

ORIGINAL RESEARCH

Prevalence and Associated Risk Factors for Secondary Diabetes in Canadian Children Followed in Pediatric Tertiary Care Centres

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ABSTRACT

OBJECTIVE: To assess the prevalence of secondary diabetes seen in pediatric tertiary care centres in Canadian children with acute lymphoblastic leukemia (ALL), cystic fibrosis (CF), thalassemia major, or heart, liver or renal transplant. A secondary objective was to determine risk factors associated with the development of secondary diabetes in these populations.

METHODS: A multicentre, retrospective descriptive study of pediatric patients <18 years of age was performed to assess the prevalence of reported secondary diabetes. A case-control design was used to assess associated risk factors using odds ratios.

RESULTS: The prevalence of reported secondary diabetes was 1.8% in ALL, 2.9% in CF, 0% in thalassemia major, 3.4% in heart transplant, 2.6% in liver transplant and 1.5% in renal transplant. An odds ratio of 15.0 (95% CI 1.2–747.4) was found for developing secondary diabetes in children >12 years of age with ALL compared to those ≤12 years of age with ALL; 50% of cases of secondary diabetes with ALL had a body mass index greater than the 95th percentile, compared to 0% of control patients with ALL ($p=0.005$). No other significant risk factors were found to be associated with the development of secondary diabetes.

CONCLUSIONS: This is the first study examining the prevalence of secondary diabetes in children seen in pediatric tertiary care centres from multiple at-risk populations. The

prevalence of secondary diabetes was lower than that previously reported in predominantly young adult populations. Assessment for associated risk factors was limited by the small number of cases and controls available.

KEYWORDS: acute lymphoblastic leukemia, cystic fibrosis, organ transplant, secondary diabetes, thalassemia major

RÉSUMÉ

OBJECTIFS : Évaluer la prévalence du diabète secondaire observée dans des centres de soins pédiatriques tertiaires chez des enfants canadiens atteints de leucémie lymphoblastique aiguë (LLA), de fibrose kystique ou de thalassémie majeure, ou ayant subi une greffe du cœur, du foie ou du rein. La détermination des facteurs de risque associés à la survenue du diabète secondaire chez ces enfants était un objectif secondaire.

MÉTHODES : Une étude multicentrique descriptive et rétrospective a été menée auprès de patients de moins de 18 ans pour évaluer la prévalence des cas de diabète secondaire signalés. Un plan cas témoin a été utilisé pour évaluer, au moyen de rapports de cotes, les facteurs de risque associés à la survenue du diabète secondaire.

RÉSULTATS : La prévalence des cas signalés de diabète secondaire a été de 1,8 % en présence de LLA, de 2,9 % en présence de fibrose kystique, de 0 % en présence de thalassémie majeure, de 3,4 % chez les transplantés cardiaques, de 2,6 % chez les transplantés hépatiques et de 1,5 % chez les

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transplantés rénaux. Le rapport de cotes a été de 15,0 (IC de 95 % : 1,20 à 747,37) pour ce qui est de la survenue du diabète secondaire chez les enfants de plus de 12 ans atteints de LLA par rapport à ceux de 12 ans et moins atteints de LLA; dans 50 % des cas de diabète secondaire en présence de LLA, les enfants avaient un indice de masse corporelle supérieur au 95^e percentile, par rapport à 0 % des patients témoins atteints de LLA ($p = 0,005$). Aucun autre facteur de risque significatif n'a été associé à la survenue du diabète secondaire.

CONCLUSIONS : Cette étude est la première à examiner la prévalence du diabète secondaire chez les patients de centres de soins pédiatriques tertiaires de plusieurs populations à risque. La prévalence du diabète secondaire a été inférieure à celle signalée dans le passé dans des populations surtout composées de jeunes adultes. L'évaluation des facteurs de risque associés à la survenue du diabète secondaire a été limitée par le petit nombre de cas et de témoins.

MOTS CLÉS : diabète secondaire, fibrose kystique, thalassémie majeure, leucémie lymphoblastique aiguë, greffe d'organes

INTRODUCTION

Diabetes mellitus can result from increased insulin resistance, decreased insulin production or a defect in glucose or insulin signalling pathways. Secondary diabetes can develop as a consequence of a therapy for an underlying disease or as a complication of the disease itself. It may occur in diseases that require high-dose steroid therapy (e.g. cancer, inflammatory bowel disease or rheumatological diseases), antiretroviral therapy (e.g. HIV), immunosuppressive therapy (e.g. following solid-organ transplants), multiple blood transfusions leading to iron overload (e.g. thalassemia major) and diseases that cause pancreatic damage (e.g. cystic fibrosis [CF]) (1).

There are currently no published guidelines in Canada for screening for secondary diabetes in children or adults. The Canadian Diabetes Association 2008 clinical practice guidelines for the management of diabetes in Canada does not include screening recommendations for secondary diabetes (2). Nevertheless, close monitoring of children at risk is important for early recognition, diagnosis and treatment. Signs of diabetes can be subtle in children who have underlying chronic diseases and can include unexplained polyuria or polydipsia, poor growth velocity, delayed progression of puberty and failure to maintain or gain weight. Children can present with diabetic ketoacidosis if symptoms are missed.

Most studies on secondary diabetes have involved adult populations, and little is known about the prevalence of and risk factors for secondary diabetes in children (1). The present study specifically assesses the prevalence of secondary diabetes in at-risk populations of Canadian children with

acute lymphoblastic leukemia (ALL), CF, thalassemia major, heart transplant, liver transplant and renal transplant. In addition, we explored the association of various risk factors with the development of secondary diabetes, including gender, age, body mass index (BMI), family history of diabetes, medications (dose and duration), number of transfusions and associated CF mutations.

METHODS

Subjects

An invitation letter and protocol summary were sent to all 83 pediatric endocrinologists and pediatric endocrinology fellows practicing in Canada in January 2003. Endocrinologists agreed to participate at Alberta Children's Hospital (Calgary, Alberta, Canada), Winnipeg Children's Hospital (Winnipeg, Manitoba, Canada), Children's Hospital of Eastern Ontario (Ottawa, Ontario, Canada) and Izaak Walton Killam Hospital (Halifax, Nova Scotia, Canada).

Reasons cited by centres that did not participate were lack of a clinical diabetes database to identify cases of secondary diabetes; inability to identify appropriate controls with current disease-specific databases; or lack of resources, personnel and time to assist with the study.

Underlying diseases included in the study were ALL, CF, thalassemia major, heart transplant, liver transplant and renal transplant. Patients were enrolled if they were ≤ 18 years at time of diagnosis of 1 of the above underlying diseases; they were followed at a research site between January 1, 1990, and December 31, 2002. Subjects were excluded if health records from the time of initial diagnosis were not available for review, or if they had a diagnosis of diabetes mellitus prior to presentation of the underlying disease.

Measurements

The prevalence of reported secondary diabetes was determined for each underlying disease. Secondary diabetes was defined as hyperglycemia requiring a minimum of 2 weeks of insulin or oral hypoglycemic therapy, with a diagnosis by the attending physician of secondary diabetes according to Canadian Diabetes Association 2008 clinical practice guidelines criteria (2). Patients treated with dietary management alone were not included, since they could not be reliably identified through a retrospective review of clinical databases.

To determine prevalence, denominator data for each condition was identified by either the health records department or from clinical databases. Denominator data was defined as the number of patients followed at each site from January 1, 1990, to December 31, 2002, with 1 of the underlying diseases included in the study (i.e. ALL, CF, thalassemia major, heart transplant, liver transplant or renal transplant). Controls were identified using the lists

generated for the denominator data. Cases were matched to controls based on underlying disease alone.

To reduce information bias, a single study investigator (JH) reviewed all charts at every site and extracted data. At 1 site, the research ethics board required that the original attending physician perform the chart review for deceased patients, rather than the study investigator.

Exposures extracted from the charts included age at diagnosis of underlying disease, gender, ethnicity, BMI percentile, family history of diabetes mellitus in first- and second-degree relatives (type 1 diabetes, type 2 diabetes, gestational diabetes), medications at time of diagnosis of secondary diabetes, number of transfusions (in patients with thalassemia) and the high-risk mutation delta-F508 homozygosity (in patients with CF).

Data analysis

The prevalence of secondary diabetes was reported for each underlying disease. A 1:4 ratio of cases to controls was used to detect a risk ratio of 3, with an alpha of 0.05 and a beta of 0.80. Odds ratios (ORs) were used to describe the odds of developing secondary diabetes in those exposed to a risk factor compared to those not exposed to a risk factor. Fisher's exact test was used to compare the proportions of cases exposed to the risk factor with controls exposed to the risk factor. The sample size was too small to test for evidence of effect modification or confounding.

In order to ensure inter-rater reliability in data abstraction, approximately 15% of charts were reviewed again by an independent researcher using the same data abstraction form. No discrepancies were found when comparing data abstraction forms from the original investigator and independent reviewer for the variables analyzed (gender, date

of birth, underlying diagnoses, family history of diabetes). This resulted in a calculated kappa statistic of 1.0, which indicates excellent inter-rater reliability.

Ethics approval

This study was approved by the ethics committee of human experimentation of each participating centre in accordance with the Declaration of Helsinki. One site required individual written consent for chart reviews, which limited the number of cases and controls that could be studied.

RESULTS

The prevalence of reported secondary diabetes was: 1.8% in ALL, 2.9% in CF, 0% in thalassemia major, 3.4% post-heart transplant, 2.6% post-liver transplant and 1.5% post-renal transplant. Table 1 describes the estimated prevalences of secondary diabetes, as well as the site-specific number of cases identified. For CF and thalassemia major, the prevalences presented are likely over-estimates, since denominator data is missing from 1 site. The range of age at diagnosis for the cases of secondary diabetes included in the chart review was 8 to 18 years (mean age 13.9 years). Fewer cases were included in the analysis than the number of cases identified in the prevalence assessment due to the limitations of obtaining individual written consent for chart review. Some variables collected could not be analyzed due to incomplete data.

For patients with ALL, doses of steroid and l-asparaginase were similar in all cases and controls with ALL, so this was not analyzed with ORs. The only significant OR was 15.0 (95% CI 1.2–747.4) for the development of secondary diabetes in patients with ALL >12 years of age compared to those ≤12 years of age. In patients with ALL, the proportion of cases with a BMI >95th percentile was

Table 1. Summary of site data and prevalence of secondary diabetes by disease with 95% confidence interval CI

| | <i>ALL</i> | | <i>CF</i> | | <i>Thalassemia major</i> | | <i>Heart transplant</i> | | <i>Liver transplant</i> | | <i>Renal transplant</i> | |
|------------------------|---------------|----------------|---------------|----------------|--------------------------|----------------|-------------------------|----------------|-------------------------|----------------|-------------------------|----------------|
| | Cases | Total patients | Cases | Total patients | Cases | Total patients | Cases | Total patients | Cases | Total patients | Cases | Total patients |
| Site A | 1 | 123 | 0 | 108 | 0 | 76 | 1 | 8 | 0 | 21 | 0 | 35 |
| Site B | 6 | 143 | 6 | — | 0 | — | 0 | 5 | 2 | 12 | 2 | 55 |
| Site C | 1 | 125 | 0 | 12 | 0 | 5 | 0 | 5 | 0 | 17 | 0 | 35 |
| Site D | 1 | 119 | 0 | 87 | 0 | 0 | 0 | 11 | 0 | 28 | 1 | 79 |
| Total | 9 | 510 | 6 | 207 | 0 | 81 | 1 | 29 | 2 | 78 | 3 | 204 |
| Prevalence, % (95% CI) | 1.8 (0.8–3.3) | | 2.9 (1.1–6.2) | | 0 (0–4.4) | | 3.4 (0.09–17.8) | | 2.6 (0.3–9.0) | | 1.5 (0.3–4.2) | |

Dashed lines indicate that data was not available from that particular research site.

ALL = acute lymphoblastic leukemia

CF = cystic fibrosis

significantly greater than in controls: 50% of cases of secondary diabetes with ALL had a BMI > the 95th percentile compared to 0% of control patients with ALL ($p=0.005$). Positive family history in a first- or second-degree relative with type 1 diabetes, type 2 diabetes or gestational diabetes was not significant as a risk factor.

No cases of secondary diabetes were identified in patients with thalassemia major at any of the collaborating centres. In patients with heart transplants, gender or age >12 years was not found to have an increased OR for developing secondary diabetes. In patients with renal transplants, gender, age >12 years, BMI > 95th percentile or family history of diabetes were not significant risk factors in developing secondary diabetes. Although there were cases of secondary diabetes identified in patients with CF or liver transplant, case control analyses were not possible, since these cases were unavailable for chart review due to the limitations of obtaining individual written consent.

DISCUSSION

Secondary diabetes is rare in the pediatric population, and therefore challenging to study. In addition, uniform standards for screening for secondary diabetes in different centres are lacking. This study is unique, in that it includes 4 participating hospitals in different provinces that provide tertiary care for children aged 0 to 18 years for a total population base of approximately 6 million people. Unfortunately, the sites included in the study were not major heart, liver or renal transplant centres. This may have contributed to the lower prevalence identified in the transplant groups studied.

The prevalence estimates for secondary diabetes in this study are all lower than those described in the literature, even though missing denominator data for CF and thalassemia would have been expected to result in an overestimation of prevalence (Table 1). The most likely explanation is that most previous studies included mainly young adult populations that may be at increased risk for secondary diabetes due to increasing insulin resistance with age, obesity or a longer duration of underlying disease, whereas our study included only patients <18 years of age. This is especially true for diseases such as CF and thalassemia, where pancreatic cell damage is progressive with a longer duration of disease.

In addition, this study did not include patients with hyperglycemia of < 2 weeks' duration. In pediatric patients with ALL, Pui and colleagues (3) found 9.7% of patients developed hyperglycemia, and that hyperglycemia resolved after discontinuation of therapy for ALL. This is a much higher prevalence than the 1.8% found in this study. However, Pui and colleagues (3) defined cases as patients with 2 or more elevated random or fasting blood glucose levels, while this study defined cases as persistent hyperglycemia requiring insulin or oral hypoglycemic medication for

a minimum of 2 weeks. These differences in case definition could explain much of the variation observed in the reported prevalence of secondary diabetes. Cases identified in this study were also mainly diagnosed during acute illness, since the case definition did not include patients with mild hyperglycemia not requiring medication.

An increased odds of developing secondary diabetes in patients >12 years of age with ALL compared to those ≤ 12 years of age with ALL was found. Age >12 years was defined as a risk factor, since this would be the age that boys and girls would be expected to have pubertal changes associated with a physiologic increase in insulin resistance. This increased insulin resistance may lead to increased risk of developing diabetes in a susceptible individual. BMI >95th percentile for age and gender was also defined as a risk factor, as this cutoff is used to define obesity in pediatrics (4). Obesity is also associated with increased insulin resistance and, thus, may lead to an increased risk of developing secondary diabetes. The proportion of cases of secondary diabetes with ALL and a BMI >95th percentile was significantly greater than the proportion of controls with a BMI >95th percentile. This finding is consistent with the results of Pui and colleagues (3), who found the risk of hyperglycemia increased with age >10 years and the presence of obesity.

A wide range of prevalence rates of diabetes mellitus have been published in mixed populations of adult and pediatric patients with CF, and there appears to be a trend to higher prevalence rates over the past 20 years, increasing from 7.6% reported in 1988 (5) to 14.7% in 1994 (6), up to as high as 42.8% in 1999 (7). This could be due to earlier and more intensive screening practices or methods of screening for diabetes with variable sensitivity. Some risk factors previously reported include age (5) and presence of the delta-F508 mutation (7). In a more recent pediatric study of patients with CF, 4.3% had diabetes and 17% had impaired glucose tolerance when tested using the modified oral glucose tolerance test. The presence of at least 1 delta-F508 mutation was identified as a risk factor (8).

The prevalence of secondary diabetes in patients with transfusion-dependent thalassemia has been reported to range from 2 to 24% (9). Risk factors include older age, higher number of blood transfusions, higher serum ferritin, poor compliance with chelation therapy, family history of type 2 diabetes, hepatitis viruses and later pubertal stage (9). The fact that we did not identify any patients with secondary diabetes and thalassemia was probably due to the young age of our patient population, who would have a shorter duration of disease and likely fewer transfusions.

In adults with heart transplants, the prevalence of post-transplant diabetes mellitus (PTDM) has been estimated at 15.7% (10), with an estimated cumulative incidence of 19.6% (11). Risk factors included family history of type 2

diabetes (10) and pre-transplant glucose intolerance (11). In adults with liver transplants, the prevalence of PTDM was reported as 7.2%, and no significant risk factors were identified (12). In adults with renal transplants, the incidence of PTDM has been estimated at 20–30% (13–15). Risk factors that have been reported include age >45 years (13,14), higher body weight at transplant (13) and African-American (13) or Arab ethnicity (14). In children with renal transplants, the incidence of PTDM has been found to range from 3% to 7% (16). Risk factors include family history of type 2 diabetes (17), use of tacrolimus instead of cyclosporine (16,17) and African-American ethnicity (16).

This study has several weaknesses. First, since this was a retrospective chart review, there is the possibility of selection bias and information bias. Second, information was not always recorded in the health record. For example, ethnicity was not routinely documented at all sites, so this variable was not analyzed in this study. Third, information recorded in health records may have been subject to recall bias. Fourth, charts were not reviewed to ascertain missed diagnoses of secondary diabetes. Instead, the case definition used in this study relied on an attending physician's diagnosis. Thus, in this study it is possible that the prevalence of secondary diabetes was underestimated due to misclassification bias. Finally, denominator data for or thalassemia major and CF populations were not available for 1 site. This may have resulted in an overestimation of the prevalence of secondary diabetes in children with CF or thalassemia major (Table 1). A prospective study would have avoided some of the issues associated with recall bias and information bias, but this was not feasible. The long delay between diagnosis of the primary disease and onset of secondary diabetes makes it difficult to study.

Future research could include a prospective analysis of various cohorts of children who are at risk for secondary diabetes. This would provide stronger evidence for exposures that could be associated with developing secondary diabetes, since the baseline data collection would be more complete and a temporal association could be established for exposures preceding the outcome. This would assist with the development of evidence-based guidelines for screening for secondary diabetes in pediatrics.

This is the first pediatric study examining the prevalence of secondary diabetes in multiple at-risk populations in Canada. The prevalence of secondary diabetes was lower than that previously reported in young adult populations but emphasizes the need to be aware of secondary diabetes as a potential complication. Risk factors such as obesity and age >12 years were identified in patients with ALL. The early recognition and treatment of secondary diabetes can help to improve outcomes in children being treated for underlying diseases by maximizing nutrition, avoiding fluid imbalance,

reducing the risk of sepsis in children on immunosuppressive drugs and preventing life-threatening ketoacidosis. With the improved survival of children with chronic diseases, there needs to be a focus on monitoring for secondary diabetes in order to avoid the development of long-term and preventable complications associated with chronic hyperglycemia.

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AUTHOR DISCLOSURES

No dualities of interest declared.

AUTHOR CONTRIBUTIONS

JH, ES, HD, SH, AM, RS, CJ and DP substantially contributed to the original conception and design of the study and interpretation of the results. JH, ES, HD, SH, AM contributed substantially to the implementation of the study and acquisition of the data. All authors participated in the manuscript drafting, reviewed the manuscript for intellectual content and approved the final version.

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