Type 2 Diabetes in Youth in Manitoba, Canada, 1986 to 2002

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ABSTRACT

This paper offers a historical perspective of the evolution of type 2 diabetes mellitus in Oji-Cree youth in Manitoba and Northwestern Ontario over the past 15 years. It describes the epidemiology of the disease and the current state of knowledge regarding risk factors, genetics, diagnostic criteria, treatment and long-term follow-up. The demographics of the youth with type 2 diabetes population have changed over this period. The incidence of type 2 diabetes continues to increase and the gender distribution has changed from a female predominance of 8:1 to a more even representation of females and males. There has been no change in the mean age at diagnosis or the percentage of affected youth who reside in remote communities. Careful clinical observations are vital to gaining an increased understanding of this disease.

RÉSUMÉ

Ce compte rendu donne un aperçu de l'évolution du diabète sucré de type 2 chez les jeunes Oji-cri du Manitoba et du nord-ouest de l'Ontario au cours des 15 dernières années. Il décrit l'épidémiologie du diabète et les connaissances actuelles sur les facteurs de risque, les facteurs génétiques, les critères diagnostiques, le traitement et le suivi à long terme. Les données démographiques de la population oji-cri ont énormément changé au cours de cette période. L'incidence du diabète de type 2 continue d'augmenter et la répartition entre les sexes a changé d'une prédominance féminine de 8:1 à une représentation plus égale du sexe féminin et du sexe masculin. Ce qui n'a pas changé est l'âge moyen au moment du diagnostic et le pourcentage de jeunes atteints de diabète qui habitent dans des communautés isolées. Pour mieux comprendre cette maladie, il est essentiel de faire des observations cliniques minutieuses.

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INTRODUCTION

After the recognition of type 2 diabetes mellitus in First Nations children in Manitoba, Canada, in 1983, the authors predicted that the number of affected children would increase in every First Nations community (1,2). This prediction has been realized in Manitoba and Northwestern Ontario, Canada. It has not happened across Canada. Only a few cases of type 2 diabetes in children have been reported in First Nations communities other than in the Plains Cree in Central Canada, despite a dramatic increase in public awareness of the problem. This disease is not only a problem in First Nations children. The prevalence of type 2 diabetes in children in Canada reflects the mix of First Nations, Asian, African and Hispanic children in urban centres (3). Type 2 diabetes in children is a new disease in all of these ethnic groups, mirroring the epidemic of obesity in all children and the rates of diabetes in these adult populations (4).

This paper summarizes the rapid evolution of type 2 diabetes in First Nations children in Manitoba from 1986 to 2002. These data were derived from the longitudinal survey at the Manitoba Diabetes Education Resource for Children and Adolescents (DER-CA), the only tertiary care pediatric Diabetes Education Centre in Manitoba and Northwestern Ontario (5). Based on previous studies, the ascertainment rate of type 1 diabetes in children 0 to 14 years of age at the Manitoba DER-CA is 95% (6). The authors believe that ascertainment is similar for children 5 to 14 years of age with type 2 diabetes, based on chart reviews in biannual outreach programs across Manitoba and Northwestern Ontario. The effect of increased awareness of elders, community members, family members and healthcare professionals on the reported incidence of the disease cannot be ruled out.

One of the theories to explain the appearance of type 2 diabetes in children is that it is a direct consequence of the rapid increase in obesity in children in developed countries. Obesity in children is now a global problem. In First Nations communities in Central Canada in 1996 to 1997, the rate of obesity (body mass index [BMI] >95th percentile) was 40% in school-aged females and 34% in school-aged males (7,8). In 2 communities evaluated by the Cree Board of Health and Social Services of James Bay, Quebec, Canada, in 2000, 28% of 256 youth 10 to 19 years of age had a BMI >95th percentile (9).

EPIDEMIOLOGY

One of the vital components of the description of type 2 diabetes in children is an estimation of the point prevalence of the disease in the relevant adult population. In Manitoba, the prevalence of type 2 diabetes in registered First Nations adults ages 20 to 79 years in 1994/1995 through 1998/1999 was 189/1000 (10). In Manitoba, in 1998, the point prevalence of type 2 diabetes in First Nations women age ≥20 years was 248/1000, and for First Nations men was 170/1000 (11).

The number of new cases of type 2 diabetes per year in First Nations children referred to the DER-CA increased from 4 in 1986 to 35 in 2001 (Figure 1). For First Nations youth in Manitoba, the crude incidence of type 2 diabetes in 2001 was 23/17900, or 1.3/1000 registered First Nations youth 10 to 19 years of age (0.55/1000 for age 0 to 19 years and 0.78/1000 for age 5 to 19 years). The children with type 2 diabetes represented 35% of the children with new-onset diabetes referred to the DER-CA in 2001.

As of December 31, 2001, the DER-CA was following 92 First Nations children with type 2 diabetes. The minimum crude age-specific point prevalence of type 2 diabetes for 10- to 14-year-old youth was 26/9500, or 0.27% of registered First Nations youth age 10 to 14 years in Manitoba in 2001. In the group of youth 10 to 19 years of age, the minimum crude age-specific point prevalence of type 2 diabetes in First Nations youth living in Manitoba increased from 0.10% in 1986 to 0.22% in 1998 to 0.40% (72/17900) in 2001.

One of the major challenges to descriptive epidemiology in this group is availability of meaningful population data and standardized reporting of age groups. The accepted age groups for type 1 diabetes are in 5-year blocks: 0 to 4, 5 to 9 and 10 to 14 years. The epidemiologic studies of type 1 diabetes report only children age 0 to 14 years. The situation is complicated in type 2 diabetes by the rarity of incident cases <10 years of age, the referral of pregnant adolescents with diabetes to adult services, and the increased confidence of primary care physicians in caring for older adolescents with type 2 diabetes. Thus, the assessment of crude prevalence based on this referred case series is likely most accurate in the group of those age 10 to 14 years. Provincial health administrative databases do not differentiate type 1 vs. type 2 vs. gestational diabetes, so they cannot be used in this analysis. Recent health data on First Nations populations in Manitoba used 20-year blocks (0 to 19, 20 to 39 years, etc.) to report population data, and reported the diabetes treatment rates for those age 20 to 79 years (10). Most adult studies of diabetes using administrative databases report diabetes prevalence rates for adults age ≥25 years. Thus, the age group 15 to 24 years is lost in most epidemiologic studies of diabetes. To solve this dilemma, there must be agreement on standardized age groups, mandatory coding of type of diabetes and mandatory inclusion of children in population-based epidemiologic reports on diabetes.

There are 7 published population-based screening studies in Canada in First Nations youth. The first study, in 1993, in 2 Cree communities in Western Quebec found no cases of diabetes in youth 15 to 19 years of age (12). The second population study was conducted in the northern, remote Oji-Cree community of Sandy Lake in Northwestern Ontario, and included youth age 10 to 19 years. The prevalence of diabetes in adolescent females 10 to 19 years of age was 4% (13). The third screening study took place in Ste. Theresa Point, Manitoba, another northern, remote Oji-Cree community at the same latitude and 100 km west of Sandy Lake (14). The study included school-aged youth (7 to 19 years). The

prevalence of type 2 diabetes in youth age 7 to 19 years was 1.1% (11/1000). For the adolescent females age 10 to 19 years, the prevalence was 3.6%. In 1997, the 70 school-aged Cree children (5 to 14 years) in York Factory in Northern Manitoba were screened, and 2 new cases of type 2 diabetes were confirmed (5). The fifth population screening study in Cree children took place in 2 communities in Northern Quebec in 2000 (9,15). No cases of diabetes were diagnosed in 400 youth age 10 to 19 years (9). As well, in 2000, no cases of diabetes were found in 115 school-aged (5 to 19 years) Ojibway youth in Christian Island First Nation in Southern Ontario (16). In 2000, 1579 youth age 7 to 19 years in 4 remote Oji-Cree communities of the Island Lake Tribal Council and 7 rural Ojibway communities of the Interlake Reserves Tribal Council were screened for diabetes in schools. The crude prevalence rates were 6.7/1000 and 9.1/1000, respectively (17).

In the early years of the longitudinal survey of type 2 diabetes in Manitoba, most cases of youth with type 2 diabetes were adolescent females (18). The gender distribution has changed from the original 8:1 in 1990 to close to 1:1 in 2000 and 2001 (Figure 1, Table 1).

The average age at diagnosis of type 2 diabetes has not changed since 1986 (Table 1). The younger mean age at diagnosis during the first few years of the survey was based on only a few cases.

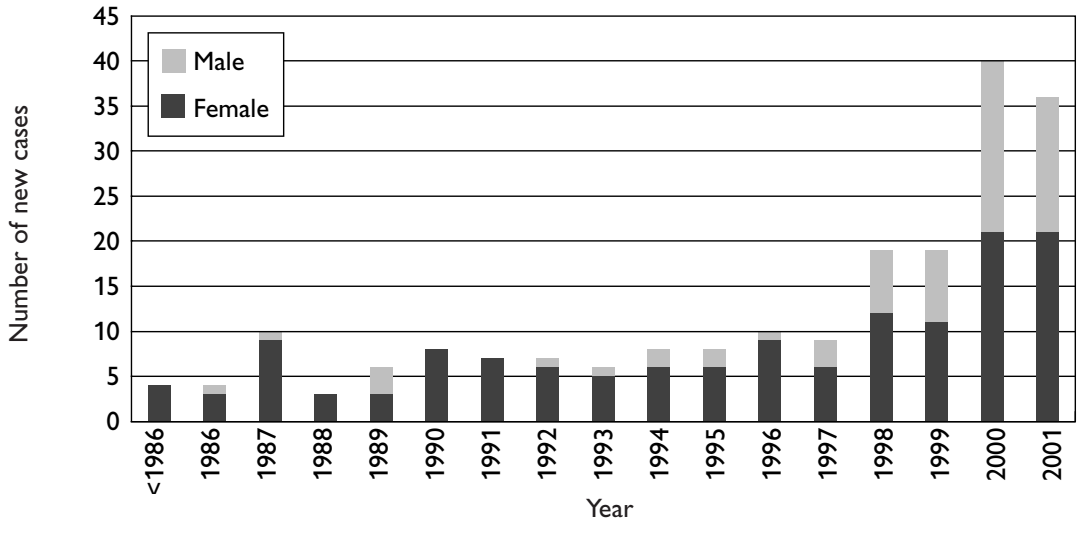
Since 1983, >50% of youth with type 2 diabetes have resided in remote or rural First Nations communities in Manitoba (Table 1). In general, 55.6% of all First Nations youth live on reserve. The greater prevalence of type 2 diabetes in children in northern and rural communities may reflect the increased public awareness of diabetes by families living in these communities, a single health centre providing diabetes screening, and comprehensive community-based diabetes awareness programs. It may also reflect different gene-environment interactions, such as the prenatal environment, different rates of breastfeeding, and different rates of obesity. In 2001, all 62 First Nations communities in Manitoba had a diabetes prevention business plan. The youth diagnosed with type 2 diabetes before the age of 19 years in Manitoba have come from 48 of the 62 (77%) First Nations communities in Manitoba. This observation supports the existence of a ubiquitous environmental factor in addition to genetic factors in First Nations people. A case-controlled study of 46 youth and their families followed at the DER-CA identified maternal diabetes, both pre-existing (odds ratio [OR]=19.8) and gestational (OR=7.05), as the strongest risk factor for onset of diabetes in childhood (19). Prolonged breastfeeding was a strong protective factor: a child who was breastfed for ≥12 months had a lower risk of diabetes compared to a bottle-fed baby (OR=0.27) (19).

GENETICS

Maturity-onset diabetes of the young (MODY) is a group of autosomal dominant, single gene disorders that cause diabetes in young adults or children (20). One of the types of MODY is caused by mutations in the hepatocyte nuclear factor (HNF) -1alpha gene on chromosome 12q24. Such patients develop progressive beta cell failure, usually starting in adolescence, and severe microvascular complications are common (20). There have been many different mutations reported in this gene that are associated with an insulin secretion defect rather than insulin resistance (21).

A unique private mutation in the HNF-1alpha gene was identified in the Aboriginal people of Sandy Lake, Ontario. The mutation accounts for approximately 40% of the diabetes in this community (22,23). The allele frequency is 21% in the population, but 34% in youth 10 to 25 years of age (23).

Figure 1. Incidence of type 2 diabetes in youth by calendar year and gender



Many people with this mutation, a G319S substitution, have early-onset diabetes. In a series of 51 youth at the DER-CA, 41.2% had 1 or 2 copies of this mutation (24). The homozygous state in adolescents is associated with hallmarks of diabetes without insulin resistance, including a low BMI, low stimulated serum insulin levels and no acanthosis nigricans. The heterozygous state is characterized by a phenotype intermediate between the homozygous and wild type states. The youth without the mutation have clinical characteristics associated with classical insulin resistance: obesity and acanthosis nigricans. The presence of the G319S HNF-1alpha mutation in Oji-Cree children may help to guide customized treatment, since adults with HNF-1alpha mutations are sensitive to sulfonylurea drugs (25).

DIAGNOSIS

The diagnosis of type 2 diabetes in youth is made based on clinical criteria, including high-risk ethnic group, strong family history of type 2 diabetes, obesity (BMI ≥95th percentile) and age >10 years (18). Most youth experience no classical symptoms of hyperglycemia. Many have acanthosis nigricans of the neck and axilla. Diabetic ketoacidosis (DKA) occurs in 5% of youth at presentation and up to 10% at any time during follow-up (26). In some cases, differentiation between type 1 and type 2 diabetes can be difficult. A First Nations adolescent with a strong family history of type 2 diabetes but with symptoms of hyperglycemia, including weight loss and ketonuria, may require insulin at diagnosis. However, it is vital to appropriately classify a patient's diabetes to provide accurate family counselling and education regarding etiology, treatment options, associated medical conditions, and acute and long-term complications. In these situations, the measurement of islet-specific antibodies may be helpful (27).

TREATMENT

The mainstay of treatment of type 2 diabetes in children is lifestyle modification. The first strategy is to limit (or ban) sugar-containing drinks and television watching (28). Some youth will require insulin at diagnosis if they present with DKA or classical symptoms with unintentional weight loss. In these situations, the insulin therapy will be short term, and conventional twice-daily insulin regimens have demonstrated success. Other youth may benefit from short-term insulin for 1 to 3 months if lifestyle modification in the first 3 to 6 months is clearly not achieving therapeutic goals (29). The goal of therapy is to achieve and maintain glycosylated hemoglobin (A1C) <7.0%.

The oral antihyperglycemic agents approved for use in type 2 diabetes in adults are not approved for use in children in Canada. The only published randomized, controlled trial of an oral antihyperglycemic agent in pediatric patients with type 2 diabetes evaluated the efficacy and safety of up to 16 weeks of treatment with metformin in subjects 10 to 16 years of age. The metformin-treated group experienced a mean reduction in fasting blood glucose (FBG) of 2.4 mmol/L from baseline compared to an increase in FBG of 1.2 mmol/L in the placebo-treated group ($p<0.001$) (30). At study end, mean A1C was significantly lower in the metformin group than in the control group (7.5 vs. 8.6%, respectively, $p<0.001$). Similar outcomes were not observed in a second randomized, controlled trial with metformin in pediatric patients with type 2 diabetes (31). One barrier to the use of oral antihyperglycemic agents is the risk of nonalcoholic fatty liver disease in children with type 2 diabetes (32).

The greatest treatment challenges in First Nations youth with type 2 diabetes are the lack of acute symptoms, lack of role models with diabetes in the community, presence of high-risk lifestyle habits in family members, lack of immediate risk to life, presence of mood disorders and a sense of despondency about diabetes.

The care, education and support of youth with type 2 diabetes in Manitoba is delivered by the DER-CA team in a structured, culture- and age-sensitive program designed specifically for First Nations youth with type 2 diabetes, in collaboration with the family, the community and the local healthcare providers (usually community health representatives or on-reserve staff from the First Nations and Inuit Health Branch). This program is delivered in the community when possible.

PROGNOSIS

Outcome data for youth with type 2 diabetes are limited because the history of this disease is <25 years. The largest outcome data to date are from the administrative data of the Indian Health Service that maintains a registry of affected Native Americans and Native Alaskans. Of a sample of 2595

Table 1. Demographics of type 2 diabetes in First Nations youth in Manitoba

Year	*N*	*Females (%)*	*Reside in remote or rural community (%)*	*Mean age at diagnosis (95% CI) (years)*
Pre-1986	6	100	83	11.50 (9.62, 13.38)
1986–1990	20	75	50	13.00 (11.79, 14.21)
1991–1995	47	74	75	13.17 (12.55, 13.79)
1996–2000	95	60	80	13.48 (13.02, 13.94)

CI = confidence interval

young adults <45 years of age (mean age: 35.4 years), in 1998, 73% were obese, 51% had an A1C ≥9.0%, 47% had hypertension (blood pressure ≥130/85 mm Hg), 48% had hypercholesterolemia, 37% smoked and 26% had proteinuria (33). These data indicate the high rates of risk factors, but not of overt end-stage diabetes complications. Preliminary follow-up data from the Manitoba cohort indicate high morbidity and mortality from end-stage diabetes complications (34). The total disease burden from early-onset complications includes family dislocation, emotional distress, pregnancy loss and congenital abnormalities.

CONCLUSION

Type 2 diabetes in youth was first described in Canada in Oji-Cree children in Manitoba. During the past 15 years, the disease has increased in frequency and the gender distribution has changed. A monogenic disorder of an HNF has been discovered that may form the basis for specific treatment and may also provide a means for early detection and modification of disease outcome. Treatment strategies have become clearer, and the first randomized, controlled studies with oral antihyperglycemic agents have been completed. It has been recognized that most of the youth with this disease differ from those with type 1 diabetes, since they have components of the insulin resistance syndrome with the associated independent cardiovascular risk factors of hypertension and dyslipidemia. Specialized outreach community-based programs for education, support and treatment have been developed for these youth. There is recognition that the young adults who transfer to adult services need coordinated services in the vulnerable young adult period. Surveillance programs for the next generation, the offspring of these young adults, must be developed. Maintenance of the regional registry and long-term follow-up of this cohort of children with type 2 diabetes is essential, because the provincial administrative database cannot provide the vital information needed to understand this evolving disease and to develop appropriate services for these vulnerable, high-risk young adults.

ACKNOWLEDGEMENTS

Bertha Flett has been the research nurse involved in all of the field studies for type 2 diabetes in youth in Manitoba since 1996. Her compassion and deep understanding of the communities is an integral component of the authors' work. The projects would not progress without her unfaltering commitment. The authors share the concern and admire the motivation of families and Aboriginal communities to understand this disease and to improve the present and future quality of life for these young people. The community partnerships and courage of these families are vital components of this work. The authors are also grateful for the dedication, creativity and passion of the staff of the Manitoba DER-CA.

This work is supported by the Children's Hospital Foundation of Manitoba, and an Interdisciplinary Health Research Teams grant to T. Kue Young from the Canadian Institutes of Health Research.

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