Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus: a temporal perspective

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Lane, James T. Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus: a temporal perspective. Am J Physiol Renal Physiol 286: F442–F450, 2004; 10.1152/ajprenal.00247.2003.—Microalbuminuria is a marker for diabetic nephropathy. It also signifies cardiovascular disease, as well as nephropathy, in type 2 diabetes (DM2). Microalbuminuria may precede DM2, occurring with the insulin resistance syndrome and its components, including obesity and hypertension. Other indicators of cardiovascular risk, such as markers of inflammation, are associated with microalbuminuria in populations of patients with and without diabetes. With the rising prevalence of DM2 in minority youth, especially in Native Americans, a marker for future disease risk would allow earlier prevention strategies to be tested. Before microalbuminuria can be used in a prevention strategy, more needs to be known about the mechanism(s) of the association between elevated excretion, its relationship to glucose intolerance, and its relative contribution to cardiovascular and renal disease. These questions are especially applicable as we begin to observe the long-term complications of diabetes in youth.

insulin resistance; American Indians; young adults

MICROALBUMINURIA IS A MARKER for diabetic nephropathy and cardiovascular disease in patients with type 1 (DM1) and type 2 (DM2) diabetes mellitus (12, 81–83, 91, 119). Microalbuminuria refers to the excretion of albumin in the urine at a rate that exceeds normal limits but is less than the detection level for traditional dipstick methods (4). Microalbuminuria has been utilized as a screening test for the presence of diabetes-related kidney disease in patients with DM1. Results are expressed as milligrams per 24-h urine specimen, micrograms per minute in a timed urine specimen, or as micrograms per milligram creatinine in a random spot urine test (4). Detection of microalbuminuria is important from a clinical standpoint because, once detected, it is an indication for the initiation of anti-angiotensin II therapy with the purpose of preventing or delaying the advance of progressive diabetic nephropathy (4, 10, 70, 79, 89, 90). Although the positive predictive value of microalbuminuria for progressive diabetic nephropathy is less than once thought, it remains a standard clinical test with important ramifications for patient management (12).

As noted below, the development of diabetes-related kidney disease is similar in patients with DM1 and DM2 (88). However, issues involving the time course of the process are blurred by the insidious onset of DM2. In patients with DM2, it has become evident that microalbuminuria is also a predictor of cardiovascular death (81). However, the presence of microalbuminuria in DM2 may be more reflective of generalized vascular disease than diabetic glomerulopathy.

The past 10 years have seen a troubling increase in the prevalence of DM2 in youth (29, 34, 71, 102, 114). This epidemic of DM2 in youth has preferentially affected ethnic minorities (29, 71). The long-term implications for micro- and macrovascular disease and quality of life are enormous. In an effort to understand the development of DM2 in youth, high-risk populations are being closely monitored with emphasis on early markers of disease. The goal is the development of treatment strategies that will prevent or change the natural history of diabetes and its complications.

The goal of this review is to summarize the evidence supporting an association of microalbuminuria with conditions that may occur before the development of DM2 in high-risk populations, including obesity, the insulin resistance syndrome, and impaired glucose tolerance. First Nation (Canadian North American Indians) and American Indians in North America are highlighted as an example of a high-risk population, but similar data exist for other ethnic groups at high-risk for DM2, including African Americans and Hispanics (36). It is clear that cardiovascular risk and disease begin before the diagnosis of DM2 in patients with insulin resistance and can be accelerated in young adults. The challenge is to learn more about the temporal pattern of disease markers that reflect disease evolution and why they occur, choose appropriate strategies for intervention, and conduct clinical trials that will prevent both cardiovascular and renal disease in patients at risk.

NATURAL HISTORY OF MICROALBUMINURIA IN DM1 DIABETES

Microalbuminuria is not usually a presenting finding at the onset of DM1. After a 5- to 10-yr duration of diabetes, susceptible patients develop intermittent microalbuminuria before having persistent microalbuminuria (84). Improved blood glucose control (23a, 110, 117a), antihypertensive therapy, and anti-angiotensin II therapy (10, 27a, 67, 70, 74, 77, 80a, 90, 120) have been shown to delay or prevent the progression of
microalbuminuria and the development of nephropathy. In DM1, microalbuminuria is a strong risk factor for the development of nephropathy. The development of microalbuminuria is associated with established extracellular matrix expansion in the glomerular and tubulointerstitial compartments of the kidney (69). The natural history results in progressive glomerulosclerosis, increasing proteinuria, and chronic renal failure. The long period between the onset of microalbuminuria and chronic renal failure (in years) offers a substantial window for therapeutic intervention (117).

Recent data suggest that microalbuminuria in DM1 may regress over time. Perkins et al. (94) reported data from the Joslin Clinic on 386 patients with DM1 who were followed for 8 yr (Table 1). Regression was defined as a 50% decrease in albumin excretion from one 2-yr study period to the next 2-yr study period and occurred in 58% of the patients (94). Interestingly, regression was not associated with angiotensin-converting enzyme inhibitor use but was associated with glycylated hemoglobin levels of <8%, systolic blood pressure of <115 mmHg, and low levels of cholesterol and triglycerides. If regression occurs with this frequency, it brings into question the underlying mechanism(s) and true specificity for microalbuminuria as a marker for progressive renal impairment.

### NATURAL HISTORY OF MICROALBUMINURIA IN DM2

Because of the insidious onset of DM2, the true duration of the disease is often not known. It has been reported that a duration of >6 yr of diabetes may have existed before diagnosis (46). Because of the variable duration of disease at diagnosis, subjects often present with microalbuminuria at that point.

#### Table 1. Human clinical studies of microalbuminuria

<table>
<thead>
<tr>
<th>Study/Ref. No.</th>
<th>Study Question</th>
<th>Study Group</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkins et al. (84)</td>
<td>Determine the rate of regression of MA</td>
<td>DM1 patients with MA: 386 patients</td>
<td>Prospective measurement of MA with retrospective analysis</td>
<td>As defined by 50% reduction in MA from one 2-yr period to the next, 58% of patients had regression.</td>
</tr>
<tr>
<td>Framingham Offspring Study (70)</td>
<td>Determine the relationship between insulin resistance and MA</td>
<td>Population study with DM2 excluded, age 28–82 yr; 1,592 subjects</td>
<td>OGGT, clinical characteristics, and MA determinations were made as part of a larger study</td>
<td>MA was associated with hyperinsulinemia and other CV risk factors.</td>
</tr>
<tr>
<td>Group et al. (33)</td>
<td>Determine the impact of MA and hypertension on insulin sensitivity</td>
<td>DM2 and controls; 52 DM2 and 19 healthy controls</td>
<td>Euglycemic glucose clamp, AER, and BP measurements</td>
<td>Insulin sensitivity was indirectly related to MA, hypertension, or both.</td>
</tr>
<tr>
<td>Botnia Study (50)</td>
<td>Determine the CV risk associated with the metabolic syndrome</td>
<td>Family study of DM2 in Finland and Sweden; 4,483 subjects (1,697 DM2, 798 IGT, and 1,988 NGT)</td>
<td>Assessment of CV mortality over time</td>
<td>CV death rate was three fold higher in subjects with the metabolic syndrome. MA was the strongest risk for CV death.</td>
</tr>
<tr>
<td>Mexico City Diabetes Study (23a)</td>
<td>Determine whether MA defines the prediabetic state</td>
<td>Nondiabetic subjects studied for CV risk factors; 1,298 subjects</td>
<td>Cross-sectional study of OGTT, MA determinations on subjects</td>
<td>Parental DM2 and IGT were associated with MA. Subjects with MA more likely to be hypertensive, dyslipidemic.</td>
</tr>
<tr>
<td>Insulin Resistance Atherosclerosis Study (77)</td>
<td>Determine the relationship between MA and insulin sensitivity</td>
<td>Nondiabetic subjects; 982 subjects, 40–69 yr old</td>
<td>Cross-sectional population study where individuals had IVGTT with minimal model and determination of AER</td>
<td>Insulin resistance is related to MA and is dependent on blood pressure, glucose level, and obesity.</td>
</tr>
<tr>
<td>Hoom Study (51)</td>
<td>Determine whether MA is part of the insulin resistance syndrome</td>
<td>General population of Caucasians, age 50–75 yr; 622 subjects</td>
<td>Cross-sectional population study with OGTT, AER determinations</td>
<td>MA was associated with hypertension but not the other parts of the metabolic syndrome.</td>
</tr>
<tr>
<td>DESIR- Study (117a)</td>
<td>Determine whether MA is associated with CV risk and insulin resistance in men and women</td>
<td>Population study, age 30–64 yr; 3,878 subjects</td>
<td>Study of baseline parameters from a prospective study</td>
<td>MA is associated with CV risk and insulin resistance in men but not consistently in women.</td>
</tr>
<tr>
<td>Inter-Tribal Heart Project (47)</td>
<td>Determine the association between MA and insulin resistance syndrome among nondiabetic Native Americans</td>
<td>Native Americans attending Indian Health Service clinics; 934 subjects</td>
<td>A cross-sectional survey from three reservations, including history, exam, and AER</td>
<td>MA was found in 15% of subjects. Components of the insulin resistance syndrome are associated with MA.</td>
</tr>
<tr>
<td>Nurses’ Health Study (48)</td>
<td>Determine whether the risk of CV disease is elevated before diagnosis of DM2 in women</td>
<td>Female nurses free of CV disease at baseline, age 30–55 yr; 117,629 subjects</td>
<td>Prospective follow-up over 20 years</td>
<td>Risk for CV disease began 15 yr before the diagnosis of DM2.</td>
</tr>
<tr>
<td>HOPE Study (65)</td>
<td>Determine the predictive value of MA for advancing proteinuria and renal insufficiency</td>
<td>Subgroup of total HOPE cohort, with and without DM2; 7,674 subjects</td>
<td>Retrospective analysis of AER in participants with baseline and follow-up AER. Randomized to ramipril or placebo</td>
<td>People with and without DM2 at risk for CV disease are at risk for increasing albuminuria, and this can be prevented by ramipril.</td>
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</table>

MA, microalbuminuria; DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; OGGT, oral glucose tolerance test; CV, cardiovascular; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; AER, albumin excretion rate; DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; HOPE, Heart Outcomes and Prevention Evaluation.
point. However, diabetic nephropathy in DM2 is similar to nephropathy in DM1 with similar pathology, response to interventions of glucose control and anti-angiotensin II therapy, and progression to chronic renal failure (12, 99). DM2 with nephropathy involves a similar proportion of patients, compared with DM1 (49). At present, there is not a similar long-term study evaluating regression in DM2 as described above for DM1. However, data taken from recent intervention studies using angiotensin II receptor antagonists demonstrate some regression. Lewis et al. (70) reported on the use of irbesartan in patients with DM2 and nephropathy. A 33% decrease in proteinuria was seen over 2.6 yr, whereas the placebo group decreased 10%. A similar study using losartan in DM2 and nephropathy found a reduction of 35%, whereas the placebo group had a rise in proteinuria (10). Parving et al. (90) reported on the use of irbesartan in a population of hypertensive patients with DM2 and microalbuminuria and found that microalbuminuria was decreased by 38% over 2 yr with only a change of 2% in the controls. Attempts at prevention of nephropathy in DM2 have focused on the prevention of microalbuminuria, the earliest clinical hallmark of nephropathy, or its progression to macroalbuminuria (89, 99). In general, the evolution of nephropathy in DM2 is similar to what is found with DM1.

MICROALBUMINURIA IS ASSOCIATED WITH CARDIOVASCULAR DISEASE

Microalbuminuria has been associated with increased cardiovascular mortality in populations of both diabetic and nondiabetic subjects (43, 57, 81, 125). In fact, microalbuminuria has been used as a marker of cardiovascular disease, along with other risk factors found in the insulin resistance syndrome. Data from the Framingham Offspring Study suggest that microalbuminuria is more likely to be present with additional cardiovascular risk factors (78). The premise is that microalbuminuria is a marker of generalized endothelial dysfunction. Microalbuminuria has been linked to increased transcapillary albumin leakage and increased von Willebrand factor and other markers of endothelial dysfunction (59, 106). In survivors of myocardial infarction, both albuminuria and the transvascular escape rate of albumin are increased (58). Albuminuria has also been shown to predict the severity of atherosclerosis (86, 116). Others have suggested that the elevated insulin levels that occur with insulin resistance increase glomerular hemodynamic pressures that increase albumin excretion (16, 115). The relative contribution of underlying vascular disease vs. diabetic nephropathy toward microalbuminuria is not clear. However, a large body of evidence suggests that microalbuminuria is an indicator of both micro- and macrovascular disease.

Cross-sectional studies have clearly demonstrated the presence of microalbuminuria with other markers of the insulin resistance syndrome. Using clamp studies, hypertension alone was found to associate with a decrease in glucose disposal by 27% (37). However, the combination of microalbuminuria and hypertension was associated with the greatest decrease in glucose disposal. The highest triglycerides and the lowest HDL-C levels, additional markers of the insulin resistance syndrome, were associated with patients having hypertension and microalbuminuria. In the Botnia Study, 84% of those with DM2 had elements of the insulin resistance syndrome (obesity, hypertension, dyslipidemia, or microalbuminuria) (55). If present, the insulin resistance syndrome increased the risk for coronary artery disease and stroke threefold. However, microalbuminuria was the strongest risk for cardiovascular death. Of those with normal glucose tolerance, 10% had microalbuminuria, suggesting the potential for microalbuminuria as a marker for the risk of coronary artery disease in nondiabetic individuals. This is such an important association that the World Health Organization has included microalbuminuria in its definition of the metabolic syndrome (2).

MICROALBUMINURIA AS A RISK FACTOR IN NONDIABETIC PEOPLE

A number of studies have demonstrated that microalbuminuria occurs in individuals without diabetes. In the Mexico City Diabetes Study, nondiabetic people with microalbuminuria were more likely to have a family history of diabetes (42). Similar findings were reported by in the Botnia study, where first-degree relatives of patients with DM2 demonstrated insulin resistance in association with elevated albumin excretion rates (32). In the Insulin Resistance Atherosclerosis Study, patients with microalbuminuria were more insulin resistant and had higher fasting insulin concentrations compared with patients without microalbuminuria (87). However, the relationship was also partially dependent on blood pressure and obesity. Although the bulk of the data supports microalbuminuria as being a component of the insulin resistance syndrome, not all results support this contention (56). The Hoorn Study evaluated a homogenous Caucasian population and found that microalbuminuria was associated with hypertension, DM2, and waist-hip ratio. It did not, however, associate with other components of the insulin resistance syndrome. This raises the alternative view that microalbuminuria is associated with hypertension but not the insulin resistance syndrome. In Data from an Epidemiological Study on the Insulin Resistance Syndrome findings, the cardiovascular events were greater in subjects with microalbuminuria (45). However, in contrast to men, women did not show the same increased cardiovascular risk with the addition of microalbuminuria. A similar trend was seen in the Inter-Tribal Heart Project, where nondiabetic Native Americans with microalbuminuria often had the insulin resistance syndrome (52). Thus hormonal differences may play a role in the expression of the increased cardiovascular risk in patients with insulin resistance and microalbuminuria. Although this may suggest that estrogen may have some protective effect, when women are administered estrogen in the pre- or postmenopausal setting, it is associated with increases in microalbuminuria in a dose- and time-dependent fashion (85). In addition, in women high levels of microalbuminuria, when present, are still predictive of cardiovascular disease, as demonstrated in an epidemiological study from The Netherlands in which women with the highest quintile of microalbuminuria were at increased risk of cardiovascular death (101).

Such terms as the “ticking clock” or the “common soil” hypothesis have been used to suggest that the time course for the development of cardiovascular disease begins before the onset of clinical diabetes (44, 107). The common factors for the development of cardiovascular disease may represent genetic or environmental factors that are present before the clinical manifestations of disease. Indeed, in the Nurses’ Health Study,
the risk for cardiovascular disease was found to be elevated at least 15 yr before the diagnosis of diabetes (53). Whether the common factors for onset of microalbuminuria and diabetes are preventable is of great interest for future therapy. The Heart Outcomes and Prevention Evaluation study provided powerful data along these lines (73). The use of the ACE inhibitor ramipril reduced the progression of albuminuria, whether this was new albuminuria or the progression of microalbuminuria to macroalbuminuria. This study also demonstrated that ramipril was effective in decreasing cardiovascular death in patients with known heart disease or DM2 patients without established heart disease. The benefits of ramipril were greatest on preventing cardiovascular events in patients with DM2 and in nondiabetic patients with albuminuria.

DM2 IS INCREASING IN YOUTH

Over the past 20 years, the prevalence of DM2 has increased 18% in the United States (3). Not only is DM2 more prevalent, but it often begins at a younger age (71, 102). This has serious consequences for long-term health as these patients are also at increased risk for cardiovascular disease, end-stage renal disease, blindness, amputation, and the associated personal and economic losses at earlier ages. The younger onset of patients with DM2 suggests that those patients will live with complications for a larger percentage of their lifetime.

Prevalence rates for diagnosed DM2 in children have been estimated at between 2 and 50/1,000, depending on the population studied, whereas that for the general adult population is estimated at between 2 and 50/1,000, depending on the population studied, whereas that for the general adult population is 30/1,000 (29). Those children and young adults with the highest prevalence rates of DM2 are from racial and ethnic minorities, including African Americans, Hispanics, and Native Americans (29, 71). The increased prevalence of DM2 in children has been attributed to increasing obesity, a sedentary lifestyle, and increased intrauterine exposure to a diabetic environment (8, 29, 34, 71, 114). The degree of obesity is significant, as most published studies have found that affected children with DM2 have a mean body mass index (BMI) exceeding the 95th percentile for age (29, 71). Because of the increased prevalence of DM2, DM1 may no longer represent the most common form of diabetes in youth, as up to 50% of new cases of diabetes in youth are DM2 in some populations (71).

DM2 IS INCREASED IN NATIVE AMERICANS, INCLUDING YOUTH

DM2 is epidemic in American Indian populations (3, 11). Data from the Indian Health Service suggest that the prevalence rate is 8.0%, over double the rate for the population as a whole (14). There is also a female predominance, with prevalence rates 25% higher in American Indian females (13). The prevalence rates for other minorities, including African Americans and Hispanics, are similar to those of American Indians (3).

Similar to national trends, American Indian children and youth are also experiencing an increased prevalence of DM2 (20, 21, 29, 47). Numbers for American Indians across the U.S. vary from 1.3/1,000 for children 0–14 yr of age to 4.5/1,000 for youth aged 15–19 yr (29). Recent Indian Health System data indicate the prevalence rate has risen to 5.4/1,000 for ages 15–19 yr, an increase of 68% over a decade (1, 7). Population-based studies demonstrate that DM2 occurs in African Americans at a rate of 7.2/1,000, in contrast to 4.1/1,000 for all U.S. adolescents aged 12–19 yr (29). Without a plateau in the increasing prevalence, DM2 will be expected to increase into the future.

MICROALBUMINURIA IN AMERICAN INDIAN CHILDREN AND ADULTS

The prevalence of microalbuminuria amongst all American Indian tribes is not known. However, the Strong Heart Study recently revealed the prevalence of microalbuminuria in Arizona, Oklahoma, and Dakota Indians to be 28.3, 15.2, and 13.8%, respectively (100). However, these subjects were all adults and may not represent the prevalence of microalbuminuria in young American Indians.

Fagot-Campagna et al. (28) reported on the prevalence of cardiovascular risk factors, including microalbuminuria, in Pima children age 5–19 yr. The group included 4,092 10- to 19-yr-old patients with normal glucose tolerance. At baseline, 6% had microalbuminuria, whereas 8% with impaired glucose tolerance had microalbuminuria. After more than 5 yr, 33% of the entire cohort had developed microalbuminuria. This is in contrast to the rates of microalbuminuria in other healthy ethnic groups. For African Americans, 7.7% of men and 10.5% of women aged 6–19 yr have microalbuminuria (60). Non-Hispanic whites (5.7/9.7, men/women) and Hispanics (5.4/9.5, men/women) have lower rates of microalbuminuria. After age 19, in all ethnic groups the rate of microalbuminuria falls in the third decade to rates roughly one-half those seen at ages 6–19 yr. If microalbuminuria serves as a marker of future cardiovascular and renal disease, efforts to define its prevalence in high-risk populations are an essential first step to a prevention strategy.

ROLE OF PUBERTY IN DEVELOPMENT OF MICROALBUMINURIA

Puberty is normally associated with complex changes in renal hemodynamics, somatic growth, and changes in sex hormones that may have important interactions with hyperglycemia and insulin resistance (68). These changes may, in turn, affect microalbuminuria during puberty. It is rare to develop microalbuminuria before puberty in DM1. In fact, there has been a suggestion that diabetic nephropathy does not occur before puberty (24, 65). Although patients may not have microalbuminuria, histological changes indicative of diabetic nephropathy occur in association with duration of diabetes, not pubertal stage (25). However, with DM2, pathological insulin resistance may interact with developmental changes to accelerate the onset of microalbuminuria.

Puberty is associated with changes in insulin sensitivity (5, 9, 17, 95). Tanner staging characterizes pubertal development, according to physical findings utilizing examination of pubic hair and genitalia in boys and pubic hair, breast size, and menarche in girls (75, 76). Tanner stages range from stages 1 (preadolescent) to 5 (fully mature). Several studies have demonstrated that insulin sensitivity decreases early in puberty in nondiabetic children as well as patients with diabetes, beginning between Tanner stages 1 and 2 and decreasing throughout puberty. Insulin sensitivity improves to normal after linear growth is complete in adults. Body fat also increases in early
puberty, but BMI does not change with Tanner stage in adolescents.

No clear association between insulin sensitivity and rising sex steroid concentrations has been found in men (123). However, polycystic ovary syndrome with its proatherosclerotic effects (123) often includes increased androgens. It has been recently reported that higher free androgen levels in children with DM1 were associated with the development of microalbuminuria (6).

Several studies have implicated a relationship between insulin sensitivity and the growth hormone-IGF-1 axis, suggesting increased tissue growth hormone effect as the cause (9, 17). One study found a significant association among IGF-1, renal hypertrophy, and microalbuminuria (19). However, others did not confirm this relationship (104). To date, studies evaluating microalbuminuria during puberty have been cross-sectional. Additional prospective studies are needed to more closely characterize the changes that occur with puberty and the development of microalbuminuria.

ASSOCIATION OF CARDIOVASCULAR DISEASE WITH MARKERS OF INFLAMMATION

The use of the highly-sensitive C-reactive protein (CRP) assay, a sensitive marker of inflammation, has been shown in a number of studies to predict the risk of cardiovascular disease events (15, 51, 64, 66, 93, 96–98, 112, 113, 128). An active role for elevated CRP levels in the pathophysiology of vascular disease has been suggested but not definitively proven (23, 92, 122, 129). Because microalbuminuria, CRP, and other markers of inflammation have been shown to be associated with cardiovascular disease, the question arises as to whether the inflammatory process causes the microalbuminuria.

A large cross-sectional study has demonstrated an association between microalbuminuria and CRP (31). Festa et al. (31) reported on 1,281 subjects from the Insulin Resistance Atherosclerosis Study. The study population contained patients with and without DM2. There was a positive association between microalbuminuria and elevated CRP and fibrinogen. The association was similar across gender and ethnic groups. The authors suggest that the association may arise from three possibilities: the independent development of atherosclerosis and microalbuminuria, the direct or indirect effect of cytokines on the glomerulus, or the presence of both from a common preexisting condition. However, a retrospective analysis of the Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study did not demonstrate an association between microalbuminuria and CRP levels in a population at high risk for DM2 (111).

Stehouwer et al. (105) prospectively followed markers of chronic inflammation and endothelial dysfunction in 328 patients with DM2 for 9.0 yr. Markers for both endothelial dysfunction and chronic inflammation, as well as microalbuminuria, were found to be interrelated, to have developed in parallel, progressed with time, and were related to death.

Stuveling et al. (108) reported on 7,317 patients without diabetes. CRP was associated with microalbuminuria and decreased renal filtration as measured by creatinine clearance. CRP was also associated with hyperfiltration (defined by an elevated creatinine clearance and seen before a decrease in creatinine clearance in patients with diabetic nephropathy), although this relationship was primarily related to BMI and has been described previously (80, 118). These data raise the point that inflammatory processes may negatively impact renal function, as well as cardiovascular end points. This may be especially true in individuals who progress from obesity to prediabetes to diabetes. No prospective data exist in patients with diabetes to provide insight into this question.

Obesity, especially visceral obesity, has been previously associated with plasma inflammatory markers, including IL-6, CRP, and TNF-α (18, 50, 62, 121, 126, 127). BMI and hemoglobin A1C have also been associated with inflammatory markers (105). Acute hyperglycemia has been shown to increase IL-6, TNF-α, and IL-18 (27). Low levels of adiponectin that occur with obesity are associated with increased IL-6 and CRP plasma levels (26). Visceral obesity is also associated with increased free fatty acid release into the portal vein (33). This leads to increased hepatic glucose output with resultant hyperglycemia and decreased hepatic insulin extraction with resultant hyperinsulinemia (30, 109). Glowinska et al. (35) reported that traditional risk factors for cardiovascular disease, such as hypertension and dyslipidemia, are also associated with nontraditional risk factors, such as decreased fibrinolytic activity and homocysteinemia, and lipoprotein (a) levels in obese, diabetic adolescents.

These findings suggest that prevention of obesity, prevention of hyperglycemia, use of antioxidants, and other anti-inflammatory treatments may be beneficial in addressing the early progressive inflammatory response associated with diabetes and vascular disease. Indeed, glutathione has been shown to prevent the rise of cytokine levels (27). The increase in oxidative stress from obesity was further supported in a community-based cohort in the Framingham Heart Study (61). Thiazolidinediones increase adiponectin levels (72, 124). Salicylates may improve fat-induced insulin resistance (63). Exercise is associated with decreased CRP levels (54). These are in addition to lifestyle changes to lose weight.
CLINICAL USE OF THE MICROALBUMIN ASSAY

Although there are clear recommendations for the measurement of microalbumin excretion in the urine, the test is not universally employed (48). Factors contributing to this include lack of availability, confusion with units of measure, increased turnaround time for the assay, and the sense by clinicians that such measurements are not needed provided patients are placed on an angiotensin-converting enzyme inhibitor or angiotensin II blocker. The latter point is incorrect for several reasons. Despite therapy with one of the renoprotective agents, there is now evidence that simultaneous use of both agents may further decrease microalbuminuria, and prospective testing needs to be performed to titrate the medications (103). The above review has also indicated that microalbuminuria is a marker of vascular disease and can be used to support further therapy directed at this complication. For the stated reasons, the recommendations for microalbuminuria testing need to be emphasized and the obstructions to its use removed.

SUMMARY

There is generally a long lag time between the initiation of atherogenesis and the first cardiac event, which provides an opportunity to intervene with preventive therapy in insulin resistance. However, before a prevention treatment can be devised and tested, more needs to be known about the temporal development of DM2, vascular disease, and renal disease. Evidence already exists of the terrible toll of diabetes and its complications occurring earlier in youth who develop diabetes. Dean and Flett (22) reported a high mortality rate of 9% after 15 yr of diabetes in First Nation populations in Manitoba and Ontario, Canada. These patients were diagnosed with DM2 before 18 yr of age and were only in their third decade of life when they died. As insulin resistance and diabetes become more prevalent, its complications loom threateningly on the horizon for these patients.

The pathophysiology of insulin resistance and diabetes-related vascular disease likely begins before the diagnosis of DM2 (Fig. 1). Inflammatory markers begin to increase with the presence of visceral obesity. Microalbuminuria is another marker of endothelial dysfunction, which may occur with early cardiovascular and renal disease. While microalbuminuria is also a marker of early diabetic nephropathy and may not always predict progression, it appears to also predict significant cardiovascular disease. Further understanding of these issues is critical to prevent mortality from cardiovascular and renal disease in diabetes, especially in young adults with DM2.

REFERENCES


