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Kidney Disease in Childhood-Onset Diabetes:

Commentary on Amin R, Widmer B, Prevost AT, et al: Risk of Microalbuminuria and Progression to Macroalbuminuria in a Cohort With Childhood Onset Type 1 Diabetes: Prospective Observational Study. *BMJ* 336:697–701, 2008.

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The increasing prevalence of obesity in children and adolescents in many parts of the world is strongly implicated in the increasing incidence of type 1 and type 2 diabetes during childhood.^{1,2} Whether youth affords some protection from the vascular complications of diabetes is uncertain, but the importance of this question is clear given the major public health and economic impact associated with earlier development of diabetic complications, including kidney disease. Some studies suggested that the prepubertal years of diabetes contribute less to the risk of diabetic kidney disease than the postpubertal years; however, this concept is controversial.^{3–8} Nevertheless, up to 40% of persons with type 1 diabetes develop overt diabetic nephropathy within 20 to 25 years of the onset of diabetes.

Most studies that examine the risk of microalbuminuria and diabetic nephropathy in patients with type 1 diabetes are based on prevalence cohorts, often with short-term follow-up, and included patients with varying durations of diabetes.^{9–12} Accordingly, selection and survivor biases may be introduced that impact on the assessment of the role of age at onset of diabetes on the development and progression of diabetic kidney disease. The Steno group¹³ recently described the frequency of microalbuminuria and macroalbuminuria in an inception cohort of patients who were followed up from the onset of type 1 diabetes. Age at the diagnosis of diabetes averaged 27.5 years in this cohort, and the investigators reported that after about 18 years of diabetes, the cumulative incidences of microalbuminuria and macroalbuminuria were 33.6% and 14.6%, respectively. They also observed that permanent regression from microalbuminuria to normoalbuminuria was rare, with most of those who experienced regression relapsing to microalbuminuria. Their findings suggest that the development of microalbuminuria in older-onset type 1 diabetes is often associated with progressive nephropathy.

WHAT DOES THIS IMPORTANT STUDY SHOW?

The Oxford regional prospective study is a population-based inception cohort of children with type 1 diabetes. It is designed to determine the course of microalbuminuria in persons who develop type 1 diabetes during childhood and adolescence.¹⁴ The goal of the present study¹⁵ is to identify predictors for the development of microalbuminuria and macroalbuminuria in this cohort and determine the prognostic value of microalbuminuria for progression to macroalbuminuria. The 527 children who participated in the study were identified from the St Bartholomew's Oxford diabetes register during a 10-year period and

were recruited for the study within 3 months of diagnosis. Participants, who were all younger than 16 years at enrollment, were invited to receive annual research examinations that included measures of height, weight, and blood pressure and collection of 3 consecutive early-morning (first void) urine specimens for measurement of urinary albumin-creatinine ratio.

Microalbuminuria was defined as a urinary albumin-creatinine ratio of 3.5 to 35 mg/mmol (31 to 309 mg/g) in men and 4.0 to 47 mg/mmol (45 to 415 mg/g) in women in at least 2 consecutive samples from the annual research examination. Persistent microalbuminuria was defined as the presence of microalbuminuria at every examination after it was originally detected; and intermittent microalbuminuria, as a positive result during a research examination followed by regression to normoalbuminuria and a subsequent return to microalbuminuria.

Macroalbuminuria was defined as a urinary albumin-creatinine ratio greater than 35 mg/mmol (>309 mg/g) in men and greater than 47 mg/mmol (>415 mg/g) in women. Blood samples were collected for measurement of glycated hemoglobin (HbA_{1c}).

During a mean follow-up of 9.8 years, 135 patients (26%) developed microalbuminuria. More women (n = 72; 53%) than men (n = 63; 47%) developed microalbuminuria ($P = 0.03$). The cumulative incidence of microalbuminuria, determined by using a life-table method, was 25.7% after 10 years and 50.7% after 19 years of diabetes. Although the cumulative incidence of microalbuminuria was lower after 5 or 10 years in those who developed diabetes as young children, after 15 years of diabetes, the cumulative incidence was similar in all age groups. In a multivariate model, female sex and poor glycemic control predicted microalbuminuria; however, blood pressure, smoking, and age at onset of diabetes did not. After adjustment for duration of diabetes, the risk of microalbuminuria increased by 39% for each 1% increase in HbA_{1c} level. Microalbuminuria was persistent in 48% of the participants.

Eighteen participants developed macroalbuminuria, and the cumulative incidence of progression from microalbuminuria was 13.9% after 19 years of diabetes. Participants treated with angiotensin-converting enzyme inhibitors had a greater rate of progression to macroalbuminuria than those who did not receive these medicines, although the number of participants receiving such treatment was small (n = 20). In a multivariate model, poor glycemic control and persistent or intermittent microalbuminuria predicted macroalbuminuria; however, sex, blood pressure, smoking, and age at onset of diabetes did not. After adjustment for duration of diabetes, the risk of macroalbuminuria increased by 42% for each 1% increase in HbA_{1c} level. The risk of macroalbuminuria was nearly 28-fold greater in participants with persistent microalbuminuria than in those without.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

The cumulative incidence of microalbuminuria in the population-based Oxford regional prospective study was greater than the incidence reported previously in clinic-based longitudinal studies of type 1 diabetes in children who were not from inception cohorts.^{16–18} The cumulative incidence was also greater than that observed in the Steno Clinic inception cohort, who developed type 1 diabetes at a mean age of 27.5 years.¹³ In the Steno cohort, the cumulative incidence of microalbuminuria was 33.6% after 18 years of diabetes compared with 50.7% after 19 years in the Oxford cohort. However, the cumulative incidence of macroalbuminuria in the childhood inception cohort¹⁵ was similar to that in the adult inception cohort¹³ (13.9% and 14.6%, respectively), suggesting that progression to more advanced diabetic kidney disease is dependent on the duration of diabetes regardless of the age at onset.

Glycemic control is a widely recognized predictor of increased albuminuria in patients with childhood-onset and older-onset diabetes. However, the role of blood pressure may be more prominent in those with older-onset diabetes, although this finding is not consistent across studies.^{9–13,15–18} In the type 1 diabetes inception cohorts, more women developed

microalbuminuria in those with childhood-onset diabetes,¹⁵ whereas more men developed microalbuminuria in those with adult-onset diabetes¹³ (Table 1). The investigators propose that these differences may be caused in part by sex steroids, which may also influence the timing of the first appearance of microalbuminuria, but not its cumulative incidence, in the childhood-onset cohort.^{13,15}

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The Oxford prospective observational study provides further evidence that the risk of progressive diabetic kidney disease is equivalent for a given duration of diabetes in both youth- and older-onset type 1 diabetes. This finding, which has also been reported in patients with type 2 diabetes,^{19,20} has significant implications for those who develop diabetes in youth. If the development of macroalbuminuria heralds subsequent progression to kidney failure at a rate not influenced by age, the major kidney complications of diabetes will appear at an earlier age in those with youth-onset disease, requiring increased and sustained health services for longer periods than in those with older-onset disease. Studies are needed to examine the rate of progression from macroalbuminuria to kidney failure and other major complications of diabetes in persons with youth-onset type 1 or type 2 diabetes and to compare these rates with those in persons with older-onset diabetes.

Such studies have already been done in the Pima Indians, a well-characterized population with a very high prevalence of type 2 diabetes and diabetic kidney disease, and these studies provide compelling evidence to justify the concerns expressed above. Although the appearance of type 2 diabetes in youth has only recently been described in other populations, it was first reported in the Pima Indians in the 1970s.²¹ Diabetes in the Pima Indians is entirely type 2,^{22–27} and those who develop type 2 diabetes before 20 years of age have a duration-specific incidence rate of proteinuria (protein-creatinine ratio ≥ 0.5 mg/g) virtually identical to that in patients with adult-onset type 2 diabetes.¹⁹ Moreover, youth-onset diabetes is associated with a nearly 5-fold increase in the incidence of end-stage kidney disease between 25 and 54 years of age relative to older-onset disease, and the death rate in Pima Indians with youth-onset diabetes is 3-fold greater in midlife than in those without diabetes.²⁰ These findings reflect the potential negative impact that early onset of diabetes has on longevity and quality of life.

Ethnic differences may influence the rate of diabetic kidney disease progression in those with youth-onset diabetes. The Multinational Study of Vascular Disease in Diabetes reported that American Indians (including Pimas) from Arizona and Oklahoma who had type 2 diabetes diagnosed before 30 years of age had a greater age-adjusted incidence rate of albuminuria, proteinuria, and kidney failure during a mean follow-up of 9.5 years than Asian and European diabetic populations with onset of type 2 diabetes at the same age.^{28,29} The development of diabetes in youth also may increase the risk of cardiovascular disease in midlife, particularly in those who develop kidney disease. In a large predominantly white population, adults with a diagnosis of type 2 diabetes between 18 and 44 years of age had 8 times the incidence of cardiovascular complications than nondiabetic age- and sex-matched control participants, whereas individuals with a diagnosis of diabetes after 45 years of age had 4 times the rate.³⁰

Because of concerns that youth-onset diabetes, regardless of its type, leads to substantially increased complication rates and mortality in middle age, clinicians should focus their efforts on preventing or delaying the onset of diabetes through lifestyle interventions in children who are at risk because of their obesity, ethnicity, or strong family history of diabetes. Efforts to reduce obesity and increase physical activity apply equally to children at risk of type 1 or type 2 diabetes because increasing obesity is strongly implicated in the increasing incidence of both types of childhood diabetes.^{1,2}

Clinicians should also aggressively manage kidney disease that appears in children with either type of diabetes. However, management of these patients with childhood-onset disease presents unique challenges because neither the safety nor efficacy of medicines typically used to treat adults with diabetic kidney disease are known with certainty in children. Safety and efficacy concerns are of particular importance in young diabetic women of childbearing potential because angiotensin-converting enzyme inhibitors and angiotensin receptor blockers pose significant risks to the fetus in early pregnancy.^{31,32} Accordingly, clinical trials to examine the renoprotective efficacy of inhibition of the renin-angiotensin system need to be conducted in children and young adults with diabetes and early kidney disease, and these age groups should be included in future studies of other promising therapeutic agents for patients with diabetic kidney disease.

In summary, the findings of the Oxford prospective observational study indicate that the probability of progression to macroalbuminuria is strongly dependent on the duration of type 1 diabetes and is not influenced by the age at onset of diabetes. Early and appropriate lifestyle interventions in children and young adults to prevent or delay the onset of diabetes combined with early and appropriate therapeutic management of those with diabetic kidney disease is required if we hope to reduce the rate of development and progression of diabetic kidney disease in these age groups. What constitutes appropriate lifestyle intervention and therapeutic management must be determined by clinical trials in these age groups.

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References

1. Knip M, Reunanen A, Virtanen SM, Nuutinen M, Viikari J, Akerblom HK. Does the secular increase in body mass in children contribute to the increasing incidence of type 1 diabetes? *Pediatr Diabetes*. 2008 Jan 19; (Epub ahead of print).
2. Hossain P, Kavar B, Nahas ME. Obesity and diabetes in the developing world—A growing challenge. *N Engl J Med* 2007;356:213–215. [PubMed: 17229948]
3. Boggetti E, Calori G, Meschi F, Macellaro P, Bonfanti R, Chiumello G. Prevalence and correlations of early microvascular complications in young type I diabetic patients: Role of puberty. *J Pediatr Endocrinol Metab* 1997;10:587–592. [PubMed: 9467128]
4. Holl RW, Grabert M, Thon A, Heinze E. Urinary excretion of albumin in adolescents with type 1 diabetes: Persistent versus intermittent microalbuminuria and relationship to duration of diabetes, sex, and metabolic control. *Diabetes Care* 1999;22:1555–1560. [PubMed: 10480525]
5. Holl RW, Pavlovic M, Heinze E, Thon A. Circadian blood pressure during the early course of type 1 diabetes. Analysis of 1,011 ambulatory blood pressure recordings in 354 adolescents and young adults. *Diabetes Care* 1999;22:1151–1157. [PubMed: 10388981]
6. Kostraba JN, Dorman JS, Orchard TJ, et al. Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. *Diabetes Care* 1989;12:686–693. [PubMed: 2612303]
7. Olsen BS, Sjolie AK, Hougaard P, et al. The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes. *J Diabetes Complications* 2004;18:160–164. [PubMed: 15145327]
8. Pavlovic M, Holl RW, Haeberle U, et al. Angiotensin I converting enzyme and angiotensinogen gene polymorphisms related to 24-hour blood pressure in paediatric type I diabetes mellitus. *Eur J Pediatr* 1999;158:18–23. [PubMed: 9950302]

9. Mathiesen ER, Rønn B, Hensen T, Storm B, Deckert T. Relationship between blood pressure and urinary albumin excretion in development of microalbuminuria. *Diabetes* 1990;39:245–249. [PubMed: 2227133]
10. Coonrod BA, Ellis D, Becker DJ, et al. Predictors of microalbuminuria in individuals with IDDM. Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 1993;16:1376–1383. [PubMed: 8269796]
11. The Microalbuminuria Collaborative Study Group. Predictors of the development of microalbuminuria in patients with type 1 diabetes mellitus: A seven-year prospective study. *Diabetic Med* 1999;16:918–925. [PubMed: 10588521]
12. Rossing P, Hougaard P, Parving H-H. Risk factors for development of incipient and overt diabetic nephropathy in type 1 diabetic patients. *Diabetes Care* 2002;25:859–864. [PubMed: 11978681]
13. Hovind P, Tarnow L, Rossing P, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: Inception cohort study. *BMJ* 2004;328:1105–1109. [PubMed: 15096438]
14. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. *Diabetes Care* 1999;22:495–502. [PubMed: 10097935]
15. Amin R, Widmer B, Prevost AT, et al. Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: Prospective observational study. *BMJ* 2008;336:697–701. [PubMed: 18349042]
16. Olsen BS, Sjölie A, Hougaard P, et al. A 6-year nationwide cohort study of glycaemic control in young people with type 1 diabetes. Risk markers for the development of retinopathy, nephropathy and neuropathy. Danish Study Group of Diabetes in Childhood. *J Diabetes Complications* 2000;14:295–300. [PubMed: 11120452]
17. Jones CA, Leese GP, Kerr S, et al. Development and progression of microalbuminuria in a clinic sample of patients with insulin dependent diabetes mellitus. *Arch Dis Child* 1998;78:518–523. [PubMed: 9713006]
18. Rudberg S, Ullman E, Dahlquist G. Relationship between early metabolic control and the development of microalbuminuria—A longitudinal study in children with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1993;36:1309–1314. [PubMed: 8307261]
19. Krakoff J, Lindsay RS, Looker HC, Nelson RG, Hanson RL, Knowler WC. Incidence of retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. *Diabetes Care* 2003;26:76–81. [PubMed: 12502661]
20. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA* 2006;296:421–426. [PubMed: 16868300]
21. Savage PJ, Bennett PH, Senter RG, Miller M. High prevalence of diabetes in young Pima Indians: Evidence of phenotypic variation in a genetically isolated population. *Diabetes* 1979;28:937–942. [PubMed: 478185]
22. Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetes mellitus in Pima Indians: Incidence, risk factors and pathogenesis. *Diabetes Metab Rev* 1990;6:1–27. [PubMed: 2192853]
23. Knowler WC, Bennett PH, Bottazzo GF, Doniach D. Islet cell antibodies and diabetes mellitus in Pima Indians. *Diabetologia* 1979;17:161–164. [PubMed: 389722]
24. Dabelea D, Palmer JP, Bennett PH, Pettitt DJ, Knowler WC. Absence of glutamic acid decarboxylase antibodies in Pima Indian children with diabetes mellitus. *Diabetologia* 1999;42:1265–1266. [PubMed: 10525671]
25. Hanson RL, Ehm MG, Pettitt DJ, et al. An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. *Am J Hum Genet* 1998;63:1130–1138. [PubMed: 9758619]
26. Janssen RC, Bogardus C, Takeda J, Knowler WC, Thompson DB. Linkage analysis of acute insulin secretion with GLUT2 and glucokinase in Pima Indians and the identification of a missense mutation in GLUT2. *Diabetes* 1994;43:558–563. [PubMed: 8138061]
27. Muller YL, Infante AM, Hanson RL, et al. Variants in hepatocyte nuclear factor 4alpha are modestly associated with type 2 diabetes in Pima Indians. *Diabetes* 2005;54:3035–3039. [PubMed: 16186411]

28. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M. WHO Multinational Study Group: Follow-up of the WHO multinational study of vascular disease in diabetes: General description and morbidity. *Diabetologia* 2001;44(suppl 2):S3–S13. [PubMed: 11587047]
29. Lee ET, Lu M, Bennett PH, Keen H. WHO Multinational Study Group: Vascular disease in younger-onset diabetes: Comparison of European, Asian and American Indian cohorts of the WHO multinational study of vascular disease in diabetes. *Diabetologia* 2001;44(suppl 2):S78–S81. [PubMed: 11587054]
30. Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes. *Diabetes Care* 2003;26:2999–3005. [PubMed: 14578230]
31. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006;354:2443–2451. [PubMed: 16760444]
32. Podymow T, August P. Hypertension in pregnancy. *Adv Chronic Kidney Dis* 2007;14:178–190. [PubMed: 17395120]

Table 1

Comparison of Oxford Regional Prospective Study Childhood Inception Cohort With Adult Inception Cohort From the Steno Clinic

	Oxford	Steno
Sample size	527 (54% men)	277 (59% men)
Patient-years of follow-up	5,182	4,706
Age at diagnosis of diabetes (y)	8.8 ± 4.0	27.5 ± 15.0
Duration of follow-up (y)	9.8 ± 3.8	18.0 (1.0–21.5)
Hemoglobin A _{1c} (%)	9.8 ± 1.6	9.9 ± 2.0
Cumulative incidence of microalbuminuria after 19 y in the Oxford cohort and after 18 y in the Steno cohort (%) [*]	50.7 (40.5–60.9)	33.6 (27.2–40.9) [†]
Men with microalbuminuria	63 (47)	55 (70) [‡]
Cumulative incidence of macroalbuminuria after 19 y in the Oxford cohort and after 18 y in the Steno cohort (%) [*]	13.9 (12.9–14.9)	14.6 (8.9–20.3)
Age at macroalbuminuria (y)	18.5 ± 5.8	41 ± 16
Duration of diabetes at macroalbuminuria (y)	10.0 ± 4.0	11.2 ± 4.4

Values expressed as mean ± SD, number (percent), or mean (range) unless stated otherwise.

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^{*} Values in parentheses are 95% confidence intervals.

[†] $\chi^2 = 39.2$; $P < 0.001$.

[‡] $\chi^2 = 21.9$; $P < 0.001$.