of diabetic nephropathy (9,10). The natural course and stages of diabetic glomerulopathy have been well described for patients with IDDM (11,12); fewer studies have examined the evolution of nephropathy in NIDDM (13). Microalbuminuria has been reported to be rare in patients with IDDM of short duration (<5 years) (14), although recent evidence indicates microalbuminuria may occur more frequently in such patients than previously realized (15). On the other hand, microalbuminuria is not uncommonly encountered in newly diagnosed NIDDM patients (16,17). However, ~30–40% of all IDDM patients will develop diabetic nephropathy during the course of their disease (18) compared with ~6% of NIDDM patients (19). Furthermore, autopsy studies show that 30–50% of patients with IDDM but only 5–10% of patients with NIDDM die from renal failure (20,21). It was perhaps these latter observations that may have left an indelible impression among some clinicians that diabetic nephropathy was somehow a more visible and more serious complication in IDDM than in NIDDM patients. However,

From the Department of Medicine, Riyadh Armed Forces Hospital, Riyadh, Saudi Arabia.

Address correspondence and reprint requests to Dr. Aus A. Alzaid, Consultant Physician, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia.

Received for publication 4 April 1995 and accepted in revised form 24 August 1995.

ACE, angiotensin-converting enzyme; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; SLC, sodium-lithium countertransport.

as will be discussed below, recent studies have stimulated a new interest and recognition of the scale and significance of NIDDM nephropathy.

LIMITATIONS OF STUDIES OF RENAL DISEASE IN NIDDM

— Interpretation of current clinical and epidemiological data on renal disease in NIDDM is fraught with difficulty, and the reader must be made wary of the pitfalls and limitations of many of the early reports.

1. Misclassification: Many of the registries for renal replacement therapy failed to differentiate between IDDM and NIDDM (not infrequently, studies consisted of an admixture of IDDM and NIDDM patients). Many NIDDM patients taking insulin when they reached terminal renal failure may have been misclassified as having IDDM (22). Not uncommonly, age at diagnosis (because of convenience) was used to categorize diabetic patients as IDDM or NIDDM. Age per se, however, is an imperfect criterion, since IDDM can actually occur in older subjects and NIDDM can occur in young individuals.
2. Referral selection bias (23): Many studies of complications of diabetes have been done in diabetic referral centers or university settings. Because more ill patients or patients with more medical problems are likely to be referred to large medical centers for treatment, referral bias may distort the natural history of a disorder, as well as result in spurious relationships.
3. Indeterminate onset of NIDDM: Onset of NIDDM has been estimated to occur at least 4–7 years before clinical diagnosis (24). Undiagnosed NIDDM is not a benign condition, and significant clinical morbidity (e.g., nephropathy) may be present at diagnosis and for many years before. Imprecise dating of NIDDM thus obscures attempts to understand the natural history of the disease and its complications. Imprecise onset and/or variations in NIDDM diagnostic rates in differing health-care systems may also contribute to the discrepancies in prevalence rates reported for diabetic nephropathy.
4. The contribution of diabetes per se to the etiology of nephropathy in the diabetic patient with renal disease differs between the two types of diabetes. Whereas diabetes is the underlying cause of renal disease in the vast majority (~90%) of IDDM patients with nephropathy (25), nearly one-third of the cases of renal failure in patients with NIDDM are nondiabetic in origin (26,27).
5. Confounding factors: Coexistent obesity, hypertension, and other medical conditions compete with uremia as causes of death in patients with NIDDM and may therefore distort (dilute) the real contribution of diabetic renal disease into overall mortality in NIDDM. Indeed, when nonrenal causes are controlled for, the risk of renal disease is similar in NIDDM to that in IDDM patients (28,29). Furthermore, since many of these patients are old and have associated cardiovascular disease, they may be denied renal replacement therapy or they may die before reaching end-stage renal failure, thus undermining the true contribution of renal disease to overall mortality in patients with NIDDM (30).

Therefore, epidemiological data on the prevalence of diabetic nephropathy in patients with NIDDM must be carefully scrutinized before any meaningful interpretation can be drawn. In fact, deficiencies and limitations in study design and/or patient selection such as those described above may well have been responsible for the prevailing trend in underestimating the importance of microalbuminuria and of renal disease in general in patients with NIDDM. The difficulty in dating the onset of NIDDM remains, however, a serious and somewhat intractable problem, preventing a clearer understanding of the course of NIDDM nephropathy (and indeed, that of other chronic complications of NIDDM). As is often the case, the initiating pathophysiological processes may be missed by the time the disease is finally recognized and studied. Such a limitation to reliably detect the early renal changes in NIDDM (e.g., state of glomerular filtration, albumin excretion, etc.) has left a large blind spot in our understanding of the natural history of NIDDM nephropathy. Further, it has become a source of constant controversy. Thus, greater efforts should be made in the future to encourage workers in this field to conduct further research and prospective (renal) follow-up studies of individuals at risk of NIDDM, i.e., at the prediabetes stage (for example, first-degree relatives of NIDDM patients).

DEFINITION OF MICROALBUMINURIA IN NIDDM

— There is a general consensus on what constitutes microalbuminuria in IDDM, namely a urinary albumin excretion rate of 20–200 μg/min (30–300 mg/24 h), since rates within this range have been shown to predict progression of diabetic nephropathy in patients with IDDM (31). In contrast, there are few studies available to justify use of this definition in people with NIDDM. In fact, the boundaries where microalbuminuria begins and where it ends in people with NIDDM remain uncertain. Dipstick testing for urine proteins, though simple and convenient, should not be applied to the classification of renal disease in diabetes, for it has many limitations. It is nonspecific, provides only a semiquantitative estimate of albumin concentration, and can be influenced by urinary output and may therefore allow misclassification of patients passing very concentrated or very dilute urines (32). It is relevant to note that urinary albumin excretion rarely exceeds 10 μg/min in normal individuals. The status of diabetic patients with only borderline albuminuria (i.e., albumin excretion rates that are above those in normal people but still below the cutoff value of 30 mg/24 h) is not entirely known. Although often not appreciated, a surprisingly substantial number (~20%) of NIDDM patients fall into this group (14,33,34). Recently published data, however, indicate that even minor elevations of albumin excretion are associated with excess mortality in patients with NIDDM (35,36). Based on current evidence, therefore, it is probably reasonable to state that all shades of albuminuria outside that of the normal range for most people (e.g., urinary albumin excretion >10 μg/min) should be considered clinically significant (to warrant instigation of appropriate medical intervention). Interestingly, in an attempt to address this and

Table 1—*Prevalence of microalbuminuria in white NIDDM populations*

Author (Ref.)	Population	Description of study population	Definition of albuminuria	Prevalence rate (%)
Damsgaard et al. (38)	Danish (age 60–75 years)	Population-based, known NIDDM (n = 211)	>15 and <140 μg/ml	36
Schmitz et al. (39)	Danish	Cross-sectional follow-up (n = 503)	15-200 μg/ml	30
Uusitupa et al. (17)	Finnish	Cross-section, 132 newly diagnosed NIDDM	>35 mg/24 h	19
Gatling et al. (33)	English	Population-based, 842 diabetic subjects (76% NIDDM)	>30 μg/min	7.6
Jerums et al. (40)	Australian	Cross-section, 115 diabetic subjects (57% NIDDM)	30-150 μg/min (albumin clearance 11-55 nl/s)	17
Garancini et al. (41)	Italian	Cross-sectional multicenter (n = 476; 88% NIDDM)	30-350 μg/min	26
Marshall et al. (14)	English	Cross-section (n = 524)	30-150 μg/min	9.7
Patrick et al. (42)	Scottish	Cross-sectional follow-up, (albustix-negative) newly diagnosed NIDDM (n = 149)	Albumin-to-creatine ratio >2.5 mg/mmol	26
Gall et al. (43)	Danish	Cross-section (n = 557)	31-299 mg/24 h	27
Mattock et al. (44)	English	Cross-section cohort follow-up (n = 141)	20-200 μg/min	25
Neil et al. (45)	English	Cohort follow-up (n = 236)	UAC 15-200 mg/l	34
Olivarius et al. (46)	Danish	Large cross-section, newly diagnosed (age >40 years) NIDDM (n = 1,267)	Albumin-to-creatine ratio 2 to <20 mg/mmol	30
Standl et al. (34)	German	Random cohort (representative sample of multicenters)	UAC 30-200 mg/l	19
Klein et al. (47)	American	Wisconsin diabetic population age >30 years (n = 798)	UAC 30-300 mg/l	26

UAC, urinary albumin concentration.

other issues related to diabetic nephropathy, a group of eminent experts recently gathered to formulate strategies for the diagnosis and management of renal disease in diabetic patients (37). While acknowledging that their proposed classification of albuminuria was based on "somewhat arbitrary distinctions," the authors nevertheless defined microalbuminuria according to the conventional range (i.e., albumin excretion rate 20–200 μg/min), a definition also presumed to be equally applicable in both types of diabetes. The panel also laid out recommendations for the screening and treatment of diabetic renal disease, recommending, for example, that dipstick testing (or testing using newer and more sensitive strips) should be performed as part of the initial screening test in NIDDM patients. The consensus team presented a useful and schematic approach for the detection of albuminuria, proposing that screening in NIDDM should be done at the time of presentation and thereafter on an annual basis. Clinicians and researchers with interest in this area should become familiar with these important guidelines. Although the position of the group with respect to the issue of definition of microalbuminuria in NIDDM might be open to question (on the basis of its scientific merits), one clearly sees though the overwhelming need to establish guidelines that are simple, practical, and workable for everyday clinical practice. Until such time when new information becomes available to contest the views expressed above, the consensus proposals should continue to offer the best available clinical guidelines.

PREVALENCE OF MICROALBUMINURIA IN NIDDM

— The prevalence rates for microalbuminuria in NIDDM subjects have been determined in many populations (Tables 1 and 2). Substantial variations, however, have been described in different studies (14,17,33,34,38–58). Factors such as definition of microalbuminuria (i.e., cutoff values), method of urine collection (timed versus random), quality of albumin assay and mode of expression of urinary albumin (excretion rate, ratio to creatinine, or concentration), size of study (small cohort versus large population-based), and ethnic background of patients studied are important determinants contributing to the wide and sometimes discrepant literature. Tables 1 and 2 illustrate some of these points.

The influence of ethnicity on the prevalence of microalbuminuria in NIDDM is interesting. Higher rates have generally been reported in nonwhite compared with white (European) populations (Tables 1 and 2). In fact, the scale, severity, and outcome of diabetic nephropathy in general is less favorable among such ethnic groups as Native Americans, American blacks, and Hispanics than among whites. What is even more intriguing is the greater frequency of microalbuminuria among ethnic nondiabetic populations, where in some groups the rates of microalbuminuria reported approach 12% (50,58,59) compared with that of ~5% among nondiabetic whites (16,60–62). Genetic vulnerability therefore must be an important determinant in the development of diabetic renal disease.

CONCOMITANT/CONTRIBUTING FACTORS IN THE PATHOGENESIS OF MICROALBUMINURIA IN NIDDM

— Several risk factors have been associated with the presence of microalbuminuria in patients with NIDDM. In particular, elevated blood pressure and poor metabolic control have been the two factors most closely related to microalbuminuria (Table 3). In some studies, the duration of diabetes, male sex, and preexisting retinopathy also have been associated with increased risk of microalbuminuria. Age and obesity, on the other hand, have been shown to exert little or no influence on the development of microalbuminuria in most studies.

The role of hypertension in the

Table 2—*Prevalence of microalbuminuria in nonwhite NIDDM populations*

Author (Ref.)	Population	Description of study population	Definition of albuminuria	Prevalence rate (%)
Allawi et al. (48)	Asian immigrants in Britian	Cross-sectional (n = 154 Indians, n = 82 European)	Albumin/creatine >2 mg/mmol	Indian 26 European 20.7 (calculated estimates)
Haffner et al. (49)	Hispanic-American	San Antonio Heart Study, biethnic, (n = 317 Mexican-American, n = 67 non-Hispanic white)	UAC >30 mg/l (albustix-negative)	Mexican-American 26 non-Hispanic white 9
Nelson et al. (50)	Pima Indians	Population-based (NIDDM = 830)	UAC 30-299 mg/g	26
Collins et al. (51)	Nauruan	Entire Nauruan population (diabetic = 318) (presumed mostly NIDDM)	UAC 30-299 mg/ml	42
Tai et al. (52)	Chinese (Taiwan)	Cross-sectional (n = 63)	>8.55 μg/min (> mean ± 3 SD of control group)	24
Gupta et al. (53)	Indian	Cross-sectional (n = 64)	>20 μg/min	27
Hamman et al. (54)	Hispanic-American	San Luis Valley Colorado Study (n = 1,187 Hispanic, n = 92 white)	UAC >25.5 μg/ml	35
Haffner et al. (55)	Mexican-American	San Antonio Heart Study (n = 234) (80% Mexican-Americans)	UAC >30 mg/l (albustix-negative)	31
Metcalf et al. (56)	New Zealanders	Survey of work force (n = 5,467) (3.3% NIDDM: 7.7% Maori, 11.7% Pacific Islander, 78.8% European, 1.86% Asian)	UAC ~29-299 mg/l	European 7 Asian 14 Pacific Islander 31 Maori 42
Dasmahapatra et al. (57)	African-American	Cross-sectional (n = 116)	20-200 μg/min	31
Alzaid et al. (58)	Saudi Arabian	Cross-sectional (n = 211)	30-300 mg/24 h	36

UAC, urinary albumin clearance.

pathogenesis of microalbuminuria in NIDDM deserves a special mention. Clinical hypertension *1*) is common among newly diagnosed NIDDM subjects (63), *2*) is not necessarily associated with the presence of microalbuminuria (64), and *3*) in longitudinal studies does not appear to predict later development of proteinuria (65) (except in Pima Indians, in whom it has been suggested that blood pressure at presentation [66] or at the prediabetic stage [67] predicted future progression of urinary albumin excretion). These observations therefore indicate that coexistent hypertension in newly diagnosed NIDDM patients may not necessarily be a contributing factor in the initiation of diabetic nephropathy. More importantly, these findings indicate that onset of hypertension in patients with NIDDM is unlikely to be the result of diabetic renal disease. This contrasts sharply with the strong relationship known to exist between hypertension and the evolution of diabetic nephropathy in patients with IDDM, in whom clinical hypertension is rarely seen at the time of initial presentation but develops at a much later stage in parallel with the decline in renal function (68). Furthermore, the relationship between blood pressure and albuminuria in NIDDM, when present, seems to be confined largely to systolic blood pressure (Table 3). Indeed, at least two recent prospective studies examining progression of albuminuria in NIDDM have found raised systolic blood pressure to be a determining factor in the development of microalbuminuria (69,70). This is important, since isolated systolic hypertension is frequently encountered among elderly diabetic patients, is reported to correlate with the decline in glomerular filtration rate (71), and is a serious risk factor for mortality from cardiovascular disease (72).

Given the conclusive findings recently reported in the Diabetes Control and Complications Trial (73), it is perhaps not surprising to find glycemic control also implicated in the development and progression of diabetic nephropathy in patients with NIDDM. It is well known, for example, that urinary albumin excretion generally declines after short-term improvement in glycemic control such as that seen shortly after presentation with NIDDM (42,74–76). In long-term prospective studies in NIDDM patients, poor glycemic control has been identified as a risk factor for progression from normoalbuminuric to microalbuminuric stage in one study (77) but not in another (64). As for cross-sectional studies, most (though not all) investigators have so far reported a significant correlation between indexes of metabolic control and albuminuria in NIDDM (Table 3). However, when interpreting data such as that described in Table 3, it is important that the reader draw the important distinction between cause and simple association. The finding of a statistical correlation during the conduct of a study (often small and cross-sectional) obviously does not prove

Table 3—*Association between physical and metabolic characteristics and albuminuria in NIDDM subjects*

Author (Ref.)	Age	Sex	BMI	Duration of diabetes	Glycemic control	BP (s/d)	Retinopathy	Other associating factors
Damsgaard and Morgensen (38)		+		−		+		Insulin therapy
Klein et al. (47)	+	+			+	+ (s)		Insulin therapy, alcohol intake
Gall et al. (43)			+		+	+	+	Foot ulcers
Schmitz and Vaeth (39)	+			+	+	+ (s)	+	−
Haffner et al. (55)					+	+		−
Marshall and Alberti (14)	−					+ (s)	+	Peripheral vascular disease
Patrick et al. (42)		−	−		+	+ (s)		Peripheral vascular disease
Jerums et al. (40)				−	−	−		−
Olivarius et al. (46)	+		−		+	+ (s)	+	Smoking, lipids, vascular disease
Nelson et al. (50)	+	−	−	+	+	+		Insulin therapy
Dasmahaptra et al. (57)	−		+	−	−	+		−
Collins et al. (51)	−		+	−	+	+		Fasting insulin concentrations
Alzaid et al. (58)	−	−	−	+	+	−		−
Uusitupa et al. (17)					−	−		−
Allawi et al. (48)			−	−	−	+		−

Associations present (+) or absent (−). BMI, body mass index; BP, blood pressure; s, systolic; d, diastolic. Note: correlations may be confined to a subgroup (e.g., males) of the study population.

causality (78). It is also relevant to note that the correlations reported in Table 3, albeit statistically significant, are generally weak (e.g., for hypertension versus albuminuria, average r value <0.3). Further, prospective data from a recent follow-up study suggest that changes in blood pressure account for only a small fraction of the wide interindividual variability in the rate of progression of albuminuria in NIDDM (69). In the final analysis, therefore, the interplay between variables such as hypertension and the development of renal disease in patients with NIDDM remains far from clear and is certainly an area that warrants further studies.

MICROALBUMINURIA AND GLOMERULAR FILTRATION FUNCTION IN NIDDM

— It has long been established that a state of glomerular hyperfiltration is a characteristic feature of newly diagnosed IDDM patients (79,80). Furthermore, it has been proposed that such a hyperdynamic state may play a critical (detrimental) role in the initiation and progression of diabetic glomerulopathy in IDDM (81,82). Somewhat similar, though less striking, renal hemodynamic changes have now been described in newly diagnosed NIDDM patients. Studying a large series of newly diagnosed normotensive NIDDM patients, Vora et al. (83) recently concluded that glomerular hyperfiltration (defined as glomerular filtration rate [GFR] above the mean ± 2 SD of a control group) was relatively common, present in some 45% of their patient population. Other workers have described a variable degree of increased filtration in some of the patients with recent-onset NIDDM (74,84,85). Of particular interest, however, is that most studies have failed to detect a consistent relationship between the presence of microalbuminuria and indexes of glomerular filtration (83,86). During a 3.4-year prospective follow-up study of patients with known NIDDM, Nielsen et al. (87) found the rate of decline of GFR to be similar in normo- and microalbuminuric patients. In addition, the authors found no correlation between the rate of fall of the GFR and the level of albuminuria. Thus, while it may be acceptable, following the pioneering work of Mogensen, to consider microalbuminuria as a marker of clinical proteinuria in NIDDM, the role of microalbuminuria in relation to the eventual decline of renal function (GFR) is as yet far from certain. In this context, it is relevant to point out that it is the state of the GFR (more than any other renal parameter) that ultimately dictates the course of clinical management (e.g., initiation of renal replacement therapy). Therefore, large long-term prospective studies are warranted to explore the role of microalbuminuria as a predictor of future progression (deterioration) of glomerular function in NIDDM.

If the above observations may seem to question the role of microalbuminuria in the development of renal (microvascular) complications in NIDDM, the place of microalbuminuria as a predictor of macrovascular disease remains well beyond dispute (below).

MICROALBUMINURIA AND ATHEROSCLEROTIC DISEASE: THE PLOT THICKENS

— NIDDM is associated with a two- to threefold excess mortality (88,89), mainly from cardiovascular disease (90,91). This propensity for vascular disease among NIDDM patients cannot be explained by coexistent conventional cardiovascular risk factors such as hypertension or dyslipidemia, since the effect of diabetes per se persists even after controlling for the confounding effects of other risk factors (92). Nor can it be entirely attributed to the hyperglycemic state, since available data on the relationship between glycemia and cardiovascular complications in NIDDM, if not conflicting, are certainly inconclusive (93–97). Indeed, vulnerability to atherosclerotic disease may be acquired long before the onset of overt hyperglycemia (e.g., in individuals with only impaired glucose tolerance) (98).

Mogensen (99) in Denmark and Jarrett et al. (100) in Britain were first to explore the role of microalbuminuria as a marker for cardiovascular disease in patients with NIDDM. Both reported independently in 1984 that microalbuminuria predicted all-cause mortality (chiefly from cardiovascular disease) in NIDDM subjects. Data from both retrospective (39) and, more importantly, prospective studies from a variety of NIDDM populations (43,44,101,102) have confirmed the findings of Mogensen and Jarrett and have shed further light on the nature of the relationship between microalbuminuria and atherosclerotic disease. A recent meta-analysis and extensive review of the literature carried out by Dinneen and Gerstein (103) has confirmed the strong association between microalbuminuria and cardiovascular mortality in NIDDM. Lastly, the association between microalbuminuria and cardiovascular risk factors is not confined to diabetic individuals, since it has recently been shown also to extend to the general population (61). Indeed, the recent demonstration by Yudkin et al. (104) and others (59,105) that microalbuminuria predicts vascular disease in the nondiabetic population has elevated microalbuminuria to being a more universal marker of early death from cardiovascular disease in humans.

Exactly why the development of microalbuminuria, in itself reflecting a trivial urinary loss of albumin, should herald such serious and anatomically far-reaching consequences is not yet entirely understood. In an attempt to explain this, the Steno group (106) has put forward an interesting hypothesis: microalbuminuria is caused by loss of positive charges on the glomerular basement membrane, permitting the leakage of albumin, and similar changes occur in blood vessels elsewhere that allow atherosclerotic lipoprotein particles to penetrate into the vascular wall. In other words, increased urinary albumin loss merely reflects a glomerular manifestation of an otherwise generalized (albeit less clinically visible) vascular hyperpermeablity state. The Steno hypothesis, plausible as it may seem (107), awaits supportive evidence from studies in patients with NIDDM. Other workers have proposed abnormalities in lipid metabolism [e.g., elevated lipoprotein(a)] and/or changes in cation membrane transport (e.g., sodium-lithium countertransport [SLC]) as possible mechanisms for tying together proteinuria and vascular disease (108). However, while lipoprotein(a) concentration and SLC levels may be elevated in IDDM patients with microalbuminuria, evidence for such abnormalities in albuminuric NIDDM patients has been either scarce or conflicting (109–114). Changes in urinary albumin excretion have been shown, however, to be related to disturbances in coagulation and endothelial function in patients with NIDDM. In a follow-up study of a cohort of NIDDM patients, Stehouwer et al. (115) have reported a strong relationship between plasma von Willebrand factor level (a measure of endothelial dysfunction), urinary albumin excretion, and cardiovascular complications. Microalbuminuria was shown to be associated with an increased risk of cardiovascular disease only in patients with elevated concentrations of von Willebrand factor, a risk that was further modified by high-density lipoprotein (HDL) cholesterol concentration. Collier et al. (116) also found increased levels of von Willebrand factor and also of free radical activity in NIDDM patients with microalbuminuria. Niskanen et al. (117) have demonstrated that persistent microalbuminuria predicts and exacerbates abnormalities in lipoprotein composition and a decrease in HDL cholesterol in NIDDM patients. Even in nondiabetic individuals and those predisposed to diabetes, microalbuminuria is not a benign phenomenon but is closely associated with multiple cardiovascular risk factors (118,119). Thus, the onset of microalbuminuria in diabetic and nondiabetic humans signals the presence of a highly atherogenic milieu. Two recent findings (below) have further strengthened the link between microalbuminuria and atherosclerotic disease.

MICROALBUMINURIA: THE FIFTH PILLAR OF SYNDROME X?

— Reaven (120), in a seminal article, has proposed that insulin resistance/hyperinsulinemia forms the common denominator between conventional cardiovascular risk factors and the development of atherosclerosis. Thus, individual risk factors such as hypertension, obesity, hyperlipidemia, and glucose intolerance, which commonly aggregate, simply represent the "rainbow colors" of a clinical syndrome characterized by an underlying state of insulin resistance and a devastating cardiovascular outcome in what Reaven referred to collectively as syndrome X (120). Interestingly, there is now evidence to promote microalbuminuria as a distinct and independent facet of this disorder (121–124). Investigating the influence of microalbuminuria and hypertension on insulin resistance in NIDDM patients, Groop et al. (121) reported that glucose metabolism, as measured during insulin clamp technique, was impaired in normotensive NIDDM patients with microalbuminuria compared with normotensive normoalbuminuric patients. The defect in insulin action was shown to correlate with urinary albumin excretion. Furthermore, diabetic subjects with a combination of hypertension and microalbuminuria had a greater reduction in insulin-mediated glucose disposal and widespread disturbances in lipid metabolism. Perhaps the most surprising finding of these experiments was the observation that insulin-stimulated glucose disposal was remarkably normal (i.e., not impaired) in normotensive NIDDM patients who did not have microalbuminuria. A similar conclusion has also been reached by Nosadini et. al. (122) and Zambon et al. (123), who showed that insulin sensitivity was not compromised in healthy NIDDM patients unless either microalbuminuria or hypertension or both existed. The relationship between insulin resistance and albuminuria in NIDDM subjects was also confirmed by Niskanen and Laakso (124), who showed that insulin-mediated glucose uptake determined during euglycemic clamp study was significantly lower in microalbuminuric compared with normoalbuminuric patients, independent of the confounding effect of hypertension. Finally, recent work indicates that the association between insulin resistance and albuminuria may be evident even among nondiabetic first-degree relatives of patients with NIDDM (125). Thus, the association between insulin resistance and microalbuminuria in NIDDM, as revealed by the findings of these elegant studies, raises the interesting question of whether the two phenomena might in some way be causally related. However, the presence of microalbuminuria in NIDDM has not been marked by a reduction in insulin sensitivity in all of the studies thus far reported (126). For the present, therefore, the mechanism relating insulin resistance/hyperinsulinemia to albuminuria remains largely speculative.

Finally, two recent reports have shed further insights into the significance of microalbuminuria in NIDDM. Haffner et al. (127), in a cross-sectional study, and Mykkänen et al. (118), in a prospective study, have reported that microalbuminuria in nondiabetic individuals may precede and even predict the onset of NIDDM. Moreover, in the latter, microalbuminuric subjects who remained glucose tolerant after 3.5 years of follow-up still demonstrated multiple cardiovascular abnormalities, including elevated blood pressure, high triglyceride concentration, high insulin concentration, and low HDL cholesterol concentration, i.e., a cardiovascular risk profile akin to that observed in prediabetic individuals. Microalbuminuria may be regarded as a prominent feature of the prediabetic state. The above findings therefore provide probably the most damaging evidence against microalbuminuria as a serious phenomenon in the evolution of NIDDM and atherosclerotic disease.

INTERVENTIONAL TRIALS — The merits of antihypertensive therapy in the treatment of IDDM patients with clinical hypertension are unquestionable, regardless of the presence or absence of renal disease. Moreover, it is becoming increasingly common practice to use antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors (known for their renal protective effects) in normotensive IDDM patients with microalbuminuria. In contrast, one can not advocate such sweeping statements on the benefits of antihypertensive therapy in normotensive or even mildly hypertensive NIDDM patients with subclinical nephropathy. Indeed, the efficacy of antihypertensive therapy in NIDDM subjects remains less certain.

Nevertheless, the seemingly appealing and clinically justifiable practice of initiating ACE inhibitor therapy in IDDM patients with early nephropathy is frequently extrapolated to the treatment of patients with NIDDM. Many workers now consider the institution of ACE inhibitor therapy desirable, if not essential, for the protection of renal function in albuminuric normotensive NIDDM patients (128,129). Indeed, several studies have recently suggested that use of ACE inhibitors in NIDDM subjects can preserve renal function and, in some studies, even reverse urinary albumin loss independent of the effect of these agents on blood pressure. In this regard, the work of Ravid et al. (130) from Israel stands out: at the end of a 5-year placebo-controlled double-blind randomized study of 94 normotensive patients with NIDDM who had microalbuminuria and normal renal function at baseline, urinary albumin excretion remained stable in enalapril-treated patients but increased by ~150% (from mean 123 to 310 mg/24 h) in the placebo-treated group. Furthermore, kidney function (expressed, albeit crudely, as mean reciprocal creatinine) did not change in the enalapril group, whereas it declined by ~13% in the placebo group. The recent publication of another (4-year) prospective study supports these findings. Sano et al. (131) have shown that treatment with enalapril (versus no enalapril) significantly reduced urinary albumin excretion in normotensive as well as well-controlled hypertensive NIDDM patients with microalbuminuria without altering blood pressure or blood glucose control. Together, the observations of Ravid et al. (130), Sano et al. (131), and others (132,133) support a renal protective effect of ACE inhibitors in albuminuric nonhypertensive NIDDM patients. These findings therefore raise an important and somewhat troubling question: Should we as clinicians now advocate lifelong therapy with ACE inhibitors to every normotensive NIDDM patient at the sight of trivial amounts of albumin traced in their urine? I believe the answer to this question lies in a wider circle of as yet unresolved but important issues as outlined below.

1. What does a reduction in urinary albumin excretion of some 100 mg/day after several years of drug therapy mean in terms of the eventual decline in renal function and ultimate survival? It is indeed not entirely clear whether alterations in urinary albumin excretion necessarily parallel changes in glomerular filtration rates or eventual renal prognosis. Furthermore, most published studies to date have been short-term (none have exceeded 5 years of follow-up) or have included a small number of patients or, more typically, both. Since normotensive NIDDM patients with microalbuminuria represent a large proportion of the NIDDM population, the issue of cost-effectiveness will also have to be addressed in any future studies.
2. Are ACE inhibitors truly unique in their acclaimed antiproteinuric effects, and should they thus be considered as first-choice therapy in albuminuric NIDDM patients? The answer to this question, surprisingly, may not be as conclusive as many might think. While there is generally a body of evidence and perhaps a general recognition, at least on theoretical ground, of the "renal-preserving characteristics" of ACE inhibitors (especially in patients with IDDM), intervention with other antihypertensive agents also has been associated with beneficial effects on renal function in NIDDM patients with albuminuria. Comparing the effects of perindopril, an ACE inhibitor, and nifedipine, a calcium antagonist, in microalbuminuric NIDDM patients, the Melbourne Diabetic Nephropathy Study concluded that the two agents had similar effects on urinary albumin excretion, both preventing increases in albuminuria in normotensive patients and decreasing albuminuria in hypertensive NIDDM patients (134). Similarly, Baba et al. (135) in a short-term study reported effectively similar renal effects in hypertensive NIDDM patients with microalbuminuria who were treated with enalapril compared to those treated with the calcium antagonist nicardipine. Stornello et al. (136) showed that enalapril and atenolol, a β-blocking agent, were equally effective in preventing renal decline in normotensive NIDDM patients with persistent albuminuria (136). Thus, it is possible that any favorable effects of antihypertensive therapy on renal function in albuminuric normotensive NIDDM patients may be mediated through a common mechanism inherent to their antihypertensive effects rather than being specific to any class of antihypertensive therapy. However, the favorable (neutral) metabolic effects of ACE inhibitors confer special advantage over other pharmacological agents, al-

though it is equally important to recognize the fact that patients with NIDDM are likely to have coexistent hyporeninemic hypoaldosteronism and therefore are particularly vulnerable to dangerous hyperkalemia with ACE inhibitor use.

3. Atherosclerotic disease remains the primary cause of death in the NIDDM population. While albuminuria is reported to be a marker of cardiovascular risk in NIDDM patients, it is still not known whether a pharmacological amelioration of urinary albumin excretion diminishes the high cardiovascular risk observed in these patients. This must await future long-term prospective trials. In the meantime, however, the clinical management of the NIDDM patient with albuminuria should be based on optimization of glycemic control and a global approach to risk factors, with equal attention given to the control and prevention of known cardiovascular risk factors, such as smoking cessation and treatment of lipid abnormalities, as well as to efforts to halt progression of renal disease (37).

SUMMARY — We have come a long way in our understanding of the epidemiology, pathophysiology, and clinical significance of albuminuria in patients with NIDDM. However, substantial gaps remain to be defined. NIDDM nephropathy is a serious and increasingly burdensome disease for both the diabetic individual and the society at large. Onset of microalbuminuria, an early but common manifestation of NIDDM nephropathy, marks an ominous turn for the NIDDM patient, in whom its development forecasts a grave cardiovascular outcome. Interception of albuminuria with antihypertensive agents such as ACE inhibitors in otherwise healthy NIDDM subjects holds a significant promise but must first await further investigation.

References

1. Cordonnier D, Bayle F, Benhamou PY, Milongo R, Zaouli P, Maynard C, Halimi S: Future trends of management of renal failure in diabetics. *Kidney Int* 43 (Suppl. 41):8–13, 1993
2. U.S. Renal Data System: *1989 Annual Data Report*. Bethesda, MD, National Institute of Diabetes and Digestive and Kidney Diseases, 1989
3. Eggers PW: Effect of transplantation on the Medicare end-stage renal disease program. *N Engl J Med* 318:223–229, 1988
4. Walker WG: Hypertension-related renal injury: a major contributor to end-stage renal disease. *Am J Kidney Dis* 22:164–173, 1993
5. Raine AEG: Epidemiology, development and treatment of end-stage renal failure in type 2 (non-insulin-dependent) diabetic patients in Europe. *Diabetologia* 36: 1099–1104, 1993
6. Anonymous: The chronic dialysis patients registry in Japan, 1991. *J Japanese Soc Dial Ther* 26:17–30, 1993
7. Hussein MM, Mooij JMV, Roujouleh H, El-Sayed H: Observations in a Saudi-Arabian dialysis population over a 13-year period. *Nephrol Dial Transplant* 9:1072–1076, 1994
8. Port FK: Worldwide demographics and future trends in end-stage renal disease. *Kidney Int* 43 (Suppl. 41):4–7, 1993
9. Mogensen CE, Steffes MW, Deckert T, Christiansen JS: Functional and morphological renal manifestations in diabetes mellitus. *Diabetologia* 21:89–93, 1981
10. Viberti GC, Keen H: The patterns of proteinuria in diabetes mellitus: relevance to pathogenesis and prevention of diabetic nephropathy. *Diabetes* 33:686–692, 1984
11. Mogensen CE, Christiansen CK, Vittinghus E: The stages of diabetic nephropathy: with emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 32 (Suppl. 2):64–78, 1983
12. Mogensen CE, Schmitz O: The diabetic kidney: from hyperfiltration and microalbuminuria to end-stage renal failure. *Med Clin North Am* 72:1465–1492, 1988
13. Gall M-A, Nielsen FS, Smidt UM, Parving H-H: The course of kidney function in type 2 (non-insulin-dependent) diabetic patients with diabetic nephropathy. *Diabetologia* 36:1071–1078, 1993
14. Marshall SM, Alberti KGMM: Comparison of the prevalence and associated features of abnormal albumin excretion in insulin-dependent and non-insulin-dependent diabetes. *Q J Med* 70:61–71, 1989
15. Stephenson JM, Fuller JH: Microalbuminuria is not rare before 5 years of IDDM. *J Diabetic Complications* 8:166–173, 1994
16. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT: The kidney in maturity onset diabetes mellitus: a clinical study of 510 patients. *Kidney Int* 21:730–738, 1982
17. Uusitupa M, Sitonen O, Penttilä I, Aro A, Pyörälä K: Proteinuria in newly diagnosed type 2 diabetic patients. *Diabetes Care* 10:191–194, 1987
18. Andersen AR, Sandhal Christiansen J, Andersen JK, Kreiner S, Deckert T: Diabetic nephropathy in type one insulin-dependent diabetes: an epidemiological study. *Diabetologia* 25:496–501, 1983
19. Humphrey LL, Ballard D, Frohnert PP, Chu C, O'Fallon WM, Palumbo PJ: Chronic renal failure in non-insulin-dependent diabetes mellitus: a population-based study in Rochester, Minnesota. *Ann Intern Med* 111:788–796, 1989
20. Marks HH: Longevity and mortality of diabetics. *Am J Public Health* 55:416–422, 1965
21. Balodimus MC: Diabetic nephropathy. In *Joslin's Diabetes Mellitus*. 11th ed. Marble A, White P, Bradly RF, Krall LP, Eds. Philadelphia, Lea and Febiger, 1971, p. 525–561
22. Benhamou PY, Marwah T, Balducci F, Zmirou D, Borgel F, Cordonnier D, Halimi S, Papoz L: Classification of diabetes in patients with end-stage renal disease: validation of clinical criteria according to plasma C-peptide. *Clin Nephrol* 38:239–244, 1992
23. Melton LJ III, Ochi JW, Palumbo PJ, Chu CP: Referral bias in diabetes research. *Diabetes Care* 7:12–18, 1984
24. Harris MI, Klein R, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4–7 years before clinical diagnosis. *Diabetes Care* 15:815–819, 1992
25. Amoah E, Glickman JL, Malchoff CD, Sturgill BC, Kaiser DL, Bolton WK: Clinical identification of non-diabetic renal disease in diabetic patients with type 1 and type 2 disease presenting with renal dysfunction. *Am J Nephrol* 8:204–211, 1988
26. Parving HH, Gall MA, Skøtt P, Jørgensen HE, Jørgensen F, Nielsen B, Larsen S: Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. *Kidney Int* 41:758–762, 1990
27. Grenfell A, Bewick M, Parsons V, Snowden S, Taube D, Watkins PJ: Non-insulin-dependent diabetes and renal replacement therapy. *Diabetic Med* 5:172–176, 1988
28. Hasslacher C, Ritz E, Wahl P, Michael C: Similar risks of nephropathy in patients with type 1 or type 2 diabetes mellitus. *Nephrol Dial Transplant* 4:859–863, 1989
29. Ordonez JD, Hiatt RA: Comparison of type 2 and type 1 diabetics treated for end-stage renal disease in a large prepaid health plan population. *Nephron* 51: 524–529, 1989
30. Ritz E, Norwack R, Pliser D, Koch M: Type II diabetes mellitus: is the renal risk

adequately appreciated? *Nephrol Dial Trasplant* 6:679–682, 1988
31. Mogensen CE, Chachati A, Christiansen CK, Close CF, Deckert T, Hommel E, Kastrup J, Lefebvre P, Mathiesen ER, Feldt-Rasmussen B, Schmitz A, Viberti GC: Microalbuminuria: an early marker of renal involvement in diabetes. *Uremia Invest* 9:85–95, 1986
32. Rowe DJF, Dawnay A, Watts GF: Microalbuminuria in diabetes mellitus: review and recommendations for measurement of albumin in urine. *Ann Clin Biochem* 27:297–312, 1990
33. Gatling W, Knight C, Mullee MA, Hill RD: Microalbuminuria in diabetes: a population study of the prevalence and an assessment of three screening tests. *Diabetic Med* 5:343–347, 1988
34. Standl E, Stiegler H: Microalbuminuria in a random cohort of recently diagnosed type 2 (non-insulin-dependent) diabetic patients living in the greater Munich area. *Diabetologia* 36:1017–1020, 1993
35. Mogensen CE, Damsgaard EM, Frøland A, Nielsen S, Olivarius NDF, Schmitz A: Microalbuminuria in non-insulin-dependent diabetes. *Clin Nephrol* 38 (Suppl. 1):28–38, 1992
36. MacLeod JM, Lutale J, Marshall SM: Albumin excretion and vascular death in NIDDM. *Diabetologia* 38:610–616, 1995
37. American Diabetes Association: Consensus development conference on the diagnosis and management of nephropathy in patients with diabetes mellitus. *Diabetes Care* 17:1357–1361, 1994
38. Damsgaard EM, Mogensen CE: Microalbuminuria in elderly hyperglycaemic patients and controls. *Diabetic Med* 3:430–435, 1986
39. Schmitz A, Vaeth M: Microalbuminuria: a major risk factor in non-insulin-dependent diabetes: a 10-year follow-up study of 503 patients. *Diabetic Med* 5:126–134, 1987
40. Jerums G, Cooper ME, Seeman E, Murray RM, McNeill JJ: Comparison of early renal dysfunction in type I and type II diabetes: differing associations with blood pressure and glycaemic control. *Diab Res Clin Pract* 4:133–141, 1988
41. Garancini P, Gallus G, Calori G, Micossi P, Pozza G: Microalbuminuria and its associated risk factors in a representative sample of Italian type II diabetics. *J Diabetic Complication* 2:12–14, 1988
42. Patrick AW, Leslie PJ, Clark BF, Frier BM: The natural history and associations of microalbuminuria in type 2 diabetes during the first year after diagnosis. *Diabetic Med* 7:902–908, 1990
43. Gall MA, Rossing P, Skøtt P, Damsbo P, Vaag A, Bech K, Dejgaard A, Lauritzen M, Lauritzen E, Hougaard P, Beck-Nielsen H, Parving HH: Prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease in European type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 34:655–661, 1991
44. Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G: Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes* 41:736–741, 1992
45. Neil A, Hawkins M, Potok M, Thorogood M, Cohen D, Mann J: A prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. *Diabetes Care* 7:996–1003, 1993
46. Olivarius N, Andreasen AH, Keiding N, Mogensen CE: Epidemiology of renal involvement in newly-diagnosed middle-aged and elderly diabetic patients: cross-sectional data from the population-based study "Diabetes care in general practice", Denmark. *Diabetologia* 36: 1007–1016, 1993
47. Klein R, Klein BEK, Moss SE: Prevalence of microalbuminuria in older-onset diabetes. *Diabetes Care* 16:1325–1329, 1993
48. Allawi J, Rao PV, Gilbert R, Scott G, Jarrett RJ, Keen H, Viberti GC, Mather HM: Microalbuminuria in non-insulin-dependent diabetes: its prevalence in Indian compared with Europid patients. *Br Med J* 296:462–464, 1988
49. Haffner SM, Braxton D, Mitchell D, Pugh JA, Stern MP, Kozlowski K, Hazuda HP, Patterson JK, Klein R: Proteinuria in Mexican Americans and non-Hispanic whites with NIDDM. *Diabetes Care* 12: 530–536, 1989
50. Nelson RG, Kunzelman CL, Pettit DJ, Saad MF, Bennett PH, Knowler WC: Albuminuria in type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in Pima Indians. *Diabetologia* 32:870–876, 1989
51. Collins VR, Dowse GK, Finch CF, Zimmet PZ, Linnane AW: Prevalence and risk factors for micro- and macroalbuminuria in diabetic subjects and entire population of Nauru. *Diabetes* 38:1602–1610, 1989
52. Tai TY, Chuang LM, Tseng CH, Wu HP, Chen MS, Lin BJ: Microalbuminuria and diabetic complications in Chinese non-insulin-dependent diabetic patients: a prospective study. *Diab Res Clin Pract* 9:59–63, 1990
53. Gupta DK, Verma LK, Khosla PK, Dash SC: The prevalence of microalbuminuria in diabetes: a study from North India. *Diab Res Clin Prac* 12:125–128, 1991
54. Hamman RF, Franklin GA, Mayer EJ, Marshall SM, Marshall JA, Baxter J, Kahn LB: Microvascular complication of NIDDM in Hispanics and non-Hispanic whites. *Diabetes Care* 14:655–663, 1991
55. Haffner SM, Morales PA, Gruber MK, Hazuda HP, Stern MP: Cardiovascular risk factors in non-insulin-dependent diabetic subjects with microalbuminuria. *Arterioscler Thromb* 13:205–210, 1993
56. Metcalf PA, Baker JR, Robert KR, Dryson E, Scott AJ, Wild CJ: Microalbuminuria in a middle-aged workforce. *Diabetes Care* 16:1485–1493, 1993
57. Dasmahapatra A, Bale A, Raghuwanshi MP, Reddi A, Byrne W, Suarez S, Nash F, Varagiannis E, Skurnick JH: Incipient and overt diabetic nephropathy in African Americans with NIDDM. *Diabetes Care* 17:297–303, 1994
58. Alzaid A, Sobki S, De Silva V: Prevalence of microalbuminuria in Saudi Arabians with NIDDM: a clinic-based study. *Diab Res Clin Prac* 26:115–120, 1994
59. Haffner SM, Stern MP, Gruber KK, Hazuda HP, Mitchell BD, Patterson JK: Microalbuminuria: potential marker for increased cardiovascular risk factors in nondiabetic subjects? *Arteriosclerosis* 10: 727–731, 1990
60. Diehl HS, McKinlay CA: Albuminuria in college men. *Arch Intern Med* 49:45–55, 1932
61. Winocour PH, Harland JOE, Millar JP, Laker MF, Alberti KGMM: Microalbuminuria and associated cardiovascular risk factors in the community. *Atherosclerosis* 93:71–81, 1992
62. Samanta A, Burden AC, Feehally J, Wallis J: Diabetic renal disease: differences between Asian and white patients. *Br Med J* 293:366–367, 1986
63. Uusitupa M, Siitonen O, Aro A: Prevalence of coronary heart disease, left ventricular failure and hypertension in middle-aged newly diagnosed Type 2 (non-insulin-dependent) diabetic subjects. *Diabetologia* 28:22–27, 1985
64. Cooper ME, Frauman A, O'Brien RC, Seeman E, Murray LMN, Jerums G: Progression of proteinuria in type 1 and type 2 diabetes. *Diabetic Med* 5:361–368, 1988
65. Ballard DJ, Humphrey LL, Melton LJ, Frohnert PP, Chu CP, O'Fallon WM, Palumbo PJ: Epidemiology of persistent proteinuria in type II diabetes mellitus. *Diabetes* 37:405–412, 1988
66. Kunzelman CL, Knowler WC, Pettitt DJ, Bennett PH: Incidence of nephropathy in type 2 diabetes mellitus in the Pima Indians. *Kidney Int* 35:681–687, 1989
67. Nelson RG, Pettitt DJ, Baird HR, Charles MA, Liu QZ, Bennett PH, Knowler WC: Pre-diabetic blood pressure predicts urinary albumin excretion after the onset of type 2 diabetes mellitus in Pima Indians. *Diabetologia* 36:998–1001, 1993

68. Mogensen CE, Østerby R, Hansen KW, Damsgaard EM: Blood pressure elevation versus abnormal albuminuria in the genesis and prediction of renal disease in diabetes. *Diabetes Care* 15:1192–1204, 1992
69. Schmitz A, Væth M, Mogensen CE: Systolic blood pressure relates to the rate of progression of albuminuria in NIDDM. *Diabetologia* 37:1251–1258, 1994
70. John L, Sunder Rao PSS, Kanagasabapathy AS: Rate of progression of albuminuria in type 2 diabetes. *Diabetes Care* 17: 888–890, 1994
71. Schmitz A: Renal function changes in middle-aged and elderly Caucasian type 2 diabetic patients: a review. *Diabetologia* 36:985–992, 1993
72. Ibsen H, Hilsen T: New views on the relationship between coronary heart disease and hypertension. *J Intern Med* 227: 77–79, 1990
73. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
74. Schmitz A, Hvid Hansen H, Christensen T: Kidney function in newly diagnosed type 2 (non-insulin-dependent) diabetic patients, before and during treatment. *Diabetologia* 32:434–439, 1989
75. Martin P, Hampton KK, Walton C, Tindall H, Davies JA: Microproteinuria in type 2 diabetes mellitus from diagnosis. *Diabetic Med* 7:315–318, 1990
76. Cull CA, Manley SE, Turner RC, UK Prospective Diabetes Study: Non-progressors of microalbuminuria over 3 years in 740 Type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 35 (Suppl. 1):61A, 1992
77. Haneda M, Kikkawa R, Togawa M, Koya D, Kajiwara N, Uzu T, Shigeta Y: High blood pressure is a risk factor for the development of microalbuminuria in Japanese subjects with non-insulin-dependent diabetes mellitus. *J Diabetic Complications* 6:181–185, 1992
78. Glynn JR: A question of attribution. *Lancet* 342:530–532, 1993
79. Ditzel J, Junker K: Abnormal glomerular filtration rate, renal plasma blood flow and renal protein excretion in recent and short-term diabetes. *Br Med J* 2:13–19,1972
80. Mogensen CE, Andersen MJF: Increase kidney size and glomerular filtration rate in early juvenile diabetes. *Diabetes* 22: 706–712, 1973
81. Mogensen CE: Early glomerular hyperfiltration in insulin-dependent diabetes and late nephropathy. *Scan J Clin Lab Invest* 46:201–206, 1986
82. Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy- an 8-year prospective study. *Kidney Int* 41: 822–828, 1992
83. Vora JP, Dolben J, Dean JD, Thomas D, Williams JD, Owens DR, Peters JR: Renal haemodynamics in newly presenting non-insulin-dependent diabetes mellitus. *Kidney Int* 41:829–835, 1992
84. Myers BD, Nelson RG, Williams GW, Bennett PH, Hardy SA, Berg RL, Loon N, Knowler WC, Mitch WE: Glomerular function in Pima Indians with non-insulin-dependent diabetes mellitus of recent onset. *J Clin Invest* 88:524–530, 1991
85. Palmisano JJ, Lebovitz HE: Renal function in black Americans with type II diabetes. *J Diabetic Complications* 3:40–44, 1989
86. Schmitz A, Christensen T, Moller A, Mogensen CE: Kidney function and cardiovascular risk factors in non-insulin-dependent diabetics (NIDDM) with microalbuminuria. *J Intern Med* 228: 347–352, 1990
87. Nielsen S, Schmitz A, Rehling M, Mogensen CE: Systolic blood pressure relates to the rate of decline of glomerular filtration rate in type 2 diabetes mellitus. *Diabetes Care* 16:1427–1432, 1993
88. Panzram G: Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 30:123–131, 1987
89. Pyörälä K: Diabetes and heart disease. In *Prevention and Treatment of Diabetic Late Complications*. Mogensen CE, Standl E, Eds. New York, de Gruyter, 1989, p. 151–168
90. Kannel WB, McGee DL: Diabetes and cardiovascular risk factors: the Framingham Study. *Circulation* 59:8–13, 1979
91. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141–1147, 1991
92. Uusitupa M, Siitonen O, Pyörälä K, Aro A, Hersio K, Vontilainen E: The relationship of cardiovascular risk factors to the prevalence of coronary heart disease in newly diagnosed type 2 (non-insulin-independent) diabetes. *Diabetologia* 28: 653–659, 1985
93. Vigorita VJ, Moore GW, Hutchins GM: Absence of correlation between coronary arterial atherosclerosis and severity or duration of diabetes mellitus of adult onset. *Am J Cardiol* 46:535–542, 1980
94. Jarrett RJ: Type II (non-insulin-dependent) diabetes mellitus and coronary heart disease: chicken, egg, or neither? *Diabetologia* 26:99–102, 1984
95. Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Coronary heart disease risk and impaired glucose tolerance: the Whitehall Study. *Lancet* i:1373–1376, 1980
96. Uusitupa M, Niskanen LK, Siitonen O, Vontilainen E, Pyörälä K: Ten-year cardio-vascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 36:1175–1184, 1993
97. Kuusisto J, Mykkänen L, Pyörälä K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
98. Diabetes Drafting Group: Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres: the World Health Organization multinational study of vascular disease in diabetics. *Diabetologia* 28:615–640, 1985
99. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–360, 1984
100. Jarrett RJ, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murrels TJ: Microalbuminuria predicts mortality in non-insulin-dependent diabetes. *Diabetic Med* 1:17–19, 1984
101. Mattock MB, Keen H, Viberti GC, El-Gohari MR, Murrels TJ, Scott GS, Wing JR, Jackson PG: Coronary heart disease and urinary albumin excretion rate in type 2 (non-insuline-dependent) diabetic patients. *Diabetologia* 31:82–87, 1988
102. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE: Eight to nine year mortality in known non-insulin dependent diabetics and controls. *Kidney Int* 41:731–735, 1992
103. Dinneen S, Gerstein H: Microalbuminuria and mortality in NIDDM: a systematic review of the literature (Abstract). *Diabetes* 44 (Suppl. 1):124A, 1995
104. Yudkin JS, Forrest RD, Jackson CA: Microalbuminuria as predictor of vascular disease in non-diabetic subjects. *Lancet* ii:530–533, 1988
105. Damsgaard EM, Frøland A, Jorgensen OD, Mogensen CE: Microalbuminuria as a predictor of increased mortality in elderly people. *Br Med J* 300:297–300, 1990
106. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage: The Steno hypothesis. *Diabetologia* 32:219–226, 1989
107. Deckert T: Nephropathy and coronary death: the fatal twins in diabetes mellitus. *Nephrol Dial Transplant* 9:1069–1071, 1994

108. Yudkin JS: Microalbumuria: a genetic link between diabetes and cardiovascular disease? *Ann Med* 24:517–522, 1992
109. Jerums G, Allen TJ, Tsalamandris C, Akdeniz A, Sinha A, Gilbert R, Cooper ME: Relationship of progressively increasing albuminuria to apoprotein (a) and blood pressure in type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetic patients. *Diabetologia* 36:1037–1044, 1993
110. Schnack C, Pietschmann P, Knobl P, Schuller E, Prager R, Schernthaner G: Apolipoprotein (a) levels and other atherogenic lipid fractions in relation to the degree of urinary albumin excretion in type 2 diabetes mellitus. *Nephron* 66: 273–277, 1994
111. Trevisan M, Vaccaro O, Laurenzi M, Chiara FD, Muro MD, Iacone R, Franzes A: Hypertension, non-insulin-dependent diabetes, and intracellular sodium metabolism. *Hypertension* 11:264–268, 1988
112. Fujita J, Tsuda K, Seno M, Obayashi H, Fukui I, Seino Y: Erythrocyte sodium-lithium countertransport activity as a marker of predisposition to hypertension and diabetic nephropathy in NIDDM. *Diabetes Care* 17:977–982, 1994
113. Gall MA, Rossing P, Jensen JS, Funder J, Parving HH: Red cell Na/Li countertransport in non-insulin dependent diabetics with diabetic nephropathy. *Kidney Int* 39:135–140, 1991
114. Pinkney JH, Foyle WJ, Denver AE, Mohammed-Ali V, MacKinlay S, Yudkin JS: The relationship of urinary albumin excretion rate to ambulatory blood pressure and erythrocyte sodium-lithium countertransport in NIDDM. *Diabetologia* 38:356–362, 1995
115. Stehouwer CDA, Nauta JJP, Zeldenhurst GC, Hackeng WHL, Donker AJM, Den Ottolander GJH: Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. *Lancet* 340:319–323, 1992
116. Collier A, Rumley A, Rumley AG, Patterson JR, Leach JP, Lowe GDO, Small M: Free radical activity and hemostatic factors in NIDDM patients with and without microalbuminuria. *Diabetes* 41:909–913, 1992
117. Niskanen L, Uusitupa M, Sarlund H, Siitonen O, Voutilainen E, Penttilä I, PyöräläK: Microalbuminuria predicts the development of serum lipoprotein abnormalities favouring atherogenesis in newly diagnosed type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 33:237–243, 1990
118. Mykkänen L, Haffner SM, Kuusisto J, Pyorälä K, Laakso M: Microalbuminuria precedes the development of NIDDM. *Diabetes* 43:552–557, 1994
119. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
120. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1495–1507, 1988
121. Groop L, Ekstrand A, Forsblom C, Widen E, Groop PH, Teppo AM, Eriksson J: Insulin resistance, hypertension and microalbuminuria in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 36:642–647, 1993
122. Nosadini R, Cipollina MR, Solini A, Velussi M, Muollo B, Sambataro M, Morocutti A, Doria A, Fioretto P, Brocco E, Frigato F: Close relationship between microalbuminuria and insulin resistance in essential hypertension and non-insulin dependent diabetes mellitus. *J Am Soc Nephrol* 3:S56–S63, 1994
123. Zambon S, Manzato E, Solini A, Sambataro M, Brocco E, Sartore G, Crepaldi G, Nosadini R: Lipoprotein abnormalities in non-insulin-dependent diabetic patients with impaired extrahepatic insulin sensitivity, hypertension, and microalbuminuria. *Arterioscler Thromb* 14: 911–916, 1994
124. Niskanen L, Laakso M: Insulin resistance is related to albuminuria in patients with type II (non-insulin-dependent) diabetes mellitus. *Metabolism* 42:1541–1545, 1993
125. Forsblom CM, Ericksson JG, Ekstrand AV, Teppo AM, Taskinen MR, Groop LC: Insulin resistance and abnormal albumin excretion in non-diabetic first-degree relatives of patients with NIDDM. *Diabetologia* 38:363–369, 1995
126. Nielsen S, Schmitz O, Orskov H, Mogensen CE: Similar insulin sensitivity in NIDDM patients with normo- and microalbuminuria. *Diabetes Care* 18:834–842, 1995
127. Haffner SM, Gonzales C, Valdez RA, Mykkänen L, Hazuda HP, Mitchell BD, Monterrosa A, Stern MP: Is microalbuminuria part of the prediabetic state? The Mexico City Diabetes Study. *Diabetologia* 36:1002–1006, 1993
128. Molitch ME: ACE inhibitors and diabetic nephropathy. *Diabetes Care* 17:756–760, 1994
129. Lebovitz HE, Wiegmann TB, Cnaan A, Shahinfar S, Sica DA, Broadstone V, Schwartz SL, Mengel MC, Segal R, Versaggi JA, Kline Bolton W: Renal protective effects of enalpril in hypertensive NIDDM: Role of baseline albuminuria. *Kidney Int* 45:S150–S155, 1994
130. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M: Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 118:577–581, 1994
131. Sano T, Kawamura T, Matsumae H, Sasaki H, Nakayama M, Hara T, Matsuo S, Hotta N, Sakamoto N: Effects of long-term enalapril treatment on persistent micro-albuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes Care* 17:420–424, 1994
132. Marre M, Chatellier G, Leblanc H, Guyene TT, Menard J, Passa P: Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. *Br Med J* 297:1092–1095, 1988
133. Kasiske BL, Kalil RSN, Ma JZ, Liao M, Keane WF: Effect of antihypertensive therapy on the kidneys in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 118:129–138, 1993
134. Melbourne Diabetic Nephropathy Study Group: Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. *Br Med J* 302:210–216, 1991
135. Baba T, Murabayashi S, Takebe K: Comparison of the renal effects of angiotensin converting enzyme inhibitor and calcium antagonist in hypertensive type 2 (non-insulin-dependent) diabetic patients with microalbuminuria: a randomised controlled trial. *Diabetologia* 32:40–44, 1989
136. Stornelllo M, Valvo EV, Scapellato L: Persistent albuminuria in normotensive non-insulin-dependent (type II) diabetic patients: comparative effects of angiotensin-converting enzyme inhibitors and β-adrenoceptor blockers. *Clin Sci* 82:19–23, 1992