Macroalbuminuria and Renal Pathology in First Nation Youth With Type 2 Diabetes

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OBJECTIVE — To determine the prevalence of macroalbuminuria and to describe the clinical and renal pathological changes associated with macroalbuminuria in a population of Canadian First Nation children and adolescents with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We conducted a retrospective chart review at a single tertiary care pediatric diabetes center, and a case series was constructed. We collected data on microalbuminuria (≥3 mg/mmol creatinine [26.5 mg/g]) and macroalbuminuria (≥28 mg/mmol creatinine [247.5 mg/g]), estimated glomerular filtration rate, renal pathology, and aggravating risk factors (poor glycemic control, obesity, hypertension, glomerular hyperfiltration, hypercholesterolemia, smoking, and exposure to diabetes in utero).

RESULTS — We reviewed 90 charts of children and adolescents with type 2 diabetes. A total of 53% had at least one random urine albumin-to-creatinine ratio ≥3 mg/mmol (26.5 mg/g). There were 14 of 90 (16%) who had persistent macroalbuminuria at or within 8 years of diagnosis of diabetes. Of these 14 subjects, 1 had orthostatic albuminuria and 3 had spontaneous resolution of albuminuria. A total of 10 had renal biopsies performed. There were 9 of 10 who exhibited immune complex disease or glomerulosclerosis, and none had classic diabetic nephropathy.

CONCLUSIONS — This study suggests that the diagnosis of renal disease in children with type 2 diabetes cannot be reliably determined by clinical and laboratory findings alone. Renal biopsy is necessary for accurate diagnosis of renal disease in children and adolescents with type 2 diabetes and macroalbuminuria. The additional burden of nondiabetic kidney disease may explain the high rate of progression to end-stage kidney failure in this population.

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The increasing prevalence of type 2 diabetes in children and youth has been well recognized over the past 2 decades. The geographic area in central Canada including Manitoba and northwestern Ontario has the highest reported prevalence of type 2 diabetes in youth in Canada. The prevalence is 1% in First Nation children age 4–19 years in specific communities from this region (1). A total of 95% of the youth with type 2 diabetes from this region have Canadian First Nation heritage.

Hepatic nuclear factor (HNF)-1α is a transcription factor expressed in many tissues including the liver, intestine, pancreatic β-cell, and kidney. A private polymorphism of this gene (HNF-1α G319S) is found in the Oji-Cree of Manitoba and northwestern Ontario. It has been associated with early-onset diabetes in this population and demonstrates a genotype-phenotype relationship (2,3).

Youth-onset type 2 diabetes is associated with an increased incidence of end-stage kidney disease (ESKD) and mortality in middle-age in the Pima Indians of the southwestern U.S. (4). ESKD has been reported before the age of 30 years in Canadian First Nation young adults who had type 2 diabetes diagnosed in adolescence (5). In this series, the cause of ESKD was attributed to diabetic nephropathy, since proteinuria was detected after the onset of diabetes. Renal biopsy was not performed to confirm the diagnosis and/or exclude other causes of kidney disease. Several small studies have reported an increased frequency (27–40%) of microalbuminuria in youth with type 2 diabetes (6,7). These studies assessed microalbuminuria at a single time point and did not describe evolution over time.

Primary nondiabetic renal disease is frequent in the First Nation population. Canadian First Nation children without diabetes have an increased rate of both congenital and acquired primary renal disease (8). First Nation adults also have an increased risk ratio for nondiabetic ESKD (9). In both First Nation children and First Nation adults, the most common renal pathology is primary glomerulonephritis. Childhood obesity is also increasingly common in this population and independently predisposes to secondary focal glomerulosclerosis and renal failure in children and adults (10,11).

Diabetes-associated ESKD is seven times more frequent in First Nation compared with non–First Nation people in Canada (12). There is also a twofold increase in premature mortality rate in First Nation adults with diabetes compared with individuals with diabetes from the general Canadian population (12). It is thus imperative to describe and understand the natural history and etiology of renal disease in First Nation youth with type 2 diabetes as the first step in the development of intervention and treatment strategies in this vulnerable population.

The frequency of macroalbuminuria has not previously been described in the pediatric population with type 2 diabetes, nor has the nature of the associated renal pathology. The objectives of this study were to determine the prevalence of macroalbuminuria and to characterize the clinical and renal pathological changes associated with macroalbuminuria in a population of First Nation children and adolescents with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Clinic charts of children and adolescents with type 2 diabetes followed at the Diabetes Education Re-

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source for Children and Adolescents (DER-CA) at the Winnipeg Children's Hospital, MB, Canada, were reviewed between September and October 2003, and a case series of patients with macroalbuminuria was constructed. Case subjects were identified through the clinical database maintained at the DER-CA. The DER-CA is associated with the only tertiary care pediatric hospital in the province of Manitoba, Canada, with a catchment population of 1.2 million people.

Height, weight, blood pressure, self-declared ethnicity, sex, age, self-reported smoking status, history of prenatal exposure to hyperglycemia, and laboratory data (A1C, albumin, creatinine, urine albumin-to-creatinine ratio [ACR] and/or timed urinary collections for albumin and protein, and HNF-1α G319S genotype) were extracted from the chart. BMI was calculated and presented as BMI *z* score. Obesity was defined as ≥95th percentile for age and sex (13). Blood pressure percentiles were defined using the National Heart, Lung, and Blood Institute blood pressure levels for age, sex, and height percentile (14), and fasting cholesterol level was defined according to the National Cholesterol Education Program data (acceptable <4.4 mmol/l). Glomerular filtration rate was estimated using the Schwartz formula and expressed as ml/min per 1.73 m^2.

The diagnosis of diabetes was made according to the criteria of the American Diabetes Association (15). The diagnosis of type 2 diabetes was based on clinical criteria including presence of obesity, acanthosis nigricans, family history of type 2 diabetes, and family heritage from a high-risk ethnic group (16). When available, the absence of diabetes-associated autoantibodies was used to support the diagnosis of type 2 diabetes (17).

Microalbuminuria was defined as urine ACR 3–28 mg/mmol (26.5–247.5 mg/g) or quantitatively as 30–300 mg albumin/24 h. Macroalbuminuria was defined as urine ACR >28 mg/mmol (247.5 mg/g) or quantitatively as >300 mg albumin/24 h. Persistent micro- or macroalbuminuria was defined as two of three positive samples over 6 months. These patients underwent split timed-urine collections and/or a minimum of three first-morning urine collections to identify subjects with orthostatic proteinuria. The standard approach to treatment of albuminuria in our clinic is the use of an ACE inhibitor and investigations aimed at confirmation of etiology.

Renal biopsy was performed in patients with persistent nonorthostatic macroalbuminuria (>28 mg/mmol [247.5 mg/g]). Standard renal histology techniques included light microscopy (hematoxylin and eosin, periodic acid-Schiff, periodic acid methenamine silver, trichrome, sirius red), immunofluorescence studies (IgG, IgA, IgM, C1q, C3, properdin, fibrinogen, κ, and λ), and electron microscopy. Renal biopsy samples were considered adequate if they contained a minimum of two cores with a minimum of 10 glomeruli. All biopsies were interpreted by a single pathologist (I.W.G.) who is a specialist renal pathologist. For those undergoing renal biopsy, clinical and biochemical findings are reported at the time of biopsy or the most proximal clinic visit.

A1C was measured using the DCA 2000 immunoassay (normal range 4–6%, Bayer Diagnostics). Fasting total cholesterol was measured before April 2003 using the Hitachi 917 Clinical Chemistry Autoanalyzer (Roche) and on the Roche Modular Analytics Analyzer after 2003. Plasma and urine creatinine were measured by kinetic colorimetric assay using the Jaffe method. Urine albumin was measured by immunoturbidimetric assay using an anti-excess reagent. Genotyping for the HNF-1α G319S polymorphism was performed by the Molecular Genetic Laboratory (Health Sciences Centre, Winnipeg, MB, Canada).

RESULTS — All clinical records of children and adolescents with type 2 diabetes followed at the DER-CA during the study period were reviewed. All patients had random urine ACR done at diagnosis and annually unless abnormal. If elevated, a first-morning ACR was performed at each clinical visit (typically every 4 months). Of the 90 records reviewed, 88 (98%) were of self-declared First Nation or Métis heritage. The male-to-female ratio was 1:1.2. The mean age of this population was 15.2 years with a range from 10 to 19 years. Mean duration of diabetes was 2.5 years (range 0.4–5). Mean BMI *z* score at diagnosis was 1.88 (range −1.17 to 2.95). Approximately 80% lived outside urban centers in rural or remote settings.

Of the 90 children and adolescents, 48 (53%) had at least one ACR >3 mg/mmol (>26.5 mg/g). A total of 26 of 90 (29%) had an elevated ACR at diagnosis of diabetes. A total of 14 of 90 (16%) had persistent macroalbuminuria. All youth with persistent macroalbuminuria were of self-declared First Nation descent.

Of the 14 with persistent macroalbuminuria, 1 was shown with further testing to have orthostatic albuminuria, 3 had resolution of the albuminuria over a 6-month period awaiting workup and continued to be monitored closely, and 10 had a renal biopsy (3 female and 7 male).

Of those biopsied, the mean age at diagnosis of diabetes was 12 years (range 9.7–16.7). The duration of diabetes at the time of biopsy ranged from 4 months to 8 years. Four of these 10 youth had macroalbuminuria at diagnosis. A total of 7 of 10 were on an ACE inhibitor at the time of biopsy (case subjects 1, 2, 3, 4, 5, 9, and 10). The remaining three were started on an ACE inhibitor after biopsy (case subjects 6, 7, and 8). These three had all been diagnosed with diabetes for <12 months. The mean A1C in the year preceding biopsy ranged from 5.3 to 12.5%. In 6 of 10 individuals, systolic blood pressure was above the 95% percentile for age and sex. Fasting total cholesterol was elevated in all 10 (Table 1). A total of 4 of 10 were self-reported smokers (2 girls, 2 boys), and 6 of 10 were exposed in utero to diabetes, either from conception (prepregnancy type 2 diabetes) or during pregnancy (gestational). The HNF-1α G319S polymorphism haplotype was present in 4 of 7 patients in whom genotyping was available (Table 1). Seven of 10 were obese with unbalanced distribution among individuals with the HNF-1α G319S polymorphism haplotype present (mean BMI *z* score 1.4) and those without (mean BMI *z* score 2.6).

Biopsy results indicate significant nondiabetic renal pathology (Table 2). Two or three cores were obtained for each patient with 12–25 total glomeruli per sample. Histological changes typically associated with diabetes were infrequently noted and were insufficient to make a definitive diagnosis of diabetic nephropathy in any of the cases. Diabetes-related lesions seen included focal, mild hyaline arteriolosclerosis (case subject 10), focal and mild glomerular basement membrane thickening (case subjects 6 and 10), and a single Bowman's capsular drop (case subject 6).

Half of the patients exhibited evidence of immune complex deposition that was either IgA ($n = 3$) or "full-house" immune complex deposition ($n = 2$). In the latter group, a diagnosis of systemic lupus was eventually confirmed in both. One of these (case subject 1) had World

Table 1—*Patient characteristics*

	Sex	Age at diagnosis (years)	Age at biopsy (years)	BMI *z* score	Systolic blood pressure >95th percentile	Mean A1C (%)*	Fasting total cholesterol (mmol/l)	Maternal diabetes during pregnancy	HNF-1α G319S polymorphism
1	F	10.0	17.8	1.0	No	10.1	5.09	No	Homozygote
2	M	12.3	12.9	2.9	Yes	6.3	5.02	Pre-pregnancy	NA
3	M	11.1	15.1	1.8	Yes	11.2	8.26	No	Heterozygote
4	M	13.9	17.4	2.1	No	8.5	4.41	No	Wild-type
5	F	13.3	15.6	2.6	No	6.0	6.00	No	NA
6	M	10.3	10.7	1.1	No	8.5	5.26	Gestational	Heterozygote
7	M	16.7	17.1	2.8	Yes	6.0	4.71	Gestational	NA
8	M	11.3	12.5	2.7	Yes	12.5	5.94	Pre-pregnancy	Wild type
9	M	12.3	13.5	2.5	Yes	5.3	5.00	Gestational	Wild type
10	F	9.7	17.7	1.6	Yes	11.0	6.44	Gestational	Heterozygote

*Mean A1C in 12 months before biopsy. NA, not available.

Health Organization (WHO) Class V lupus with membranous nephropathy changes; the other (case subject 5) had WHO class IIB mesangial lupus nephritis. In those with IgA deposition, there was minimal-to-mild mesangial proliferation despite significant albuminuria.

A total of 90% of biopsies had at least one glomerulus exhibiting segmental or global glomerulosclerosis, and 60% had more than one glomerulus involved. In 70%, there was focal segmental glomerulosclerosis, with three cases showing perihilar lesions, one case showing glomerular tip lesion, and three cases showing peripheral segmental lesions. In 80%, the glomeruli were diffusely enlarged (case subjects 1, 2, 3, 4, 5, 7, 8, and 9).

Complete and accurate timed urine collections to calculate creatinine clearance are difficult to obtain reliably, and thus the Schwartz estimate was used. To validate this approach, a subcohort analysis was done using all available urine collections for the patients reported in this study ($n = 90$). Only nine urine collections were suitable and complete (a minimum of 8 mmol/day [0.13 $mmol \cdot kg^{-1} \cdot day^{-1}$] of creatinine excretion). The urinary creatinine clearance was calculated and correlated with the Schwartz estimated glomerular filtration rate (eGFR), using $k = 0.7$ for boys >12 years old, and $k = 0.55$ for the remainder. Schwartz eGFR showed good correlation ($r = 0.67$, $P = 0.046$) and overestimated GFR in pair-wise comparison by 12 ± 15% (data not shown). The mean body surface area in this subcohort was 2.1 ± 0.4, so as a conservative measure, the eGFR corrected to 1.73 m^2 rather than the absolute clearance was reported.

For the patients reported in this series, all but one patient (subject 9) had elevated eGFR suggesting hyperfiltration,

Table 2—*Hyperfiltration, albuminuria, and histological findings*

	eGFR‡	Urine ACR (mg/mmol)	Focal segmental glomerulosclerosis	Global glomerulosclerosis	Mesangial proliferation	Immunofluorescence	Other pathological findings
1	156	>270*	—	—	Mild	Mesangial and capillary loop IgG, IgA, IgM, C3, C1q	Subepithelial and mesangial deposits, epimembranous spikes
2	204	66	2/12 perihilar	1/12	Mild	Mesangial IgA	Focal mild chronic tubulointerstitial damage
3	162	105	—	1/25	—	Negative	—
4	144	61	3/9 perihilar	1/9	—	Negative	Mild-moderate chronic tubulointerstitial damage
5	415	17†	2/19	—	Mild	Mesangial and capillary loop IgG, IgA, IgM, C3, C1q	Paramesangial deposits and mesangial sclerosis
6	194	178	1/22	1/22	—	Negative	Mild GBM thickening, capsular drop
7	215	117	1/22	1/22	—	Negative	—
8	190	215	1/14 tip lesion	—	Minimal	Mesangial IgA	Focal arteriolosclerosis
9	118	290	5/13 perihilar	1/13	—	Negative	Mild-moderate chronic tubulointerstitial damage
10	210	23†	—	1/18	Segmental mild	Mesangial IgA	Focal arteriolosclerosis, mild GBM thickening

*Estimated based on proteinuria of 3.6 g/day. †Persistent macroalbuminuria documented in these patients; ACR most proximal to time of biopsy demonstrated microalbuminuria. ‡eGFR (ml/min per 1.73 m^2) estimated by calculation of size-adjusted creatinine clearance using the Schwatrz formula. When ACR >200 mg/mmol, the urine total protein-to-creatinine ratio is reported. GBM, glomerular basement membrane.

and 40% exhibited hyperfiltration in excess of 200 ml/min per 1.73 m^2. The patient with "normal" eGFR (subject 9) and 38% segmental glomerulosclerosis at the time of biopsy had demonstrable hyperfiltration at initial diagnosis (eGFR = 217 ml/min per 1.73 m^2) and has continued to have declining glomerular filtration rate in follow-up (at age 16 years, eGFR = 44 ml/min per 1.73 m^2).

Three cases exhibited nephrotic range proteinuria (ACR >200 mg/mmol [1,768 mg/g]), including one patient whose biopsy showed membranous nephropathy changes. Two of these three (subjects 1 and 9) had hypoalbuminemia (serum albumin: 27 and 32 mg/l, respectively). Two cases (5 and 10) with persistent macroalbuminuria before biopsy had ACR <28 mg/mmol (<247.5 mg/g) at the time of biopsy. In these cases, concomitant immune complex deposition was noted in association with mild mesangial proliferation. The remaining cases had glomerulosclerosis and/or immune complex disease of sufficient severity to account for the presence of macroalbuminuria.

CONCLUSIONS — Persistent macroalbuminuria was documented in 16% of this population of children and adolescents with type 2 diabetes at, or within 8 years of, diagnosis. The biopsy results demonstrate that nondiabetic renal disease in the form of immune complex disease or glomerulosclerosis is the most common etiology of macroalbuminuria in this young population.

In adults with type 2 diabetes, renal biopsy frequently identifies nondiabetic pathology. In a multicenter study of adults with type 2 diabetes undergoing renal biopsy, 45% (177/393) were diagnosed with nondiabetic glomerular disease, either superimposed on diabetic nephropathy (17% of all biopsies) or more commonly without underlying diabetic disease (28%) (18). The most common disease superimposed on diabetic nephropathy was postinfectious glomerulonephritis, and the most common glomerular diseases without underlying diabetic changes were membranous glomerulonephritis, IgA nephropathy, and minimal change disease or focal segmental glomerulosclerosis. This is the first report to our knowledge of a similar finding in the pediatric population. Our study confirms that renal pathology in children with type 2 diabetes cannot be reliably predicted by clinical and laboratory findings alone and that renal biopsy is necessary for accurate diagnosis of renal disease in such patients.

HNF-1α is involved in the differentiation of the nephron (19). Other dominant mutations of the HNF-1α gene are characterized by reduced renal tubular reabsorption of glucose (20). While the effect of the private Oji-Cree polymorphism of the HNF-1α gene on the development and function of the kidney is not known, the observation that the polymorphism is present in 4 of 7 in whom genotyping was available is intriguing. We speculate that this polymorphism may play a role in the development of the renal pathology found in this population.

Obesity is a well-recognized risk factor for insulin resistance and the development of type 2 diabetes. Obesity is associated with glomerular hyperfiltration and the development of glomerulosclerosis and kidney failure independent of the presence of diabetes (10,11). The biologic mechanisms explaining this association are not fully understood but appear to be mediated through both hemodynamic and hormonal effects. Those include increased renal blood flow, GFR, glomerular filtration pressure and filtration fraction, hyperinsulinemia, and activation of the renin-angiotensin system (11).

Furthermore, medications such as ACE inhibitors, which may mitigate hyperfiltration injury, are beneficial in this context (11,21). In our series, all of the patients without the HNF-1α G319S polymorphism had a BMI *z* score >2. Although 8 of 10 patients had a body surface area >1.73 m^2 (mean 2.1 m^2), the eGFR corrected to 1.73 m^2 was reported instead of the absolute GFR. By this conservative estimate, all patients currently or previously had an eGFR >140 ml/min per 1.73 m^2 and 4 of 10 had eGFR >200 ml/min per 1.73 m^2, which is higher than is reported in adults with recent-onset type 2 diabetes (22). In those with obesity, this was associated histologically with glomerulomegaly and significant glomerulosclerosis. The contribution of obesity, diabetes, or the combination of the two to the hyperfiltration seen cannot be differentiated. However, the presence of obesity and hyperfiltration likely contributes to the evolution of renal injury in this population and is likely additive to the other effects that are typically associated with hyperglycemia.

In humans, nephrogenesis occurs between the 5 and 36 weeks of gestation, and new nephron formation ceases after 36 weeks of gestation (23). In the rat model, exposure to hyperglycemia during gestation decreases nephron number in the offspring by 35%. Minor elevations in glucose are associated with abnormal metanephros development in the offspring of streptozotocin-treated diabetic rats (24). A decrease in nephron number may predispose to renal pathology in later life due to a reduction in renal reserve. Both glomerulomegaly and glomerulosclerosis are associated with decreased nephron number, likely resulting from the decreased filtration surface and subsequent glomerular damage resulting from hyperfiltration. In young adult Pima Indians with type 2 diabetes, exposure to diabetes in utero increases the odds of having an elevated ACR by almost fourfold (25). A total of 60% of the youth in our series were exposed to either gestational or pregestational type 2 diabetes. We postulate that this may have resulted in a decreased nephron mass, accelerating their presentation with macroalbuminuria. As rates of youth-onset type 2 diabetes increase, the frequency of fetal exposure to a diabetic environment will also increase. This may have significant detrimental effects on the renal health of subsequent generations.

Multiple risk factors for aggravating renal disease were found in this cohort, including obesity, glomerular hyperfiltration, hypertension, hyperlipidemia, smoking, poor glycemic control, and fetal exposure to a diabetic environment. This multiplicity of risk factors may explain the progression to ESRD at a relatively young age that has been observed in this population (5). Aggressive treatment of modifiable risk factors is warranted to prevent progression of renal disease and to prevent early cardiovascular disease associated with both renal disease and these aggravating risk factors.

Limitations to this report include the inability to obtain adequate, timed urine samples in all patients. Despite attempts, this testing presents significant practical challenges, particularly in adolescents and in remote communities. In addition, the findings of this report may not be generalizable to other pediatric populations affected by type 2 diabetes.

Our study suggests that the diagnosis of renal disease in children with type 2 diabetes cannot be reliably determined by clinical and laboratory findings alone. Renal biopsy is necessary for accurate diagnosis in this population. This finding needs confirmation in other populations

to ensure its generalizability. The incidence of type 2 diabetes in First Nation youth is increasing at an alarming rate. The additional burden of nondiabetic kidney disease may contribute to the high rate of progression to end-stage kidney failure in this population.

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