Renal Insufficiency in the Absence of Albuminuria and Retinopathy Among Adults With Type 2 Diabetes Mellitus

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End-stage renal disease (ESRD) in adults with type 2 diabetes mellitus (DM) represents a medical problem with worldwide dimensions. Currently, approximately 40% of all prevalent ESRD cases and almost half of all new cases in the United States are attributed to type 2 DM. Due to the increasing incidence of type 2 DM and the increased survival of these individuals due to improved medical treatment, the number of patients with ESRD is expected to double over the next decade, with costs escalating to $28 billion.

Most of our knowledge concerning the nature of kidney disease in adults with type 2 DM is derived from studies of patients with type 1 DM. The classic clinical course of type 1 diabetic nephropathy (glomerulosclerosis) is described as the development of microalbuminuria, which eventually leads to macroalbuminuria and then to progressive loss of glomerular filtration rate (GFR). Among adults with type 1 DM and nephropathy, more than 95% will have diabetic retinopathy. The extent to which renal disease in adults with type 2 DM is a consequence of classic diabetic glomerulosclerosis remains controversial. Biopsy series among those with macroalbuminuria (or some other clinical indication for a biopsy, such as active urine sediment or a rapidly rising creatinine level) has been a major source of knowledge concerning the distribution of renal pathology in persons with type 2 DM. Autopsy series and clinical examination of patients presenting for renal replacement therapy have also provided valuable information. However, by their nature, these studies may

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be subject to significant referral and selection bias.

An unbiased estimate of the likelihood of diabetic glomerulosclerosis (vs other parenchymal disease) as the etiology of renal insufficiency among patients with type 2 DM has important implications. For example, the current strategies for screening and treatment of renal disease in patients with type 2 DM implicitly assume the underlying disease process is uniformly diabetic glomerulosclerosis. While this is true for many individuals, our clinical experience leads us to hypothesize that a substantial number of adults with type 2 DM and decreased GFR may not have diabetic glomerulosclerosis, as inferred from the absence of albuminuria and retinopathy.

In this study, we used data from a nationally representative sample of the US population to determine the frequency of chronic renal insufficiency (CRI), defined as a GFR less than 60 mL/min per 1.73 m² body surface area (BSA) in the absence of albuminuria or diabetic retinopathy in adults with type 2 DM.

**METHODS**

**Study Population**

The Third National Health and Nutrition Examination Survey (NHANES III) was designed as a probability sample of the total US civilian noninstitutionalized population 2 months of age or older and collected health and nutritional data on 33994 men, women, and children from 1988-1994. Certain subgroups, such as young children, older persons, non-Hispanic blacks, and Mexican Americans, were oversampled. Details of the survey design may be found in the NHANES III operations manual.

**Definition of Type 2 DM**

There were 9737 NHANES III adults who were 40 years of age or older and completed a standardized interview and a detailed physical examination. Diabetes was self-reported as being previously diagnosed by a physician (except during pregnancy) or as current or past use of insulin or oral agents. Overall, 1187 reported a previous diagnosis of DM. The NHANES III did not collect information on type of DM. Thus, we excluded 7 adults with likely type 1 DM (diagnosed with DM prior to 30 years of age or continuous use of insulin), leaving a total of 1180 adults with previously diagnosed type 2 DM.

Adults who completed the examination in the morning were instructed to fast for at least 9 hours, while those who completed the examination in the afternoon were instructed to fast for at least 4 hours. Among the 8550 adults without previously diagnosed DM, we excluded 318 (4%) who did not have fasting serum glucose levels measured and an additional 624 (7%) who did not fast as instructed. Among individuals who fasted appropriately and had serum glucose levels measured, 356 were classified as having type 2 DM according to the American Diabetes Association (ADA). We repeated the analyses using the World Health Organization (WHO) criteria to define newly diagnosed type 2 DM. A 75-g oral glucose challenge test was administered to 5776 (76%) of adults who fasted appropriately and had fasting serum glucose levels measured. Overall, 575 adults with a fasting glucose level less than 126 mg/dL (6.9 mmol/L) had serum glucose values of at least 200 mg/dL (11.1 mmol/L) 2 hours (± 15 minutes) after an oral glucose challenge, leaving 931 adults classified as having newly diagnosed type 2 DM according to the WHO criteria.

**Definition of Retinopathy**

In the NHANES III, photographs of the ocular fundus of one eye were taken in all examined adults who were 40 years of age or older, regardless of diabetes status. These photographs were taken with a nonmydriatic fundus camera (Canon CR-4-45NM, Canon, Kanagawa, Japan), which incorporated the use of an infrared video camera to allow photographs to be taken in a darkened examination room without the use of dilating drops. A nonstereoscopic, color, 45° photograph, centered between the optic nerve and the macula, was taken of one randomly selected eye, and the fundus images were then reviewed at the University of Wisconsin–Madison Department of Ophthalmology. The grading system for classifying diabetic retinopathy was based on a modification of the Air- line House Classification Scheme. Adults with any evidence of current retinopathy (nonproliferative [mild, moderate, or severe] or proliferative) or previous treatment for proliferative diabetic retinopathy were classified as having diabetic retinopathy. A gradeable photograph of the ocular fundus of one eye was obtained in 939 (80%) of the adults with previously diagnosed type 2 DM, 288 (81%) with newly diagnosed type 2 DM using the ADA criteria, and 804 (86%) with newly diagnosed type 2 DM using the WHO criteria. Adults without gradeable funduspic examinations were excluded.

**Quantification of Albuminuria**

Solid-phase fluorescent immunoassay was used to measure urinary albumin levels, and urine creatinine levels were measured with the Jaffe rate reaction. Spot urine albumin (µg/mL)/creatinine (mg/mL) ratios (ACR) were calculated for all adults, and those with missing urine data were excluded (27 previously diagnosed and 3 newly diagnosed using the ADA criteria, and 8 newly diagnosed using the WHO criteria). To define microalbuminuria in random urine specimens, we used sex-specific ACR cut points (≥17 and ≥25 µg/mg for men and women, respectively). Macroalbuminuria was defined as an ACR of at least 250 µg/mg in men and at least 355 µg/mg in women. Albuminuria was defined as the presence of microalbuminuria or macroalbuminuria.

**Estimation of GFR**

The GFR per 1.73 m² BSA was calculated with serum creatinine, urea nitrogen, and albumin levels using an equation developed from the Modification of Diet in Renal Disease (MDRD) Study, as follows:

\[
GFR = 170 \times \left[\frac{\text{serum creatinine}}{\text{[serum albumin]}}\right]^{-0.990} \times \left[\frac{\text{blood urea nitrogen}}{\text{[serum albumin]}}\right]^{-0.117} \times \left[0.762 \text{ if female}\right] \times \left[1.180 \text{ if non-Hispanic black}\right] \times \left[\text{[serum albumin]}^{-0.318}\right]
\]
We subtracted 0.23 mg/dL from the measured serum creatinine level to adjust for differences in the calibration of serum creatinine level between NHANES III and the MDRD study.\textsuperscript{21} We defined CRI as a GFR less than 60 mL/min per 1.73 m\textsuperscript{2} BSA. This corresponds to the newly proposed National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative guidelines for defining chronic kidney disease stages 3 to 5.\textsuperscript{22}

### Assessment of Covariates

Age was defined as the age at the time of the interview, and race or ethnicity were self-reported as non-Hispanic white, non-Hispanic black, and Mexican American. Other races or ethnicities were grouped into "other." Blood pressure was determined by the mean of 6 readings. Body mass index was calculated from the weight and height measured during the physical examination. We also analyzed information regarding use of angiotensin-converting enzyme (ACE) inhibitors.

### Statistical Analysis

All statistical analyses were completed with SAS-callable SUDAAN version 8 (Research Triangle Institute, Research Triangle Park, NC) to incorporate sample weights and adjust for the clusters and strata of the complex sample design and provide prevalence estimates, which reflect the entire US population. The NHANES III data are weighted to account for the probability of selection and to adjust for nonresponse; thus, the actual percentage of adults in a particular sampled stratum of the complex sample design and strata is based on weighted data. Percentages are based on weighted data.

Table 1. Characteristics of the US Type 2 Diabetic Population Compared With the Nondiabetic Population 40 Years of Age or Older*  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 2 Diabetic Population† (Sampled n = 1197)</th>
<th>Nondiabetic Population (Sampled n = 7462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (0.6)</td>
<td>57 (0.4)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>137 (0.9)</td>
<td>129 (0.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76 (0.6)</td>
<td>76 (0.2)</td>
</tr>
<tr>
<td>Body mass index‡</td>
<td>30 (0.3)</td>
<td>27 (0.1)</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m\textsuperscript{2} BSA§</td>
<td>88 (1.3)</td>
<td>90 (0.6)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Mexican American</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Presence of albuminuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SE) unless otherwise indicated. Percentages are based on weighted data.
†Newly diagnosed type 2 diabetes mellitus defined by American Diabetes Association criteria,\textsuperscript{13} with gradable funduscopic examinations and data on urine albumin excretion.
‡Calculated as weight in kilograms divided by the square of height in meters.
§Glomerular filtration rate (GFR) calculated with the Modification of Diet in Renal Disease Study formula.\textsuperscript{16}

### RESULTS

Characteristics of adults with type 2 DM (previously diagnosed and newly diagnosed by ADA criteria) with gradeable funduscopic examination and data on urine albumin excretion (n=1197) compared with nondiabetic adults at least 40 years of age (sampled n=7462) are shown in TABLE 1. Adults with type 2 DM had higher systolic blood pressure and were more likely to have increased urine albumin excretion compared with the nondiabetic population age 40 years or older. Adults with ungradeable funduscopic examinations (who were excluded from subsequent analyses) were significantly older (68 years vs 61 years; P=.002) and had a lower GFR (74 mL/min per 1.73 m\textsuperscript{2} BSA vs 88 mL/min per 1.73 m\textsuperscript{2} BSA; P<.001) compared with adults with type 2 DM and gradeable funduscopic examinations. However, there were no other significant differences between the 2 groups. Among the adults with previously diagnosed type 2 DM, the mean reported duration of DM was 9.1 years, and 25% and 51% reported the use of insulin and diabetes pills, respectively. The use of ACE inhibitors was noted in 13% of the type 2 diabetic population and 5% of the nondiabetic population.

The percentage and population estimate of adults with type 2 DM (previously diagnosed and newly diagnosed by ADA criteria) aged 40 years or older with CRI are shown in TABLE 2. Chronic renal insufficiency was noted in 13% (sampled n=171) of adults with type 2 DM (population estimate, 1.1 million), which was significantly higher than the 7% (n=636) prevalence noted in the nondiabetic population aged 40 years or older (P<.001). No substantial change in the prevalence of CRI was noted after excluding diabetic adults who were using ACE inhibitors (12% [n=132]). Compared with adults with type 2 DM and no CRI, adults with type 2 DM and CRI were more likely to have macroalbuminuria (19% vs 5%), microalbuminuria (45% vs 32%), and diabetic retinopathy (28% vs 15%). Among all adults with type 2 DM (previously diagnosed and newly diagnosed by ADA criteria) with macroalbuminuria (population estimate, 0.5 million), 31% (n=56) had diabetic retinopathy (population estimate, 0.2 million). Among individuals with microalbuminuria (population estimate, 3.0 million), 21% (n=107; population estimate, 0.6 million) had diabetic retinopathy. Thirteen percent (n=84; population estimate, 0.6 million) with diabetic retinopathy did not have microalbuminuria or macroalbuminuria. When we excluded ACE inhibitor users, diabetic retinopathy was noted in 31% (n=42) of adults with macroalbuminuria, 21%
Table 2. Prevalence of Chronic Renal Insufficiency Among Subjects 40 Years of Age or Older With Type 2 Diabetes Mellitus*

<table>
<thead>
<tr>
<th>GFR, mL/min per 1.73 m² BSA†</th>
<th>Subjects With Type 2 Diabetes Mellitus, % (95% Confidence Interval)‡</th>
<th>Population Estimate in Millions (95% Confidence Interval)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 (sampled n = 981)</td>
<td>87 (84-90)</td>
<td>7.3 (6.4-8.1)</td>
</tr>
<tr>
<td>59-30 (sampled n = 151)</td>
<td>12 (9-15)</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>&lt;30 (sampled n = 20)</td>
<td>1 (0.4-1.6)§</td>
<td>0.1 (0.03-0.1)§</td>
</tr>
</tbody>
</table>

*Excludes subjects with type 2 diabetes mellitus without gradeable funduscopic examinations or missing urine data.
†Glomerular filtration rate (GFR) calculated with the Modification of Diet in Renal Disease Study formula.20
‡Subjects with newly diagnosed type 2 diabetes mellitus as defined by American Diabetes Association criteria.13 Percentages are based on weighted data.
§Number of sample subjects too small to provide stable population estimate.

Table 3. Presence of Microalbuminuria and Macroalbuminuria and Retinopathy in Subjects With Type 2 Diabetes Mellitus With Chronic Renal Insufficiency*

<table>
<thead>
<tr>
<th>Subjects With Type 2 Diabetes Mellitus, % (95% Confidence Interval)‡</th>
<th>Population Estimate in Millions (95% Confidence Interval)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria (sampled n = 64)</td>
<td>45 (31-59)</td>
</tr>
<tr>
<td>Macroalbuminuria (sampled n = 47)</td>
<td>19 (10-28)</td>
</tr>
<tr>
<td>Retinopathy (sampled n = 58)</td>
<td>28 (10-62)</td>
</tr>
<tr>
<td>No retinopathy or albuminuria (sampled n = 51)†</td>
<td>30 (21-39)</td>
</tr>
</tbody>
</table>

*Includes angiotensin-converting enzyme users. Chronic renal insufficiency defined as glomerular filtration rate less than 60 mL/min per 1.73 m² body surface area calculated with the Modification of Diet in Renal Disease Study formula.20
†Newly diagnosed type 2 diabetes mellitus defined by American Diabetes Association criteria.13 Percentages are based on weighted data.
‡Albuminuria includes microalbuminuria or macroalbuminuria.

(n=83) with microalbuminuria, and 12% (n=70) of adults without macroalbuminuria or microalbuminuria.

Among adults with type 2 DM and CRI (sampled n=171), diabetic retinopathy was noted in 28% (n=58), while the frequency of microalbuminuria and macroalbuminuria was 45% (n=64) and 19% (n=47), respectively (Table 3). Retinopathy and albuminuria (microalbuminuria or macroalbuminuria) were both absent in 30% (n=51) of adults with type 2 DM and CRI. The population estimate of adults with type 2 DM and CRI in the absence of diabetic retinopathy and albuminuria was approximately 0.3 million. After excluding diabetic adults who were using ACE inhibitors, 33% (n=43) with CRI had no retinopathy or albuminuria.

When we used the WHO criteria to define newly diagnosed type 2 DM, 43% of adults with type 2 DM and a GFR less than 60 mL/min per 1.73 m² BSA did not have retinopathy or albuminuria.

COMMENT

In this nationally representative sample of adults with type 2 DM in the United States, we noted the absence of diabetic retinopathy and albuminuria (microalbuminuria or macroalbuminuria) in 30% of individuals with a GFR less than 60 mL/min per 1.73 m² BSA when we used the ADA criteria to define newly diagnosed type 2 DM. Use of the WHO criteria to define newly diagnosed type 2 DM showed similar results.

Currently, almost half of all ESRD in individuals initiating renal replacement therapy in the United States is attributed to type 2 DM,3 and the number of individuals with type 2 DM and ESRD is projected to almost double over the next 10 years.4 Therefore, improved understanding of the etiology of CRI among adults with type 2 DM will be paramount in controlling this epidemic of kidney failure.

The renal pathology of classic diabetic glomerulosclerosis (in both type 1 and 2 adults) is characterized by increased basement membrane thickness, diffuse mesangial sclerosis with nodular formation, hyalnosis, microaneurysm, and hyaline arteriolosclerosis.23 These pathological lesions lead to albuminuria and are accompanied by other systemic manifestations of microvascular disease, such as proliferative retinopathy.6 Among individuals with type 1 DM, diabetic retinopathy is present in virtually all patients with diabetic nephropathy.25 However, among patients with type 2 DM, the concordance rate between diabetic retinopathy and nephropathy is lower.25 Nevertheless, the presence of retinopathy does support a diagnosis of diabetic nephropathy. Indeed, Parving et al9 stated that the absence of retinopathy greatly reduced the likelihood that albuminuria was due to diabetic glomerulosclerosis in type 1 or type 2 DM. In the absence of retinopathy or albuminuria in 30% of adults with a GFR less than 60 mL/min per 1.73 m² BSA, classic diabetic glomerulosclerosis is unlikely to be the underlying renal pathology.

What could be the reason for decreased GFR in adults with type 2 DM who do not have retinopathy or albuminuria? A number of factors may contribute to nephron loss, including “age-associated” renal senescence, interstitial fibrosis, and ischemic vascular disease, such as atherosclerotic involvement of the renal artery (and smaller-caliber arteries). Moreover, we agree with Rychlik et al10 that cholesterol emboli are likely an underappreciated contributor to the burden of CRI among patients with type 2 DM.

Because a substantial number of adults with type 2 DM with reduced GFR do not have retinopathy or albuminuria, the current strategy of screening for microalbuminuria and retinopathy alone among type 2 diabetic adults may not be sufficient for the early detection of renal disease. In addition, the serum creatinine level is an insensitive measure of GFR loss. The National Kidney Foundation now recommends that physicians should monitor GFR using prediction equations such as the MDRD formula26 or the Cockcroft-Gault formula26 in addition to assessing blood pressure, funduscopic changes, and urine albumin excretion in adults with type 2 DM.12 The findings of this study also suggest that more research is needed on the association between lipid-lowering medi-
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