ARTICLE

Type 2 Diabetes Mellitus in Children

Prenatal and Early Infancy Risk Factors Among Native Canadians

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Background: Type 2 diabetes mellitus is increasingly being observed among children and youth, including the Native population of Canada. Only one study has investigated prenatal and early infancy risk factors for the disease.

Methods: A case-control study was conducted; 46 patients younger than 18 years were recruited from the only clinical center for the treatment of diabetes serving the province of Manitoba, and 92 age- and sex-matched controls were recruited from a pediatric ambulatory clinic serving a large Native population in Winnipeg, Manitoba. Information on exposure to prenatal and early infancy risk factors was obtained through questionnaires administered by a Native nurse-interviewer.

Results: Multiple logistic regression modeling identified preexisting diabetes (odds ratio [OR], 14.4; 95% confidence interval [CI], 2.86-72.5), gestational diabetes (OR, 4.40; 95% CI, 1.38-14.1), and breastfeeding longer than 12 months (OR, 0.24; 95% CI, 0.13-0.99) as significant independent predictors of diabetic status. Other factors, such as low (<2500 g) and high (>4000 g) birth weight and maternal obesity, were also associated with diabetes in our population, but the elevated risks were not statistically significant.

Conclusion: Breastfeeding reduces the risk of type 2 diabetes among Native Canadian children and should be promoted as a potential intervention to control the disease.

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AN EPIDEMIC of type 2 diabetes mellitus has progressed among many Native North American populations during the past several decades, and it shows no sign of abating.[1] The onset of the disease has shifted toward childhood and adolescence, and more cases are being recognized because of increased awareness and intensified screening.[2-4] Although type 2 diabetes in youth most commonly affects populations with a high prevalence of type 2 diabetes among adults,[5] such as the Pima Indians of the southwestern United States,[6] it is increasingly being observed in other populations.[7,8]

Despite the young age of onset, the diabetes that is diagnosed among Native Canadian children should be classified as type 2.[9,10] These children are not dependent on insulin for long-term survival, and they do not fit the classical autosomal dominant mode of inheritance of the so-called maturity-onset diabetes of youth. Islet cell, glutamic acid decarboxylase, and insulin antibodies are absent.[11] Many patients with diabetes are obese, in a population already marked by widespread obesity.[12]

The emerging pattern and burden of childhood type 2 diabetes has been attributed to the increasing prevalence of obesity among Native North American children,[6,13] which is a result of changing lifestyles, especially diet and physical activity level, perhaps interacting with a genetic predisposition. In a retrospective cohort study among the Pima, maternal diabetes, low and high birth weight, and not breastfeeding were implicated as specific risk factors for diabetes.[14,15]

Type 2 diabetes in children and adolescents is of serious concern because of the increased duration of the disease and the appearance of microvascular and macrovascular complications during young adulthood. This study seeks to identify explanatory factors to which the child may have been exposed in the intrauterine environment and during early infancy. Given the substantial variation in genetic susceptibility, sociocultural environment, and lifestyle patterns among Native populations in North America, results from the Pima study may not be readily generalizable to other populations.

RESULTS

A total of 46 cases and 92 controls were recruited and interviewed. The mean age

SUBJECTS AND METHODS

A case-control design was used, and selection was based on disease status (cases with type 2 diabetes vs controls without diabetes). We included as cases Native children with type 2 diabetes diagnosed before age 18 years who were currently under the clinical care of 2 of us (H.J.D. and E.A.C.S.) at the Diabetes Education Resource Centre for Children and Adolescents, Health Sciences Centre, Winnipeg, Manitoba. It is the only provincial center for the treatment of diabetes in children and receives referrals from across Manitoba and adjacent northwestern Ontario. These patients were scheduled for regular follow-up care at the center and were asked to participate by the project nurse (B.F.). Patients were not specifically recalled for the study but were interviewed after their regular appointments. No patients refused to participate in the study. Population-based, prevalent cases were ascertained independent of exposure to any of the risk factors of interest.

To be included in the study, all cases must have satisfied the diagnostic criteria proposed by the American Diabetes Association,[16] namely, that fasting plasma glucose must equal or exceed 126 mg/dL (7.0 mmol/L). There were no exclusion criteria because characteristics such as the subject's pregnancy status, level of glycemic control, frequency of health care contact, coexisting complications, and treatment modality are not concerns when examining prediagnosis exposure to risk factors.

Nondiabetic controls were matched to cases by sex and age within 5 years. We selected controls from the active patient caseload of the Ambulatory Care Clinic at Winnipeg Children's Hospital; the control-case ratio was 2:1. The study nurse was stationed at the clinic 1 day a week and recruited Native patients for interviews. Recruitment ceased after the required number of controls in the various age-sex groups had been reached. Controls were selected independent of exposure status. The clinic has a large Native clientele, most of whom are residents of the inner-city area where the clinic is located. However, these children have moved to Winnipeg from Indian reserves all across the province, and many move back and forth frequently between their home reserves and the city, which approximates the geographic diversity of the case series.

Information on potential risk factors was collected through questionnaires administered during in-person interviews with the parents or caregivers of the cases and controls. The study nurse, who is of Native ancestry, conducted all interviews over a 12-month period from September 2000 through August 2001. Maternal risk factors were history of diabetes prior to and during pregnancy, prepregnancy height and weight, and alcohol intake, smoking, and diet during pregnancy. Infant risk factors were birth weight and method of infant feeding. Neither cases nor controls underwent clinical examination or laboratory tests for this study. Many of the items on the questionnaire were tested for cultural relevance in the province-wide Manitoba First Nations Regional Health Survey, conducted in 1997.

One of us (P.J.M.) has conducted extensive research on breastfeeding prevalence, duration, and determinants among Native women in Manitoba[17,18] and developed survey instruments that were adapted for use in the present study. The informants were asked if the child was ever breastfed. Those who answered in the affirmative were further queried regarding the duration of the breastfeeding, the age when formula, evaporated milk, or other milk was started, and the age when solids were started. From these questions, the durations of any breastfeeding and exclusive breastfeeding were determined. Instead of conducting a full-fledged dietary survey, we focused on the frequency of consumption of "traditional foods," ie, foods derived from the land by hunting and fishing, as a measure of the adoption of a nontraditional lifestyle. Respondents said that they ate a traditional diet "daily," "several times per week," "several times per month," "several times during the entire pregnancy," or none at all. The body mass index (weight in kg/height in m^2) was computed and categorized according to the National Institutes of Health (Bethesda, Md) clinical guidelines.[19]

This study was approved by the Health Research Ethics Board of the University of Manitoba, Winnipeg. Signed, informed consent was obtained from the parents or guardians of all respondents.

We compared cases and controls with respect to the distribution of various variables and computed unadjusted odds ratios (ORs) and their 95% confidence intervals (CIs). To control for potential confounding beyond the matching factors of age and sex, we conducted multivariate matched analysis using conditional maximum likelihood estimation with the SAS program PROC PHREG (version 8.1; SAS Institute Inc, Cary, NC).

of the cases, 14.0 years (95% CI, 13.3-14.6), was slightly higher than that of the controls, whose mean age was 12.7 years (95% CI, 12.1-13.3). Cases and controls had exactly the same sex distribution (54% girls vs 46% boys). We matched the ages of 56% of controls to within ±2 years of the cases and 33% to within ±2 to ±3 years, with only 11% matched to within ±3 to ±5 years.

Table 1 compares the distribution of several variables of interest between cases and controls. In multivariate analysis, an initial full model included all variables from Table 1. **Table 2** presents the adjusted ORs and 95% CIs for patients with diabetes and compares different categories of risk factors, controlling for all other risk factors. After backward stepwise elimination, only 3 statistically significant ($P<.05$) independent explanatory variables remained: preexisting diabetes (OR, 14.4; 95% CI, 2.86-72.5), gestational diabetes (OR, 4.40; 95% CI, 1.38-14.1), and some breastfeeding for 12 months or longer (OR, 0.24; 95% CI, 0.07-0.84).

We repeated the analysis using a dichotomized variable for infant feeding: some breastfeeding, less than 6 months vs 6 months or longer. The independent predictors of diabetes status were the same: preexisting diabetes (OR, 12.6; 95% CI, 2.56-61.5), gestational diabetes (OR, 4.18; 95% CI, 1.30-13.4), and some breastfeeding for 6 months or longer (OR, 0.36; 95% CI, 0.13-0.99). We also used the duration of any breastfeeding, in months, as a continuous variable (OR, 0.95; 95% CI, 0.91-0.995).

Body mass index as a continuous variable was not a significant independent predictor (OR, 1.04; 95% CI, 0.97-1.13) when it substituted for body mass index cat-

Table 1. Distribution of Selected Variables Among 46 Cases and 92 Controls*

Variable	No. of Subjects	No. (%) of Subjects		Unadjusted OR (95% CI)
		Cases	Controls	
Diabetes mellitus during pregnancy				
None	102	22 (47.8)	80 (87.0)	1.00
Gestational	22	13 (28.3)	9 (9.8)	4.80 (1.52-15.1)
Preexisting	14	11 (23.9)	3 (3.3)	10.30 (2.27-46.7)
Use of traditional diet during pregnancy				
None	21	5 (10.9)	16 (17.4)	1.00
Some use	117	41 (89.1)	76 (82.6)	1.93 (0.59-6.34)
Several times during pregnancy	65	25 (54.3)	40 (43.5)	. . .
Several times/mo	27	7 (15.2)	20 (21.7)	. . .
Several times/wk	9	4 (8.7)	5 (5.4)	. . .
Daily	16	5 (10.9)	11 (12.0)	. . .
Smoking during pregnancy				
None	73	23 (50.0)	50 (54.3)	1.00
1-5 Cigarettes/d	37	12 (26.1)	25 (27.2)	1.04 (0.46-2.31)
>5 Cigarettes/d	28	11 (23.9)	17 (18.5)	1.43 (0.57-5.32)
Alcohol during pregnancy				
None	122	39 (84.8)	83 (90.2)	1.00
≥1 Drink/wk	16	7 (15.2)	9 (9.8)	1.75 (0.57-5.42)
Mother's prepregnancy BMI (kg/m^2)				
<25 (Not overweight)	73	20 (43.5)	53 (57.6)	1.00
≥25 (Overweight)	65	26 (56.5)	39 (42.4)	1.81 (0.87-3.78)
25-29.9	36	17 (37.0)	19 (20.7)	. . .
≥30	29	9 (19.6)	20 (21.7)	. . .
Birth weight, g				
2500-4000	113	36 (78.3)	77 (83.7)	1.00
Low (<2500)	10	4 (8.7)	6 (6.5)	1.41 (0.37-5.42)
High (>4000)	15	6 (13.0)	9 (9.8)	1.42 (0.46-4.37)
Breastfeeding during infancy, mo				
None	47	16 (34.8)	31 (33.7)	1.00
<6	42	19 (41.3)	23 (25.0)	1.82 (0.66-4.99)
6-11.9	18	5 (10.9)	13 (14.1)	0.74 (0.20-2.70)
≥12	31	6 (13.0)	25 (27.2)	0.42 (0.13-1.39)
Exclusive breastfeeding during infancy, mo				
None	47	16 (34.8)	31 (33.7)	1.00
<6	59	23 (50.0)	36 (39.1)	1.32 (0.51-3.42)
≥6	32	7 (15.2)	25 (27.2)	0.56 (0.19-1.67)

*OR indicates odds ratio; CI, confidence interval; BMI, body mass index; and ellipses, not applicable.

egories in the model. An interaction term (smoking during pregnancy × body mass index) was also not significant (OR, 1.83; 95% CI, 0.73-4.61).

COMMENT

Among the risk factors identified in this study, the strongest is maternal diabetes. This is of concern because both gestational diabetes and type 2 diabetes during pregnancy are prevalent in several Native Canadian populations.[20,21] Maternal diabetes is associated with various risk factors for diabetes among adults, such as higher serum triglycerides, obesity, and fasting insulin.[22] Maternal diabetes is also a strong predictor of high birth weight in the newborn.[20,21,23] Although a mother could transmit genetic susceptibility to her offspring, it is more likely that maternal diabetes increases the risk of diabetes in children by altering the intrauterine environment. The Pima study shows that in families where children were born both before and after their mother was diagnosed with diabetes, the risk of diabetes was almost 4-fold higher among siblings born after the mother developed diabetes.[24] About 40% of type 2 diabetes cases among 5- to 19-year-old Pima children can be attributed to maternal diabetes during pregnancy.[25]

The protective effect of breastfeeding confirms the observations of the Pima study.[14,15] A study of Australian 2-year-olds found that those who were exclusively breastfed had lower plasma glucose levels and higher levels of long-chain polyunsaturated fatty acids than those who were bottle-fed. Early changes in skeletal muscle membrane phospholipid fatty acid saturation have been postulated to play a role in the development of insulin resistance.[26] Our data should assist in the broader campaign to promote breastfeeding in the Native Canadian population, which has been on the decline in recent decades.[18]

Although maternal recall of infant feeding is subject to recall bias, studies in several developing countries have indicated remarkable validity and reliability,[27,28] and asking mothers to recall practices from many years earlier is common in breastfeeding studies. The Pima study of breastfeeding and diabetes published in 1997[14] used breastfeeding data that were collected in 1978 for a

Table 2. Adjusted Odds Ratio (OR) for Subjects With Diabetes Mellitus*

Variable	OR† (95% CI)
Initial Full Model, 8 Predictors	
Diabetes during pregnancy	
None	1.00
Gestational	7.05 (1.42-34.9)
Preexisting	19.8 (3.18-122.7)
Use of traditional diet	
None	1.00
Some use during pregnancy	0.81 (0.17-3.94)
Smoking during pregnancy	
None	1.00
1-5 Cigarettes/d	1.11 (0.35-3.55)
>5 Cigarettes/d	1.33 (0.40-4.39)
Alcohol during pregnancy	
None	1.00
≥1 drink/wk	2.07 (0.41-10.3)
Mother's prepregnancy BMI (kg/m^2)	
<25	1.00
≥25	1.29 (0.46-3.64)
Birth weight, g	
2500-4000	1.00
Low (<2500)	3.45 (0.58-20.5)
High (>4000)	0.53 (0.13-2.15)
Breastfeeding during infancy, mo	
None	1.00
<6	1.22 (0.16-9.2)
6-12	0.89 (0.16-5.11)
≥12	0.27 (0.06-1.26)
Exclusive breastfeeding during infancy, mo	
None	1.00
<6	0.75 (0.15-3.82)
≥6‡	. . .
Final Model After Backward Stepwise Elimination	
Diabetes during pregnancy	
None	1.00
Gestational	4.40 (1.38-14.1)
Preexisting	14.4 (2.86-72.5)
Breastfeeding during infancy, mo	
None	1.00
≥12§	0.24 (0.07-0.84)

*CI indicates confidence interval; BMI, body mass index; and ellipses, not applicable.

†OR was adjusted for all other predictor variables in the model.

‡Dummy variable for breastfeeding more than 6 months was removed from the initial model because of redundancy.

§Dummy variables for the intermediate categories (<6 mo and 6-12 mo) were eliminated from the final model.

study on childhood respiratory infections in which mothers recalled infant feeding practices from as many as 18 years earlier.[29]

High birth weight (>4000 g) and low birth weight (<2500 g) were associated with a 40% increase in risk of diabetes, although the increase was not statistically significant. High birth weight is common among many Native groups in Canada,[30] and its prevalence among nondiabetic controls may have masked the effect.

In an experimental study, fetal alcohol exposure was linked to the development of insulin resistance in adult laboratory rats.[31] Our population-based study also showed a 75%-increased risk in a human population. Although the magnitude of the association is too small, and statistically nonsignificant, to link any diabetes prevention effort explicitly with alcohol consumption during pregnancy, there are sufficient health risks associated with this behavior to warrant its reduction, regardless of its etiologic role in diabetes.

Accumulating evidence suggests an association between smoking and diabetes among adults,[32] but there is no evidence that smoking during pregnancy increases the risk of diabetes in children, beyond the effect of smoking in lowering birth weight. As with alcohol, there are sufficient grounds for reducing smoking during pregnancy, even if there is no detectable effect on diabetes.

This study used a case-control design. Although community controls are generally preferred because they are representative of the source population from which cases are generated, our cases originated from many communities across the province, making individual community visits logistically costly and inefficient. We decided to use clinic controls, who, unlike hospital controls, do not suffer from severe illness and are more representative of the general childhood population.

In the short time since the problem of type 2 diabetes in Native youth has been recognized, the burden of illness is rapidly increasing, creating considerable stress on the health care and social support systems. The associated complications of blindness, renal failure, amputations, and cardiovascular disease devastate individual patients, their families, and their communities. Although the demand for treatment, care, and support for individuals diagnosed with diabetes will increase, this demand can be reduced in the future if effective prevention is implemented. A first step toward the design of a preventive strategy is the identification of risk factors, preferably very early on in the natural history of the disease.

Based on the results of this study, any prevention strategy should involve screening for diabetes before and during pregnancy, promoting healthy lifestyles during pregnancy, reducing maternal obesity, and promoting breastfeeding during infancy. None of these measures require huge expenses, and all can be integrated into existing health care services. None are harmful, and all are beneficial in their own right. The association with type 2 diabetes in children will give these issues an even higher profile and provide the incentive for health care professionals and planners to incorporate them into routine health care programs.

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This study has been approved by the Health Research Ethics Board of the University of Manitoba (December 14, 1999; renewed March 20, 2001) and the Research Impact Committee of the Health Sciences Centre (February 10, 2000).

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What This Study Adds

The onset of type 2 diabetes, previously thought of as an adult disease, is occurring at increasingly younger ages in diverse populations. To date, only one study, among the Pima Indians, has reported on maternal and early infancy risk factors. We conducted a case-control study on Native Canadian children and identified maternal diabetes (both preexisting type 2 and gestational) as a strong risk factor and prolonged breastfeeding as a strong protective factor, with a child who was breastfed for more than 12 months having only 24% of the risk of diabetes compared with a bottle-fed child. This study suggests that there are preventive strategies that can be incorporated in existing prenatal and infant health care programs to address a new health threat.

REFERENCES

1. Young TK, Reading J, Elias B, O'Neil JD. Type-2 diabetes in Canada's First Nations: status of an epidemic in progress. *CMAJ*. 2000;163:561-566.
2. Dean HJ, Mundy RL, Moffatt M. Non-insulin-dependent diabetes mellitus in Indian children in Manitoba. *CMAJ*. 1992;147:52-57.
3. Dean H. NIDDM-Y in First Nations children in Canada. *Clin Pediatr (Phila)*. 1998; 37:89-96.
4. Dean HJ, Young TK, Flett B, Wood-Steiman P. Screening for type-2 diabetes in aboriginal children in northern Canada. *Lancet*. 1998;352:523-524.
5. Glaser N, Jones KL. Non-insulin-dependent diabetes mellitus in children and adolescents. *Adv Pediatr*. 1996;43:359-396.
6. Dabelea D, Hanson RL, Bennett PH, Roumain J, Knowler WC, Pettitt DJ. Increasing prevalence of type II diabetes in American Indian children. *Diabetologia*. 1998; 41:904-910.
7. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr*. 1996;128:608-615.
8. Ludwig DS, Ebbeling CB. Type 2 diabetes in children: primary care and public health considerations. *JAMA*. 2001;286:1427-1430.
9. Dean H. Diagnostic criteria for type-2 diabetes in youth (NIDDM-Y). *Clin Pediatr (Phila)*. 1998;37:67-71.
10. Sellers EA, Dean HJ. Diabetic ketoacidosis: a complication of type 2 diabetes in Canadian aboriginal youth. *Diabetes Care*. 2000;23:1202-1204.
11. Sellers E, Eisenbarth G, Young TK, Dean HJ. Diabetes-associated autoantibodies in aboriginal children. *Lancet*. 2000;355:1156.
12. Young TK, Dean HJ, Flett B, Wood Steiman P. Childhood obesity in a population at high risk for type-2 diabetes. *J Pediatr*. 2000;136:365-369.
13. Story M, Evans M, Fabsitz RR, Clay TE, Rock BH, Broussard B. The epidemic of obesity in American Indian communities and the need for childhood obesity-prevention programs. *Am J Clin Nutr*. 1999;69(suppl):747S-754S.
14. Pettitt DJ, Forman MR, Hanson RL, Knowler WC, Bennett PH. Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians. *Lancet*. 1997;350:166-168.
15. Pettitt DJ, Knowler WC. Long-term effects of the intrauterine environment, birth weight, and breast-feeding in the Pima Indians. *Diabetes Care*. 1998;21(suppl 2):B138-B141.
16. American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183-1197.
17. Martens PJ. Prenatal infant feeding intent and perceived social support for breastfeeding in First Nations communities: a role for health care providers. *Int J Circumpolar Health*. 1997;56:104-120.
18. Martens PJ, Young TK. Determinants of breastfeeding in four Canadian Ojibwa communities: a decision-making model. *Am J Human Biol*. 1997;9:579-593.
19. National Institutes of Health. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. Bethesda, Md: National Heart, Lung, and Blood Institute, National Institutes of Health; 1998. NIH publication 98-4083.
20. Harris SB, Caulfield LE, Sugarmori MS, Whalen EA, Henning B. The epidemiology of diabetes in pregnant Native Canadians: a risk profile. *Diabetes Care*. 1997; 20:1422-1425.
21. Rodriguez S, Robinson E, Gray-Donald K. Prevalence of gestational diabetes among James Bay Cree women in northern Quebec. *CMAJ*. 1999;160:1293-1297.
22. Ekoé JM, Thomas F, Balkau B, Eschwege E, Delisle H. Effect of maternal diabetes on the pattern of selected insulin resistance syndrome parameters in normal glucose tolerant subjects of 2 Algonquin Indian communities in Quebec. *Diabetes Care*. 1996;19:822-826.
23. Caulfield LE, Harris SB, Whalen EA, Sugamori ME. Maternal nutritional status, diabetes, and risk of macrosomia among Native Canadian women. *Early Hum Dev*. 1998;50:293-303.
24. Dabalea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity. *Diabetes*. 2000;49:2208-2211.
25. Dabalea D, Knowler WC, Pettit DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *J Matern Fetal Med*. 2000;9: 83-88.
26. Baur LA, O'Connor J, Pan DA, Kriketos AD, Storlien LH. The fatty acid composition of skeletal muscle membrane phospholipid: its relationship with the type of feeding and plasma glucose levels in young children. *Metabolism*. 1998;47: 106-112.
27. Launer LJ, Forman MR, Hundt GL, et al. Maternal recall of infant feeding events is accurate. *J Epidemiol Community Health*. 1992;46:203-206.
28. Holland B. The validity of retrospective breastfeeding duration data: an illustrative analysis of data in the Malaysian Family Life Survey. *Hum Biol*. 1987;59: 477-487.
29. Forman MR, Graubard BI, Hoffman HJ, Beren R, Harley EE, Bennett PH. The Pima Infant Feeding Study: breastfeeding and respiratory infections during the first year of life. *Int J Epidemiol*. 1984;13:447-453.
30. Rodrigues S, Robinson EJ, Kramer MS, Gray-Donald K. High rates of infant macrosomia: a comparison of a Canadian native and a non-native population. *J Nutr*. 2000;130:806-812.
31. Minuk GY, Meyers AFA, Legare DJ, Sadri P, Lautt W. Fetal exposure to alcohol results in adult insulin resistance in the rat. *Proc West Pharmacol Soc*. 1998; 41:39-40.
32. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol*. 2001;30:540-546.