UNIVERSITY OF CALGARY

Assessment of Prevalence and Associated Risk Factors for Secondary Diabetes in Canadian Children

by

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Abstract

Objective: The primary objective of this study was to assess the prevalence of secondary diabetes from 1990 to 2002 in at risk populations of Canadian children with: cystic fibrosis (CF), thalassemia major, acute lymphoblastic leukemia (ALL), heart transplant, renal transplant or liver transplant. The secondary objective was to determine risk factors associated with the development of secondary diabetes in these populations.

Methods: A multi-center, retrospective descriptive study was performed to assess for the prevalence of secondary diabetes. A multi-center, retrospective case-control design was used to assess for associated risk factors using odds ratios.

Results: The prevalence of secondary diabetes was: 2.9% in CF, 0% in thalassemia major, 1.8% in ALL, 3.4% in heart transplant, 1.5% in renal transplant and 2.6% in liver transplant. An odds ratio of 15 was found for the odds of developing secondary diabetes in those greater than 12 years of age with ALL compared to those less than or equal to 12 years of age with ALL. No other significant risk factors were found to be associated with the development of secondary diabetes.

Conclusion: This is the first pediatric study examining the prevalence of secondary diabetes in multiple at risk populations. The prevalence of secondary diabetes was lower than that previously reported in mainly adult populations. Assessment for associated risk factors was limited by the small number of cases and controls available.

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Dedication

This thesis is dedicated to my sons, Jonathan Richard Bonnett and Samuel Joseph Bonnett. They never cease to amaze me with their inquisitiveness and desire to learn.

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List of Abbreviations

ALL	Acute lymphoblastic leukemia
BMI	Body mass index (kg/m^2)
CDA	Canadian diabetes association
CF	Cystic fibrosis
CFRD	Cystic fibrosis related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
Cm	Centimeter
CPEG	Canadian pediatric endocrine group
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
HLA	Human leukocyte antigen
Kg	Kilogram
OGTT	Oral glucose tolerance test
PTDM	Post-transplant diabetes mellitus
SD	Standard deviation

Chapter One: The Research Problem

1.1 Introduction

Diabetes is a disease characterized by abnormally elevated blood glucose levels. This can be a result of one or more mechanisms that include: increased insulin resistance, decreased insulin production or a defect in glucose or insulin signaling pathways. Secondary diabetes is diabetes that develops as a consequence of a therapy for an underlying disease or as a complication of the disease itself. It can be transient or permanent depending on the underlying cause. For example, if damage to the insulin producing cells of the pancreas is caused by a disease process, then the secondary diabetes will be permanent. On the other hand, if the secondary diabetes is medication induced, then it may resolve with discontinuation of the medication.

Many conditions are associated with the development of secondary diabetes: diseases that require high dose steroid therapy (eg. cancer treatment, inflammatory bowel disease, and rheumatological diseases), anti-retroviral therapy (eg. HIV), immunosuppressive therapy (eg. following solid organ transplants), multiple blood transfusions leading to iron overload (eg. thalassemia major) and diseases that cause pancreatic damage (eg. cystic fibrosis). In this study, secondary diabetes was assessed in a select group of conditions that have been previously studied in adult populations and had some limited pediatric data available for comparison. The conditions included in the study were: cystic fibrosis (CF), acute lymphoblastic leukemia (ALL), thalassemia major and solid organ transplants (renal, liver, and heart).

With the increased survival from life threatening diseases in children, new long term complications such as secondary diabetes are emerging. Once diabetes has

developed, the risk of long term microvascular and macrovascular disease becomes yet another complication of these complex diseases. Early recognition and treatment of secondary diabetes is essential in preventing long term complications of hyperglycemia. In addition, early treatment can prevent immediate adverse outcomes from hyperglycemia such as polyuria, polydipsia, fatigue, weight loss and increased risk of infection.

1.2 Gaps in the knowledge

There is a great deal of evidence in the current literature that the prevalence of secondary diabetes is increasing due to the increasing survival rates of patients with CF, ALL, thalassemia major and solid organ transplants. However, most of the studies have been done in adult populations and less is known about the prevalence and risk factors for secondary diabetes in children (Appendix H) (1). The present study specifically assessed the prevalence of secondary diabetes in at risk populations of Canadian children. In addition, this study explored the association of various risk factors with the development of secondary diabetes.

1.3 Purpose of the study

The primary objective of this study was to assess the prevalence of secondary diabetes from 1990-2002 in at risk populations of Canadian children with CF, thalassemia major, ALL, heart transplant, kidney transplant and liver transplant.

A secondary objective was to examine risk factors associated with the development of secondary diabetes in each of the above disease categories. Possible risk factors are: gender, age, family history, medications (dose and duration), and number of transfusions.

1.4 Research question

What was the prevalence of secondary diabetes over a twelve year period in at risk populations of Canadian children, such as those with CF, thalassemia major, ALL, heart transplant, kidney transplant or liver transplant; and what are the associated medical and socio-demographic risk factors for developing secondary diabetes in these children?

1.5 Significance of this study

There is little data describing risk factors and prevalence of secondary diabetes in the pediatric population. With changes in chemotherapeutic regimes, increasing numbers of transplants and more survivors of childhood diseases such as cystic fibrosis there is need to evaluate the prevalence of secondary diabetes in our pediatric population.

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 and preventing metabolic derangements such as 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.

Chapter Two: Literature Review

2.1 Classification of diabetes

The Canadian Diabetes Association (CDA) has classified various types of diabetes according to the underlying etiology (2). Type 1 diabetes is a result of pancreatic beta cell destruction, which results in a decrease in insulin production. This type of diabetes is usually auto-immune related. Type 2 diabetes is characterized by increased insulin resistance with a relative deficiency of insulin. Gestational diabetes is glucose intolerance that is first recognized or has an onset during pregnancy. Two miscellaneous categories include specific genetically defined forms of diabetes and secondary diabetes (ie. associated with other underlying diseases or medications).

2.2 Prevalence and risk factors for secondary diabetes

2.2.1 Secondary diabetes in acute lymphoblastic leukemia

Pui et al (3) did a study in 1981 looking at various risk factors for developing hyperglycemia with L-asparaginase and prednisone therapy. This study was a retrospective review of 421 children aged 3 months to 20 years from 1972-1980 who had received L-asparaginase and prednisone for treatment of ALL. They found that 9.7% of their patients developed secondary diabetes and that all of these resolved after discontinuation of the therapy for ALL. In this study, patients with two or more elevated random or fasting blood glucose levels were identified as cases. The significant risk factors identified were age greater than 10 years, presence of obesity, Down syndrome, and family history of diabetes mellitus.

2.2.2 Secondary diabetes in cystic fibrosis

CF has been identified as a cause of secondary diabetes. The primary mechanism is insulin deficiency caused by progressive damage of the pancreas by viscous secretions. Pancreatic islets cells are gradually destroyed and replaced by fibroadipose tissue. Insulin resistance also plays a role, particularly when patients are being treated with glucocorticoids and have acute or chronic infections with significant inflammation (4).

There are many factors unique to CF that results in abnormal glucose metabolism. These include: under nutrition, acute and chronic infections, increased energy expenditure and work of breathing, malabsorption of carbohydrates, abnormal intestinal transit time, and liver dysfunction (5) .

There has been a wide range of published prevalences of diabetes mellitus in this population. This could be due to variable screening practices and age at investigation. Lanng et al (6) published a cross sectional review in 1994 of all Danish CF patients (age range of 3-40 years and median age of 20 years) and found that 14.7% had diabetes mellitus. The prevalence was found to increase with age. In a retrospective review, Finkelstein et al (7) reported that 7.6% of 448 patients with CF (age range of 8-32 years and mean age of 19.8 years) had diabetes mellitus. Cucinotta et al (8) showed in a 10 year prospective follow up of 28 CF patients (age range of 6-22 years and mean age of 14 years) that 42.8% developed diabetes mellitus. They also found that the ΔF508 mutation was seen in 66.7% of this diabetic group.

In 2003, a study of pediatric patients with CF examined 94 patients aged 10-18 years with no clinical symptoms of diabetes using a modified oral glucose tolerance test (OGTT). It demonstrated that 4.3% had diabetes and 17% had impaired glucose

tolerance when tested using the modified OGTT. No specific cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation was found to predict abnormal glucose tolerance, but all patients with diabetes or impaired glucose tolerance had severe CFTR mutations (with at least one ΔF508 mutation) on both alleles (9).

2.2.3 Secondary diabetes in thalassemia

Impaired glucose tolerance and diabetes mellitus is seen in pediatric patients receiving multiple transfusions such as those with thalassemia major. A wide range of prevalence that varies from 2%-24% has been reported (10). Risk factors include: older age, high number of blood transfusions, high serum ferritin, poor compliance with chelation therapy, family history of diabetes, hepatitis viruses and later pubertal stage (11). Chronic iron overload is hypothesized to cause insulin deficiency via toxic effects on the pancreatic islet cells. It has also been suggested that insulin resistance plays a role in the glucose intolerance and that chronic stimulation of insulin secretion may lead to secondary failure of the islet cells (12).

Merkel et al (13) studied 12 children (4 pre-pubertal and 8 pubertal) with thalassemia who required chelation therapy for multiple blood transfusions. They used euglycemic insulin clamp, hyperglycemic clamp and OGTT to determine if there was evidence of insulin resistance in these children. They found that the pubertal children had an impaired glucose metabolism response to insulin and significantly elevated insulin levels when given a hyperglycemic stimulus. It was postulated that the insulin resistance may have been due to iron deposition in the liver or muscle, thereby interfering with suppression of hepatic glucose production or glucose metabolism in muscle tissue.

2.2.4 Secondary diabetes and solid organ transplants

2.2.4.1 Renal transplants

There have been several studies reporting the incidence of post-transplant diabetes mellitus (PTDM) in adults following renal transplantation and the factors associated with this complication. Cosio et al (14) reviewed 2078 non-diabetic renal transplant recipients from 1982 until 1999 with a mean age of 40.9 years. All patients received prednisone and cyclosporine post-transplant. They found that the incidence of PTDM increased from 7.1% after 1 year to 29.8% 15 years post-transplant. Factors leading to an increased relative risk of developing PTDM included age >45years, African-American race, and higher body weight at transplant. Johny et al (15) retrospectively reviewed 631 renal transplant recipients in Kuwait with an age range of 30-60 years. Of those, 552 were non diabetic pre-transplant and of these 21.2% developed PTDM. These patients received prednisone and azathioprine, with or without cyclosporine. They identified a higher incidence of PTDM in those >45 years of age or those of Arab descent. PTDM was also more likely to be associated with infections and coronary artery disease. In a small study, Al-Asfari et al (16) found that of 41 renal transplants aged 18-64 years 24% developed diabetes.

In contrast to the above studies, there is little information on the incidence of PTDM in pediatric renal transplants and existing studies give a wide range of incidences (17). Greenspan et al (15) reviewed 229 charts of pediatric renal transplants (age range 1-18 years) and found an incidence of 7%. This is lower than found in the adult studies. Risk factors identified included: first degree or second degree family history of type 2

diabetes mellitus, tacrolimus use instead of cyclosporine and hyperglycemia in the 2 weeks post transplant.

A retrospective analysis of 1365 children done by Al-Uzri et al (16) showed an incidence of PTDM of <3%. They found that African-American ethnicity and the use of tacrolimus were significant risk factors for developing PTDM.

2.2.4.2 Heart transplants

PTDM is a known complication of adult heart transplants. A retrospective review by Depczynski et al (17) showed that 15.7% of 97 adult heart transplant patients developed PTDM. Risk factors associated included family history of diabetes and the requirement for insulin post-op day 2. Nieuwenhuis et al (18) followed 228 cardiac transplant patients with a mean age of 50 years to see if OGTT would be predictive of PTDM. They found a cumulative incidence of 19.6% and that the risk of PTDM increased with the degree of pre-transplant glucose intolerance.

2.2.4.3 Liver transplants

Liver transplantation has also been shown to be associated with PTDM. Steinmuller et al (19) studied 618 patients one year after liver transplant on tacrolimus or cyclosporine and prednisone. They found new onset PTDM in 7.2% of the patients, but they did not find any significant risk factors (including age, gender, tacrolimus or cyclosporine).

2.3 Short term complications of secondary diabetes

Secondary diabetes manifests itself acutely with clinical symptoms of hyperglycemia. These include: polyuria, polydipsia, fatigue, nocturnal enuresis, metabolic compromise, poor nutrition with weight loss, and increased risks of infections.

Regardless of a child's prognosis from their underlying disease, it is still important to recognize and treat diabetes since symptoms from hyperglycemia can affect a child's quality of life.

In addition, prolonged hyperglycemia that is untreated can lead to a serious, life-threatening condition called diabetic ketoacidosis (DKA). In this condition, lack of insulin results in altered metabolic function leading to high blood glucose, metabolism of free fatty acids in the body causing a build up of ketones as a by-product, which subsequently results in metabolic acidosis. Patients can present with severe dehydration, vomiting, respiratory distress, altered level of consciousness and cerebral edema.

2.3.1 Diabetic ketoacidosis in acute lymphoblastic leukemia

L-asparaginase has been implicated in causing DKA in pediatric patients being treated for leukemia. In 1972, Gillette et al (20) reported a 10 year old girl who developed DKA following treatment with L-asparaginase and prednisone for a relapse of her leukemia. She required insulin therapy for 18 days and subsequently had normal OGTT following discontinuation of the L-asparaginase. The authors hypothesized that their patient may have been hypoinsulinemic due to the depletion of L-asparagine by the L-asparaginase. This could have resulted in an inhibition of insulin synthesis due to lack of this component. Another possibility was that existing insulin might have been destroyed by the L-asparaginase.

A case of ketotic hyperglycemia in a 13 year old boy with leukemia has been reported. This was associated with his treatment with L-asparaginase and prednisone and required insulin therapy. The same patient subsequently developed non-ketotic hyperglycemia when being treated with prednisone. This case report emphasized the risk

of future development of hyperglycemia in a patient who previously developed secondary diabetes from receiving L-asparaginase and prednisone. It is unclear if this is caused by a permanent pancreatic damage by the L-asparaginase or an underlying predisposition (21)

2.3.2 Diabetic ketoacidosis in cystic fibrosis

DKA has been reported in rare cases of CF occurring together with diabetes. Atlas et al (22) reported an 11 year old boy who had been diagnosed with CF at 6 months of age and subsequently presented with DKA at 11 years of age. Interestingly, genetic testing confirmed a heterozygote deletion of the F508 mutation, which is consistent with CF and a homozygous absence of aspartic acid in position 57 of the human leukocyte antigen (HLA) DQ-B allele, which is associated with a greater risk of type 1 diabetes mellitus. Anti-insulin antibodies were also present. Therefore, it appeared that this child did not have secondary diabetes, but a rare situation of two distinct diseases.

2.3.3 Diabetic ketoacidosis in thalassemia

DKA has been reported as a complication of transfusion dependent thalassemia major (23). In one study, 16 out of 82 (19.5%) patients had diabetes diagnosed and 31% of those presented with DKA (9).

2.3.4 Diabetic ketoacidosis in post transplant diabetes mellitus

DKA has been reported as an unusual consequence of post-transplant diabetes. Yoshida et al (24) described DKA in a 37 year old renal transplant patient on cyclosporine, a 50 year old liver transplant patient on tacrolimus and a 58 year old liver transplant patient on cyclosporine. Each of these three patients had been on maintenance immunosuppression at the time of presentation with DKA and had not been receiving any

therapy for hyperglycemia. The authors postulated that a combination of peripheral insulin resistance and pancreatic beta cell impairment by the cyclosporine or tacrolimus resulted in the development of DKA.

2.4 Long term complications in secondary diabetes

The early onset of secondary diabetes is a serious health concern for children since they are at increased risk for complications of diabetes. Poor glycemic control of long duration could lead to significant morbidity including macrovascular (peripheral vascular disease, coronary artery disease and stroke) and microvascular (retinopathy, neuropathy and nephropathy) complications (25). Once diabetes is present, regardless of the underlying cause, better metabolic control decreases the risk or delays the onset of microvascular complications (26;27). Therefore, early treatment is critical in populations that are already burdened by a primary disease process.

In cystic fibrosis related diabetes (CFRD), severe microvascular complications have been reported in a 21 year old woman (28). This patient was diagnosed with diabetes at the age of 12 years and subsequently developed proliferative diabetic retinopathy requiring laser therapy, nephropathy, and autonomic neuropathy. The authors emphasized the need to suspect end organ damage in patients with CFRD. In a Danish study of CFRD, late diabetes complications were found in 10% of patients who had duration of diabetes from 1-17 years. The complications seen were microvascular and included retinopathy, nephropathy, and neuropathy (5).

2.5 Diagnosis of diabetes

Early detection of secondary diabetes and close monitoring of children at risk is necessary for the prevention of complications. In the Canadian Diabetes Association

2003 clinical practice guidelines, a fasting plasma glucose of greater than or equal to 7 mmol/L is defined as diabetes, 6.1 to 6.9 mmol/L as impaired fasting glucose, and less than 6.1 mmol/L as normal in children and adults. These are the same criteria currently in use for the adult population (2).

It has been recommended that the fasting (no food for at least 8 hours) plasma glucose be used for the initial screening test. It is fast, easy to perform, inexpensive, and more convenient than an oral glucose tolerance test (OGTT). A 75 gram OGTT may be necessary if the clinical suspicion is high and the fasting plasma glucose is normal. With the OGTT, a 2 hour blood glucose value of greater than or equal to 11.1 mmol/L is considered a positive test for diabetes, 7.8 mmol/l to 11.0 mmol/L is impaired glucose tolerance, and less than 7.8 mmol/L is normal in children and adults. In the absence of significant symptoms and metabolic decompensation, a confirmatory laboratory glucose test (either a fasting plasma glucose, casual plasma glucose or OGTT) must be done on a separate day (2).

2.6 Screening recommendations for secondary diabetes

There are currently no Canadian guidelines in place for screening for secondary diabetes in children or adults (2). Close monitoring of children at risk is important for early recognition, diagnosis and treatment. Signs of diabetes can be subtle in children that have underlying chronic disease and can include: unexplained polyuria or polydipsia, poor growth velocity, delayed progression of puberty, and failure to maintain or gain weight.

Screening for diabetes with fasting blood glucose is the least invasive method and is advocated by the CDA. However, if the clinical suspicion is high and the fasting plasma glucose is in the "impaired" range (6.1-6.9 mmol/L) then an OGTT may be needed.

For children with CF, a consensus report published in 1999 (29) recommended that random blood glucose be checked annually in children after 10 years of age. If the random glucose is <7 mmol/L then no further investigations would be required. An OGTT should be strongly considered if there was a normal fasting glucose but symptoms of hyperglycemia. Symptoms can be subtle in patients with CF and include: unexplained chronic decline in pulmonary function, and failure to maintain or gain weight.

It has been suggested that conventional measures of blood glucose such as fasting plasma glucose, 2 hour OGTT, and hemoglobin A1c are not appropriate to be used in patients with CF to screen for diabetes. One study showed that when comparing groups with CF and controls matched for body mass index (BMI) and age, the area under the curve for glucose values using a continuous glucose monitoring system was significantly higher in patients with CF than with controls (30).

In patients with thalassemia that require frequent blood transfusions and chelation therapy, it may be reasonable to screen yearly with fasting plasma glucose after the age of 10 years since pubertal age may increase insulin resistance. Similarly, children with ALL on L-asparaginase and prednisone therapy could be screened annually with fasting plasma glucose. For children with heart, liver or kidney transplants on anti-rejection medications and high dose steroids, annual screening with fasting plasma glucose could also be undertaken.

2.7 Treatment options for secondary diabetes

Despite the varying underlying causes of secondary diabetes, treatment options remain the same for secondary diabetes as for the more common type 1 and type 2 diabetes. The goal is to achieve euglycemia and avoid acute and long term complications of hyperglycemia in all forms of diabetes. In acute situations of hyperglycemia, insulin therapy that is either subcutaneous or intravenous is the standard therapy. In the long term, hyperglycemia can be managed with a combination of appropriate dietary intake, exercise, insulin and oral hypoglycemic agents.

Treatment of secondary diabetes in children is best accomplished through the combined efforts of a multi-disciplinary team (31). Ideally, patients would have access to dieticians, nurse educators, psychologists, social workers and physicians. Secondary diabetes has a significant impact on the entire family and psychosocial support should be offered if needed.

There have been some recent studies showing that metformin, an oral hypoglycemic medication, is an effective treatment for adolescents with type 2 diabetes (32;33). This may be a useful adjunctive therapy to insulin in secondary diabetes, but is not routinely used. A recent survey has shown that pediatric endocrinologists in the United States and Canada treat 44% of children with type 2 diabetes with oral hypoglycemic agents. Of these, 71% received metformin, 46% sulfonylureas, 9% thiazolidinediones and 4% meglitinide (34). Unfortunately, many oral hypoglycemic agents used in adult patients with type 2 diabetes have not been licensed for use in the

pediatric population. Until the safety and efficacy of these drugs is established they cannot be recommended for routine clinical use.

There is a lot of experience with the use of subcutaneous insulin injections in type 1 diabetes. Recently, it has been used in the early treatment of type 2 diabetes in decreasing glucose toxicity and achieving target blood glucose levels (35). Currently, it remains the initial treatment of choice in secondary diabetes.

Follow up for pediatric patients with secondary diabetes should involve the family and a multidisciplinary team. Children can feel well and do not see the benefits of rigorous blood glucose monitoring or dietary restrictions and exercise. The long term risks of secondary diabetes and the benefits of treatment are often not tangible to children. This can lead to frustration and poor compliance with treatment plans. Ongoing education and support is therefore essential in managing secondary diabetes.

2.8 Barriers to treatment

Management of diabetes involves changes in daily lifestyle, such as diet and activity, that need to be long term and consistent. However, there are often many barriers faced by health care professionals when treating diabetes (36). Children may feel well and do not see any immediate benefits from treatment. Families may have socioeconomic constraints or cultural differences that can make implementing healthy lifestyles difficult. Children with secondary diabetes are also managing their underlying disease, which can seem more immediately threatening to them. Children who develop secondary diabetes would have already undergone multiple medical procedures and hospitalizations due to

their primary disease and having a new diagnosis of a chronic condition could be overwhelming.

Chapter Three: Methodology

3.1 Study design

3.1.1 Design type

This is a descriptive study designed to assess the prevalence of secondary diabetes. In addition, a retrospective case control study was performed to assess risk factors for developing secondary diabetes.

3.1.2 Design description and rationale

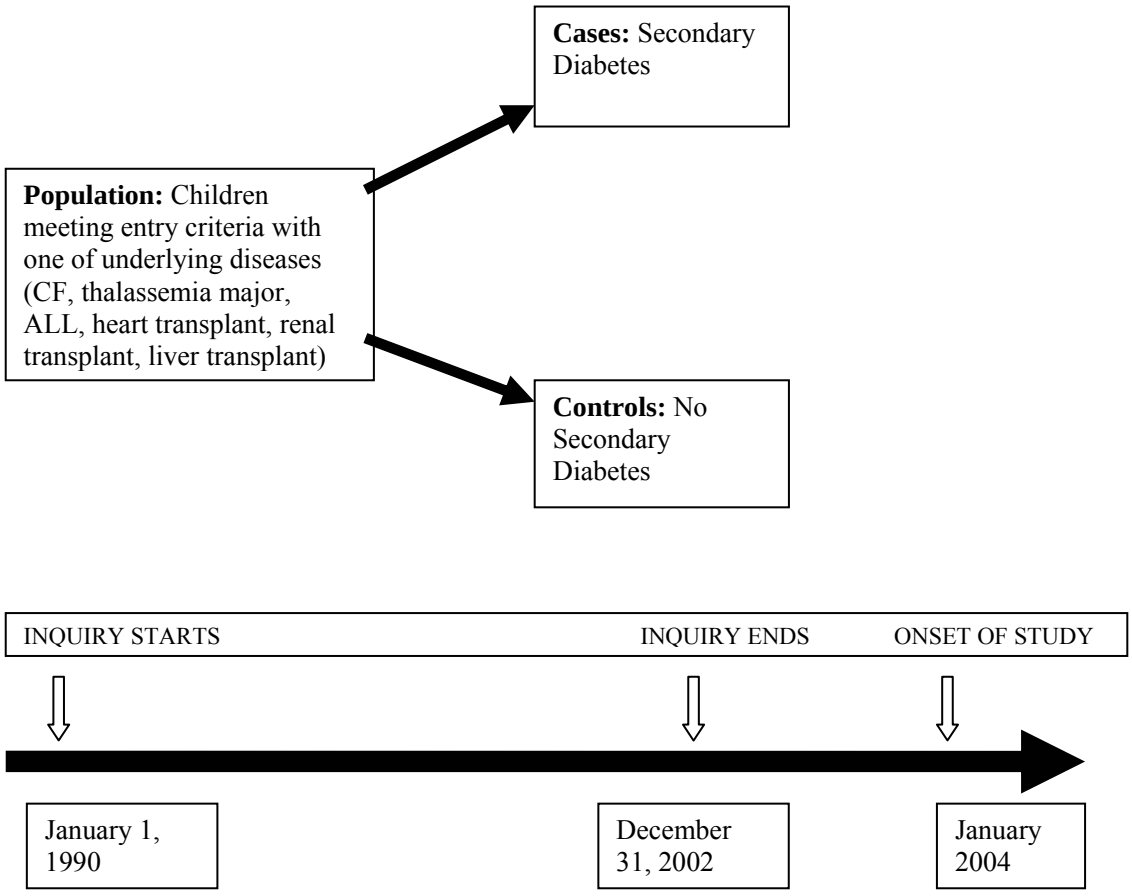
A retrospective study design was chosen since it would be less costly and require a shorter time to complete. A prospective study would have avoided some of the issues associated with recall bias and information bias, however this would have required more resources and time than was feasible. For example, there is a long delay between the diagnosis of some primary diseases and the onset of secondary diabetes. In particular, for this study, patients with cystic fibrosis or thalassemia major are usually diagnosed in the first year of life but would not be expected to develop secondary diabetes until their second to third decade of life. Therefore, a retrospective study is more appropriate for gaining information that could be used in designing future prospective studies.

Since secondary diabetes is rare in the pediatric population, a multi-center study design was chosen to increase the number of cases that could be identified. The multi-center nature of the study allows for the results of the study to be more generalizable since the subjects included were from four different provinces within Canada.

3.1.3 Design diagram

Figure 3.1 provides a visual description of the study design and time line.

Figure 3.1 Design Diagram- Retrospective Case Control



3.2 Literature search

A background literature search was conducted using the National Library of Medicine and National Institute of Health PubMed and Medline search engine. Limits applied were English language and human subjects. The following terms were used in the search: diabetes, secondary diabetes, hyperglycemia, and diabetic ketoacidosis in combination with each of: thalassemia major, cystic fibrosis, acute lymphoblastic leukemia, renal transplant, heart transplant, and liver transplant. Reference lists from selected articles were also reviewed.

3.3 Study population

3.3.1 Recruitment of participating centers

In order to recruit as many Canadian pediatric diabetes centers as possible, an invitation letter and protocol summary were e-mailed to all pediatric endocrinologists and pediatric endocrinology fellows (approximately eighty) on the mailing list for the Canadian Pediatric Endocrine Group (CPEG) in January 2003. CPEG is comprised of all pediatric endocrinologists currently practicing within Canada in fifteen different centers. An oral presentation of the protocol was also done at the CPEG annual meeting in February 2003. In April, 2003, a follow-up e-mail was sent out to confirm participating centers.

This study was conducted at the following four participating Canadian pediatric hospitals: Alberta Children's Hospital (Calgary, Alberta), Winnipeg Children'sHospital (Winnipeg, Manitoba), Children's Hospital of Eastern Ontario (Ottawa, Ontario), and Isaac Walton Killam Hospital (Halifax, Nova Scotia).

Of the centers that chose not to participate in this study, various reasons were given including: lack of appropriate data base to accurately identify cases of secondary diabetes, inability to identify appropriate controls with current data bases, lack of resources, personnel and time to assist with study (eg. to help obtain site specific ethics approval, accessing health records, approaching subspecialty clinics for controls, etc.)

3.3.2 Inclusion criteria

1. Subjects less than or equal to 18 years of age at the time of diagnosis of their underlying disease (CF, thalassemia major, heart transplant, kidney transplant, liver transplant, or ALL)
2. Followed at one of the participating research sites: Calgary, Winnipeg, Ottawa, Halifax between January 1, 1990 and December 31, 2002.
3. Cases of secondary diabetes required persistent insulin therapy and/or oral hypoglycemic medications for a minimum of two weeks.

3.3.3 Exclusion criteria

1. Patients who were currently being followed in a participating center but were initially seen at other centers where the charts from the time of initial diagnosis were not available for review.
2. Patients whose charts were not available for review.
3. Patients with transient hyperglycemia that did not require insulin therapy.
4. Patients who required transient insulin therapy as inpatients and were not followed by a diabetes clinic.

5. Patients who had known diabetes mellitus prior to their presentation for other disease (CF, thalassemia, ALL, heart transplant, kidney transplant, or liver transplant)

3.4 Sample size and sampling procedure

The retrospective cross-sectional review of prevalence was a descriptive study so samples sizes were estimated to determine the number of patients needed to have an appropriate confidence interval. It was estimated that the incidence of secondary diabetes was less than 5% (from review of adult literature). Therefore, if 200 children were studied, 5 cases could be found, which would provide an exact confidence interval of 0.8% to 6%.

In determining the sample size required to perform the retrospective case-control study to look for associated risk factors, it was estimated that 50% of controls would have the identified risk factor. In order to detect a risk ratio of 3 then the following numbers of cases and controls would be needed as described by Breslow and Day (37):

Risk ratio of 3.0	Proportion	# Cases	#Controls
(Alpha=.05)			
(Beta=.80)	1:1	53	53
	1:2	40	80
	1:4	33	132

Since it was more likely that approximately 33 cases of secondary diabetes would be detected, it was estimated that 132 controls would be required (or a 1:4 ratio of cases:controls) to detect a risk ratio of 3 with an alpha of 0.05 and a beta of 0.80.

3.5 Data collection procedure

After ethics approval was obtained for each participating site (Calgary, Winnipeg, Ottawa and Halifax), the pediatric endocrinologist who had agreed to be a collaborator accessed their clinic data bases or local health records data base to determine the cases of secondary diabetes that met the inclusion criteria. Disease status was identified from the health records as hyperglycemia requiring a minimum of 2 weeks of insulin or oral hypoglycemic therapy with a diagnosis by the attending physician of secondary diabetes (as per the CDA 2003 guidelines for diagnosis (2)). The patient's hospital record number and name were used to pull the complete health records chart for review and data collection. Data abstract forms with concise definitions of the variables were used to collect the information (Appendix A and Appendix B).

A single investigator was used when possible to review the charts and collect data in order to reduce the impact of information bias. This was not possible for all cases, since one site's research ethics board required that the original attending physician for deceased patients should be the one to perform the chart review rather than an off- site investigator. One site required individual written consent for chart reviews which limited the number of cases and controls that could be studied.

To determine prevalence of cases within each underlying disease being investigated, each site collaborator identified the denominator through either the health records department or from clinic specific data bases. Denominator data was defined as the number of patients followed at each site from January 1, 1990 to December 31, 2002 with the underlying diseases: thalassemia major, CF, heart transplant, kidney transplant, liver transplant or ALL. Each site had variations in the source of denominator data. This

was due to the following reasons: differing fiscal year for health records, changes during study period from paper based records to computer based records, changes in data base or software during the study period. All attempts were made to ensure accuracy when identifying cases and denominator data.

Controls were identified using the lists generated for the denominator data. Patients without diabetes were randomly selected for chart review and data collection (ie. Every 3rd or 4th name from an alphabetical list of control patients was used). The same data abstract form (Appendix A) was used to collect the information. When possible, a single investigator was used to review the charts and collect data in order to reduce the impact of information bias. Again, this was not always feasible since the research ethics board for one site required that the original attending physician for deceased patients should be the one to perform the chart review.

In order to assure inter-rater reliability in data abstraction, approximately 15% of charts were reviewed again by an independent researcher using the same data abstraction form and the kappa statistic was used to assess the agreement. No discrepancies were found when comparing data abstraction forms of the original investigator and the 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. The charts reviewed by the independent researcher were limited to the local site due to the ethical constraints of having an independent external reviewer at the collaborating sites, as well as financial constraints related to travel.

3.6 Data editing and management

3.7 Variables

3.7.1 Primary outcome variable

Prevalence of secondary diabetes was defined as hyperglycemia requiring persistent insulin therapy and/or oral hypoglycemic medications for a minimum of 2 weeks. Prevalence was determined for each associated underlying disease being studied (eg. CF, thalassemia major, heart transplant, kidney transplant, liver transplant, ALL)

3.7.2 Secondary outcome variables

In order to determine if there were any identifiable associated risk factors, the following variables were examined:

-Age at diagnosis of underlying disease (years)

-Gender (male, female)

-Ethnicity (aboriginal, hispanic, asian, African-american, caucasian)

-Weight (kilograms- kg) at diagnosis of underlying disease

-Height (centimetres- cm) at diagnosis of underlying disease

-Body Mass Index (BMI) kg/m2 (percentile adjusted for age and gender) at time of diagnosis of secondary diabetes in cases. In controls, BMI was assessed at time of induction therapy for ALL, the last clinic visit for CF and thalassemia, and at time of transplant.

-Family history of diabetes mellitus in first degree relatives and second degree relatives (type 1 diabetes, type 2 diabetes, gestational diabetes)

-Medications: at the time of diagnosis with secondary diabetes eg. L-asparaginase, cyclophosphamide, tacrolimus

-Thalassemia major: number of transfusions (units of packed red blood cells, serum ferritin level

-Cystic fibrosis: high risk mutation (presence of delta F508 homozygosity)

3.8 Data analysis

3.8.1 Descriptive statistics

This is a descriptive study so the results of the prevalence study were reported as a percentage of children with secondary diabetes in each specific population of children (those with CF, thalassemia major, ALL, heart transplant, kidney transplant or liver transplant). Confidence intervals were also calculated. The prevalence of secondary diabetes was reported for each disease group rather than as an overall prevalence since the underlying cause of secondary diabetes is quite distinct pathophysiologically for each.

3.8.2 Odds ratios

In the case control portion of the study, a ratio of 1 case to 4 controls was used. Cases were matched to controls on underlying disease alone and then risk factors for developing secondary diabetes were assessed using odds ratios. The risk factors were assessed in each disease group rather than combining groups, since the underlying cause of secondary diabetes is quite distinct pathophysiologically for each.

Exposures that were assessed included gender, pubertal age, obese BMI, family history of diabetes (type 1, type 2, gestational), and tacrolimus or cyclosporine use in renal transplant. Some exposures could not be examined since data was limited (eg. BMI was not examined in children with heart transplants) or if there were no cases or controls exposed (eg. no family history of type 2 diabetes in a first degree relative in children with renal transplant).

Age greater than 12 years was defined as exposure since this would be the age that boys and girls would be expected to have some pubertal changes. This would include an increase in insulin resistance that could lead to increased risk of developing diabetes in a susceptible individual. BMI greater than the 95th% tile was defined as exposure since this would be consistent with a diagnosis of obesity which also leads to increased insulin resistance and could lead to an increased risk of developing secondary diabetes.

If the target sample size were achieved, then the cases could have been stratified by treatment center and the Mantel-Haenzel test for homogeneity could have been applied to look for evidence of effect modification or confounding. However, this analysis was not performed due to the small sample size obtained.

Chi-square test was used to compare the odds ratios. Since the sample sizes were so small, Fisher's exact test was considered. The Fisher's exact test provides a probability when the expected frequency of any cell in a 2 x 2 table is less than five. However, it is purely a hypothesis test and unlike the Chi square test, it does not allow an equivalent method of estimation for comparing proportions from very small samples.

3.9 Ethical considerations

This research project was approved by the Conjoint Health Research Ethics Board of the University of Calgary (Appendix C), the Research Ethics Board of the University of Manitoba (Appendix D), the Research Ethics Board of the Children's Hospital of Eastern Ontario in Ottawa (Appendix E), and the Research Ethics Board of the IWK Children's Hospital in Halifax (Appendix F).

3.9.1 Consent

Since human subjects were not directly involved in this research project and data collection was through retrospective review of existing health records, individual consent was not required by each site. Individual consent was not feasible since the sample size was large and spread over a long time frame. The data collected from the health records was minimal and not sensitive in nature. One site did require individual written consent for health records to be reviewed in this study, which limited the number of cases and controls that could be examined.

Written or verbal consent from division heads in sub-specialty clinics was also obtained in order to utilize information from clinic specific data bases to obtain control subjects and denominator data.

3.9.2 Data collection and storage

Only the investigators in the study had access to the data collected. In order to maintain confidentiality, any information linking patient names and health record numbers to their study numbers was kept in a locked office. Information to be analyzed was stored in a secure computer with password protected data access. A study identification number was assigned to each case and control. Only the investigators and their designated research assistants had access to this computer. Data collected will be stored for 25 years then destroyed.

Any paper based information was stored in a locked office and disposal of any patient data on paper was done via shredding and disposal through the Alberta Children's Hospital confidential waste disposal.

3.9.3 Confidentiality

Data was analyzed anonymously and results were presented as aggregate group data so that no individual patient identification will be possible. Therefore, publication or release of the data would not affect patient confidentiality.

3.10 Funding

A grant proposal was submitted to the Diabetes Association (Brooks & District) in 2003 and was successfully funded (Appendix G). This covered the costs of health records chart retrieval fees, travel for data collection, and office supplies.

Chapter Four: Results

4.1 Prevalence of secondary diabetes

The estimated prevalences of secondary diabetes were: 2.9% in CF, 0% in thalassemia major, 1.8% in ALL, 3.4% in heart transplant, 1.5% in renal transplant and 2.6% in liver transplant (Table 4.1). Tables 4.2 to 4.7 describe the site specific data for each of the underlying diseases with regards to cases of secondary diabetes and denominator data. The range of age at diagnosis for the ten cases of secondary diabetes identified was 8 years to 18 years (mean age 13.9 years).

Blank spaces in the tables indicate that specific data was not available. Specifically, the denominator data for the thalassemia major and CF population were not available for one site. This may have resulted in an over-estimation of the prevalence of secondary diabetes in children with CF and thalassemia major.

The summary statistics of mean, standard errors and confidence intervals for the prevalence estimates are also presented.

Table 4.1 Summary of secondary diabetes cases

	Total # cases of secondary diabetes	**Total # of underlying disease**	**Prevalence Estimate**
Acute Lymphoblastic Leukemia	9	510	1.8 %
Cystic Fibrosis	6	207	2.9 %
Thalassemia Major	0	81	0 %
Heart Transplant	1	29	3.4 %
Liver Transplant	2	78	2.6 %
Renal Transplant	3	204	1.5 %
TOTAL	21	1109	1.9 %

Table 4.2 Prevalence in acute lymphoblastic leukemia

	# cases of secondary diabetes	**# patients with ALL followed at the site**
Site A	1	123
Site B	6	143
Site C	1	125
Site D	1	119
TOTAL	**9**	**510**

Prevalence estimate for secondary diabetes in ALL: 1.8%

95% Confidence Interval: 0.8% to 3.3%

```
                                                    -- Binomial Exact --
    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
             |        510    .0176471    .0058302        .0081003    .0332344
```

Table 4.3 Prevalence in cystic fibrosis

	# cases of secondary diabetes	**# patients with CF followed at the site**
Site A	0	108
Site B	6	
Site C	0	12
Site D	0	87
TOTAL	**6**	**207**
Prevalence estimate for secondary diabetes in CF: 2.9% **95% Confidence Interval: 1.1% to 6.2%**		

				-- Binomial Exact --	
Variable	Obs	Mean	Std. Err.	[95% Conf.	Interval]
	207	.0289855	.0116605	.0107099	.0620186

Table 4.4 Prevalence in thalassemia major

	# cases of secondary diabetes	**# patients with thalassemia major followed at the site**
Site A	0	76
Site B	0	
Site C	0	5
Site D	0	0
TOTAL	**0**	**81**

Prevalence estimate for secondary diabetes in thalassemia major: 0%

95% Confidence Interval: 0% to 4.4%

```
                                                        -- Binomial Exact --
    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
             |         81           0           0           0    .0445203*
```

(*) one-sided, 97.5% confidence interval

Table 4.5 Prevalence in heart transplant

	# cases of secondary diabetes	**# patients with heart transplant followed at the site**
Site A	1	8
Site B	0	5
Site C	0	5
Site D	0	11
TOTAL	**1**	**29**
Prevalence estimate for secondary diabetes in heart transplant: 3.4% **95% Confidence Interval: 0.09% to 17.8%**		

```
                                                        -- Binomial Exact --
    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
             |         29    .0344828     .033883        .0008726    .1776443
```

Table 4.6 Prevalence in liver transplant

	# cases of secondary diabetes	**# patients with liver transplant followed at the site**
Site A	0	21
Site B	2	12
Site C	0	17
Site D	0	28
TOTAL	**2**	**78**

Prevalence estimate for secondary diabetes in liver transplant: 2.6%

95% Confidence Interval: 0.3% to 9.0%

```
                                                    -- Binomial Exact --
    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
             |         78     .025641     .017897        .0031205    .0895733
```

Table 4.7 Prevalence in renal transplant

	# cases of secondary diabetes	**# patients with renal transplant followed at the site**
Site A	0	35
Site B	2	55
Site C	0	35
Site D	1	79
TOTAL	**3**	**204**
Prevalence estimate for secondary diabetes in renal transplant: 1.5% **95% Confidence Interval: 0.3% to 4.2%**		

```
                                                    -- Binomial Exact --
    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
             |        204    .0147059    .0084278         .003043    .0423731
```

4.2 Risk factors associated with secondary diabetes

4.2.1 Acute lymphoblastic leukemia

Tables 4.8 through to 4.16 describe the case control analyses that were performed for the group of patients with ALL. Fewer cases were included in this analysis than the number of cases identified in the prevalence assessment. This was due to the limitations of obtaining individual written consent for chart review.

Some variables collected were not analyzed. Ethnicity was not routinely recorded in the hospital charts, so data was incomplete. Doses of steroid and L-asparaginase were similar in all cases and controls so this was not analyzed with odds ratios.

The only significant finding was an odds ratio of 15 for the development of secondary diabetes in those greater than 12 years of age compared to those less than or equal to 12 years of age (Table 4.9).

Table 4.8 Case control analysis for ALL group with female gender as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. Female gender was defined as the exposure while male gender was defined as being unexposed. An odds ratio of 5 was calculated for the odds of developing secondary diabetes in females with ALL compared to males with ALL. However, the confidence interval is large and includes 1 so this is not significant.

```
. cc status femaleexposure
                                                        Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
           Cases |         5           1  |         6      0.8333
        Controls |        12          12  |        24      0.5000
----------------+------------------------+----------------------
           Total |        17          13  |        30      0.5667
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                5       |  .4354777    255.7755  (exact)
 Attr. frac. ex. |               .8       | -1.296329    .9960903  (exact)
 Attr. frac. pop |         .6666667       |
                 +-----------------------------------------------
                           chi2(1) =     2.17  Pr>chi2 = 0.1405
```

Table 4.9 Case control analysis for ALL group with age greater than 12 years as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. Age greater than 12 years was defined as the exposure while age less than or equal to 12 years was defined as being unexposed. An odds ratio of 15 was calculated for the odds of developing secondary diabetes in those greater than 12 years of age with ALL compared to those less than or equal to 12 years of age with ALL. The confidence interval is large but does not include 1 so this is significant, with a chi^2 =0.0080.

```
. cc status agegreater12years
                                                        Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
           Cases |         5           1  |         6      0.8333
        Controls |         6          18  |        24      0.2500
----------------+------------------------+----------------------
           Total |        11          19  |        30      0.3667
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |              15        |  1.187849      747.37  (exact)
 Attr. frac. ex. |         .9333333       |  .1581421     .998662  (exact)
 Attr. frac. pop |         .7777778       |
                 +-----------------------------------------------
                           chi2(1) =     7.03  Pr>chi2 = 0.0080
```

Table 4.10 Case control analysis for ALL group with BMI greater than 95th%tile as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. BMI greater than the 95th%tile was defined as the exposure while BMI less than or equal to 95th%tile was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no exposed controls in the sample).

```
. cc status bmigreater95th
                 | bmigreater95th         |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         3           3  |         6      0.5000
        Controls |         0          24  |        24      0.0000
-----------------+------------------------+----------------------
           Total |         3          27  |        30      0.1000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |  4.616443           .
 Attr. frac. ex. |                1       |   .783383           .
 Attr. frac. pop |               .5       |
                 +-------------------------------------------------
                            chi2(1) =    13.33  Pr>chi2 = 0.0003

 Note: exact confidence levels not possible with zero count cells
```

Table 4.11 Case control analysis for ALL group with positive family history of any type of diabetes (type 1, type 2 or gestational) in a first degree or second degree relative as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. A positive family history of any type of diabetes (type 1, type 2 or gestational) in a first degree or second degree relative as was defined as the exposure, while no family history of any diabetes was defined as being unexposed. An odds ratio of 3.8 was calculated for the odds of developing secondary diabetes after treatment for ALL in those with a positive family history of diabetes compared to those without a family history of diabetes. However, the confidence interval is large and includes 1 so this is not significant.

```
. cc status fhxdiabetes-any
                                                              Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         3           3  |         6      0.5000
        Controls |         5          19  |        24      0.2083
-----------------+------------------------+----------------------
           Total |         8          22  |        30      0.2667
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |              3.8       |   .368337    36.47938  (exact)
 Attr. frac. ex. |         .7368421       | -1.714905    .9725873  (exact)
 Attr. frac. pop |         .3684211       |
                 +-----------------------------------------------
                            chi2(1) =     2.09  Pr>chi2 = 0.1485
```

Table 4.12 Case control analysis for ALL group with positive family history of type 2 diabetes in a first degree or second degree relative as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. A positive family history of type 2 diabetes in a first degree or second degree relative was defined as the exposure, while no family history of type 2 diabetes was defined as being unexposed. An odds ratio of 3.8 was calculated for the odds of developing secondary diabetes after treatment for ALL in those with a positive family history of type 2 diabetes compared to those without a family history of type 2 diabetes. However, the confidence interval is large and includes 1 so this is not significant.

```
. cc status fhxdm2
                                                        Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
           Cases |         3           3  |         6      0.5000
        Controls |         5          19  |        24      0.2083
----------------+------------------------+----------------------
           Total |         8          22  |        30      0.2667
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |              3.8       |   .368337    36.47938  (exact)
 Attr. frac. ex. |         .7368421       | -1.714905    .9725873  (exact)
 Attr. frac. pop |         .3684211       |
                 +-----------------------------------------------
                            chi2(1) =     2.09  Pr>chi2 = 0.1485
```

Table 4.13 Case control analysis for ALL group with positive family history of type 2 diabetes in a first degree relative as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. A positive family history of type 2 diabetes in a first degree relative was defined as the exposure while no family history of type 2 diabetes was defined as being unexposed. An odds ratio of 5.5 was calculated for the odds of developing secondary diabetes after treatment for ALL in those with a positive family history of type 2 diabetes in a first degree relative compared to those without a family history of type 2 diabetes. However, the confidence interval is large and includes 1 so this is not significant.

```
. cc status firstdegreefhxdm2
                                                        Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         2           4  |         6      0.3333
        Controls |         2          22  |        24      0.0833
-----------------+------------------------+----------------------
           Total |         4          26  |        30      0.1333
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |              5.5       |  .2912518     90.6379  (exact)
 Attr. frac. ex. |         .8181818       | -2.433455    .9889671  (exact)
 Attr. frac. pop |         .2727273       |
                 +-------------------------------------------------
                            chi2(1) =     2.60  Pr>chi2 = 0.1071
```

Table 4.14 Case control analysis for ALL group with positive family history of type 1 diabetes in a second degree relative as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. A positive family history of type 1 diabetes in a second degree relative was defined as the exposure while no family history of type 1 diabetes was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no exposed controls in the sample).

```
. cc status seconddegreefhxdm1

                | seconddegreefhxdm1     |             Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
           Cases |         1           5  |         6      0.1667
        Controls |         0          24  |        24      0.0000
----------------+------------------------+----------------------
           Total |         1          29  |        30      0.0333
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |         0           .
 Attr. frac. ex. |                1       |         .           .
 Attr. frac. pop |         .1666667       |
                 +-----------------------------------------------
                           chi2(1) =     4.14  Pr>chi2 = 0.0419

 Note: exact confidence levels not possible with zero count cells
```

Table 4.15 Case control analysis for ALL group with positive family history of type 2 diabetes in a second degree relative as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. A positive family history of type 2 diabetes in a second degree relative was defined as the exposure while no family history of type 2 diabetes was defined as being unexposed. An odds ratio of 5 was calculated for the odds of developing secondary diabetes after treatment for ALL in those with a positive family history of type 2 diabetes in a second degree relative compared to those without a family history of type 2 diabetes. However, the confidence interval is large and includes 1 so this is not significant.

```
. cc status seconddegreefhxdm2
                                                        Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
          Cases |         3           3  |         6      0.5000
       Controls |         4          20  |        24      0.1667
----------------+------------------------+----------------------
          Total |         7          23  |        30      0.2333
                |                        |
                |      Point estimate    |  [95% Conf. Interval]
                |------------------------+----------------------
     Odds ratio |                5       |  .4580229    50.37168  (exact)
 Attr. frac. ex. |               .8       | -1.183297    .9801476  (exact)
 Attr. frac. pop |               .4       |
                +-------------------------------------------------
                           chi2(1) =     2.98  Pr>chi2 = 0.0842
```

Table 4.16 Case control analysis for ALL group with positive family history of gestational diabetes in a second degree relative as exposure

In this table, cases were defined as having secondary diabetes following treatment for ALL, while controls did not develop secondary diabetes. A positive family history of gestational diabetes in a second degree relative was defined as the exposure while no family history of gestational diabetes was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no exposed cases in the sample).

```
. cc status seconddegreefhxgdm

                 | seconddegreefhxgdm     |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         0           6  |         6      0.0000
        Controls |         1          23  |        24      0.0417
-----------------+------------------------+----------------------
           Total |         1          29  |        30      0.0333
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                0       |         0           .
 Prev. frac. ex. |                1       |         .           1
 Prev. frac. pop |                .       |
                 +-------------------------------------------------
                            chi2(1) =     0.26  Pr>chi2 = 0.6111

 Note: exact confidence levels not possible with zero count cells
```

4.2.2 Cystic fibrosis

Although there were cases of secondary diabetes identified in patients with CF in the study population, a case control analysis was not possible due to the fact that these cases were not available for chart review due to limitations from obtaining individual written consent.

4.2.3 Thalassemia

No cases of secondary diabetes in patients with thalassemia major were identified at any of the collaborating centers, so a case control analysis was not completed for this population being studied.

4.2.4 Heart transplant

Tables 4.17 through to 4.18 describe the case control analyses that were performed for the group of patients with heart transplant. The only variables examined were gender and age, since others were not available (ie. ethnicity, BMI, family history of type 1, type 2 or gestational diabetes, immunosuppression medications). Heart transplants were not performed at the research sites so charts only contained information in the follow-up period post-transplant. There were no significant findings, since odds ratios could not be calculated due to the small number of subjects resulting in some cells containing zero.

Table 4.17 Case control analysis for heart transplant group with female gender as exposure.

In this table, cases were defined as having secondary diabetes following heart transplant, while controls did not develop secondary diabetes. Female gender was defined as the exposure while male gender was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no unexposed cases in the sample).

```
. cc status exposurefemale

                | exposurefemale         |             Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
           Cases |         1           0  |         1      1.0000
        Controls |         2           2  |         4      0.5000
----------------+------------------------+----------------------
           Total |         3           2  |         5      0.6000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |         0           .
 Attr. frac. ex. |                .       |         .           .
 Attr. frac. pop |                .       |
                 +-----------------------------------------------
                            chi2(1) =     0.83  Pr>chi2 = 0.3613

 Note: exact confidence levels not possible with zero count cells
```

Table 4.18 Case control analysis for heart transplant group with age greater than 12 years as exposure.

In this table, cases were defined as having secondary diabetes following heart transplant, while controls did not develop secondary diabetes. Age greater than 12 years was defined as the exposure while age less than or equal to 12 years was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no unexposed cases in the sample).

```
. cc status agegreater12years

                 | agegreater12years      |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         1           0  |         1      1.0000
        Controls |         2           2  |         4      0.5000
-----------------+------------------------+----------------------
           Total |         3           2  |         5      0.6000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |         0           .
 Attr. frac. ex. |                .       |         .           .
 Attr. frac. pop |                .       |
                 +-------------------------------------------------
                            chi2(1) =     0.83  Pr>chi2 = 0.3613

 Note: exact confidence levels not possible with zero count cells
```

4.2.5 Liver transplant

Although there were cases of secondary diabetes identified in patients with liver transplant in the study population, a case control analysis was not possible due to the fact that these cases were not available for chart review due to limitations from obtaining individual written consent.

4.2.6 Renal transplant

Tables 4.19 through to 4.26 describe the case control analyses that were performed for the group of patients with renal transplant. Only, variables that included complete data were examined (ie. ethnicity was not examined). Fewer controls were able to be included in the analysis than expected due to the limitations of obtaining individual written consent for chart review. There were no significant findings and the calculation of odds ratios was limited by the small number of cases and controls which often lead to zero counts within a cell.

Table 4.19 Case control analysis for renal transplant group with female gender as exposure

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. Female gender was defined as the exposure while male gender was defined as being unexposed. An odds ratio of 0.8 was calculated for the odds of developing secondary diabetes in females with renal transplant compared to males with renal transplant. However, the confidence interval is large and includes 1 so this is not significant.

```
. cc status gender
                                                        Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
           Cases |         2           1  |         3      0.6667
        Controls |         5           2  |         7      0.7143
----------------+------------------------+----------------------
           Total |         7           3  |        10      0.7000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |               .8       |   .024691    70.52965  (exact)
 Prev. frac. ex. |               .2       | -69.52965     .975309  (exact)
 Prev. frac. pop |         .1428571       |
                 +-----------------------------------------------
                            chi2(1) =     0.02  Pr>chi2 = 0.8803
```

Table 4.20 Case control analysis for renal transplant group with age greater than 12 years as exposure.

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. Age greater than 12 years was defined as the exposure while age less than or equal to 12 years was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no exposed controls in the sample).

```
. cc status agegreater12

                 | agegreater12           |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         1           2  |         3      0.3333
        Controls |         0           7  |         7      0.0000
-----------------+------------------------+----------------------
           Total |         1           9  |        10      0.1000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |         0           .
 Attr. frac. ex. |                1       |         .           .
 Attr. frac. pop |         .3333333       |
                 +-----------------------------------------------
                            chi2(1) =     2.59  Pr>chi2 = 0.1074

 Note: exact confidence levels not possible with zero count cells
```

Table 4.21 Case control analysis for renal transplant group with BMI greater than the 95th%tile as exposure.

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. BMI greater than the 95th%tile was defined as the exposure while BMI less than or equal to 95th%tile was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no exposed cases in the sample).

```
. cc status bmigreater95th

                | bmigreater95th         |             Proportion
                |   Exposed   Unexposed  |     Total     Exposed
----------------+------------------------+----------------------
           Cases |         0           3  |         3      0.0000
        Controls |         1           6  |         7      0.1429
----------------+------------------------+----------------------
           Total |         1           9  |        10      0.1000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                0       |         0           .
 Prev. frac. ex. |                1       |         .           1
 Prev. frac. pop |                .       |
                 +-----------------------------------------------
                            chi2(1) =     0.48  Pr>chi2 = 0.4902

 Note: exact confidence levels not possible with zero count cells
```

Table 4.22 Case control analysis for renal transplant group with positive family history of any type of diabetes (type 1, type 2, gestational) in a first degree or second degree relative as exposure.

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. A positive family history of any type of diabetes (type 1, type 2, or gestational) in a first degree or second degree relative was defined as the exposure while no family history of diabetes was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no unexposed cases in the sample).

```
. cc status allfhxdm
                 | allfhxdm               |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         3           0  |         3      1.0000
        Controls |         2           5  |         7      0.2857
-----------------+------------------------+----------------------
           Total |         5           5  |        10      0.5000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |   1.16798           .
 Attr. frac. ex. |                .       |  .1438206           .
 Attr. frac. pop |                .       |
                 +-------------------------------------------------
                            chi2(1) =     4.29  Pr>chi2 = 0.0384

 Note: exact confidence levels not possible with zero count cells
```

Table 4.23 Case control analysis for renal transplant group with positive family history of gestational diabetes in a first degree relative as exposure.

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. A positive family history of gestational diabetes in a first degree relative was defined as the exposure while no family history of gestational diabetes was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no exposed cases in the sample).

```
. cc status firstdegfhxgdm

                 | firstdegfhxgdm         |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         0           3  |         3      0.0000
        Controls |         1           6  |         7      0.1429
-----------------+------------------------+----------------------
           Total |         1           9  |        10      0.1000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                0       |         0           .
 Prev. frac. ex. |                1       |         .           1
 Prev. frac. pop |                .       |
                 +-------------------------------------------------
                            chi2(1) =     0.48  Pr>chi2 = 0.4902

 Note: exact confidence levels not possible with zero count cells
```

Table 4.24 Case control analysis for renal transplant group with positive family history of type 2 diabetes in a second degree relative as exposure.

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. A positive family history of type 2 diabetes in a second degree relative was defined as the exposure while no family history of gestational diabetes was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no unexposed cases in the sample).

```
. cc status secdegfhxdm2

                 | secdegfhxdm2           |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         3           0  |         3      1.0000
        Controls |         2           5  |         7      0.2857
-----------------+------------------------+----------------------
           Total |         5           5  |        10      0.5000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |   1.16798           .
 Attr. frac. ex. |                .       |  .1438206           .
 Attr. frac. pop |                .       |
                 +-------------------------------------------------
                            chi2(1) =     4.29  Pr>chi2 = 0.0384

 Note: exact confidence levels not possible with zero count cells
```

Table 4.25 Case control analysis for renal transplant group with use of cyclosporine as exposure.

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. Use of cyclosporine as an immune suppressant was defined as the exposure while no use of cyclosporine was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no exposed cases in the sample).

```
. cc status cyclosporine

                 | cyclosporine           |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         0           3  |         3      0.0000
        Controls |         5           2  |         7      0.7143
-----------------+------------------------+----------------------
           Total |         5           5  |        10      0.5000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                0       |         0    .8561794
 Prev. frac. ex. |                1       |  .1438206           1
 Prev. frac. pop |                .       |
                 +-------------------------------------------------
                            chi2(1) =     4.29  Pr>chi2 = 0.0384

 Note: exact confidence levels not possible with zero count cells
```

Table 4.26 Case control analysis for renal transplant group with use of tacrolimus as exposure.

In this table, cases were defined as having secondary diabetes following renal transplant, while controls did not develop secondary diabetes. Use of tacrolimus as an immune suppressant was defined as the exposure while no use of tacrolimus was defined as being unexposed. An odds ratio was not able to be calculated because of a zero count in one cell (no unexposed cases in the sample).

```
. cc status tacrolimus

                 | tacrolimus             |             Proportion
                 |   Exposed   Unexposed  |     Total     Exposed
-----------------+------------------------+----------------------
           Cases |         3           0  |         3      1.0000
        Controls |         2           5  |         7      0.2857
-----------------+------------------------+----------------------
           Total |         5           5  |        10      0.5000
                 |                        |
                 |      Point estimate    |  [95% Conf. Interval]
                 |------------------------+----------------------
      Odds ratio |                .       |   1.16798           .
 Attr. frac. ex. |                .       |  .1438206           .
 Attr. frac. pop |                .       |
                 +-------------------------------------------------
                            chi2(1) =     4.29  Pr>chi2 = 0.0384

 Note: exact confidence levels not possible with zero count cells
```

Chapter Five: Discussion

5.1 Summary of results

The prevalence of secondary diabetes was: 2.9% in CF, 0% in thalassemia major, 1.8% in ALL, 3.4% in heart transplant, 1.5% in renal transplant and 2.6% in liver transplant. An odds ratio of 15 was found for the odds of developing secondary diabetes in those greater than 12 years of age with ALL compared to those less than or equal to 12 years of age with ALL. No other significant risk factors were found to be associated with the development of secondary diabetes.

5.2 Impact of bias on the results

This study may have been susceptible to bias and in particular selection bias (a source of error due to the manner in which participants were selected) and information bias (a source of error due to the collection of data and techniques used to obtain data). However, efforts were made to minimize these forms of bias.

Since this was a retrospective chart review, data for this study was obtained using health records which may have been a source of information bias. There was the possibility that information relevant to the study had not been recorded in the health record. For example, ethnicity was not routinely documented at all sites so this variable was not analyzed in this study. In addition, information that was recorded within the health record may have been subject to recall bias (a type of information bias where there is differential recall between cases and controls of a relevant fact). For example, the reporting of a family history of diabetes may have been more likely in a child who developed diabetes as a complication of their disease.

Charts were not reviewed to ascertain missed diagnosis of secondary diabetes. Instead, the case definition in this study relied on an attending physician's diagnosis. For example, it would have been impractical to review the charts of all patients with ALL at each of the four sites over a twelve year period to look for patients meeting the CDA criteria for diabetes. Thus, in the current study it is possible that the prevalence of secondary diabetes was underestimated due to missed diagnoses. This would be a form of information bias called misclassification bias, where some true cases were actually classified as controls.

Where possible, the data for each patient was collected by the same investigator. When it was not possible, identical data collection forms were used so that data abstraction could remain as consistent as possible. In particular, health records from one site were reviewed by the site investigator when required by the ethics review board (eg. in the case of a deceased patient). Variables were defined precisely (see Appendix B). This was done to help reduce information bias. In addition, an independent researcher also reviewed approximately 15% of the charts using the same data abstraction form to assess the inter-observer reliability.

Selection bias may have impacted on the data that was collected from one site, since individual written consent was required for chart review at that site. This could have introduced bias in the selection of both the cases and controls that were reviewed. Families that agreed to participate in this study may have been more likely to have had a serious course in the hospital with multiple complications which may have included secondary diabetes.

5.3 Comparison of the results with literature

The prevalence estimates for secondary diabetes from this study are all lower than those described in the literature for each underlying disease as outlined in the background. The most likely explanation for this is the fact that most previous studies included mainly 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. This is especially true for diseases such as CF and iron overload with thalassemia, where pancreatic cell damage is progressive with a longer duration of disease. The current study did not include patients greater than 18 years which may have accounted for the low prevalence seen in the CF and thalassemia groups.

In pediatric patients with ALL, Pui et al (3) found that 9.7% of their patients developed hyperglycemia and that all of these resolved after discontinuation of the therapy for ALL. This is a much higher prevalence compared to the 1.8% found in the current study. However, Pui et al defined cases as patients with two or more elevated random or fasting blood glucose levels while the current study defined cases as persistent hyperglycemia requiring insulin or oral hypoglycemic medication for a minimum of two weeks. Therefore, by excluding cases of transient hyperglycemia the prevalence identified in this study was lower.

It is also possible that this study may have underestimated the number of cases of secondary diabetes since it was performed retrospectively and may have been subject to misclassification bias as described previously. In addition, the small number of Canadian centers that participated in this study did not include some of the larger hospitals where more children with the underlying diseases being studied would have been seen. For

example, the sites included in the study would not have been major heart, liver or renal transplant centers. This may have contributed to the lower prevalence identified in transplant groups studied.

The only significant odds ratio found was an increased odds of developing secondary diabetes in those greater than 12 years of age with ALL compared to those less than or equal to 12 years of age with ALL. This has some biologic plausibility, since post-pubertal children would be expected to have increased insulin resistance compared to pre-pubertal children and would therefore be at greater risk for developing secondary diabetes. This is also consistent with the study by Pui et al (3), where they found that the risk of hyperglycemia increased with age greater than 10 years. Unfortunately, since the number of cases of secondary diabetes was fewer than anticipated, no other risk factors were identified.

5.4 Strengths

There is little information on secondary diabetes in children and associated risk factors. This study is the first to estimate the prevalence of secondary diabetes in at risk populations in Canadian children.

Data was collected on variables that have been identified in the literature to be associated with secondary diabetes in adults to assess for risk factors. This allowed the study to focus on variables that were more likely to be associated with the development of secondary diabetes in children.

Since this study was a retrospective cross-sectional assessment of prevalence and a retrospective case-control study to assess for risk factors, it was relatively quick and inexpensive to do and was able to answer the primary research question. In this study, a

rare clinical outcome of secondary diabetes was being assessed, so it would have been impractical and costly to do a prospective cohort study of at risk children.

Since the clinical outcome being assessed was rare, this study attempted to incorporate more cases by using a multi-center Canadian trial. This helps the results of the study to be more generalizable to other Canadian centers. In addition, including multiple centers allowed for identification of a greater number of cases of this rare condition.

5.5 Limitations

Since this was a retrospective chart review, the information collected relied on the accuracy of the heath records. The data may have been incomplete or inaccurate. For example, ethnicity was infrequently recorded in the health record and could not be included in the analysis of the data. This is unfortunate, because it has been shown the people of specific racial backgrounds are at a greater risk for developing secondary diabetes.

The prevalence of secondary diabetes may be much smaller in the pediatric population compared to adults. This may cause some difficulty in finding associated risk factors, as well as in accurately estimating the prevalence. This study attempted to avoid this small sample size problem by recruiting other Canadian pediatric centers to participate. It would have been ideal to have participation from all pediatric Canadian centers, but this was not possible.

The background prevalence of type 1 diabetes mellitus is estimated to be 1 in 500 children. Therefore, it is possible that a presumed case of secondary diabetes is in fact new onset type 1 diabetes mellitus. However, the clinical course and natural history of

these two different forms of diabetes may help in distinguishing them (eg. improvement of blood glucose with weaning of steroid medications).

Patients that are lost to follow-up or move outside of Canada were not included in the study. Assuming there is an approximately equal number of patients that move into a participating Canadian center as move out, this may not significantly affect our estimate of prevalence.

5.6 Recommendations

This current study has helped to describe the prevalence of secondary diabetes and associated risk factors in Canadian children. This has not previously been described and will help in directing future research into secondary diabetes. The prevalence of secondary diabetes in each of the conditions studied was lower than previously reported in other studies, but does still highlight the need to be aware of secondary diabetes as a complication of other diseases or their treatments.

Future research directions could include a prospective analysis of various cohorts of children who are at risk for secondary diabetes. This would give some 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. In addition, prospective studies would be useful in assessing incidence rates for secondary diabetes.

Based on the findings of this study, active screening for secondary diabetes in susceptible children would be useful in diagnosing children early as opposed to when they are frankly symptomatic. Since pubertal age was the only identified risk factor in patients with ALL, it would be reasonable to screen for secondary diabetes in pubertal

children yearly with either a random or a fasting glucose. This test would be inexpensive and minimally invasive for children who would be getting further routine laboratory investigations done for their underlying disease.

Secondary diabetes is a less frequent cause of hyperglycemia than type 1 or type 2 diabetes. However, it has a significant impact on children since the long term complications of hyperglycemia are severe and can result in increased morbidity and mortality among children who are already at risk for serious complications from other underlying diseases. Further research into determining which children are at greater risk of secondary diabetes would lead to more aggressive screening, earlier diagnosis and treatment and decreased risks of long term complications for secondary diabetes. In addition, early treatment of secondary diabetes can decrease the acute symptoms of hyperglycemia that can lead to poor quality of life in children already burdened with a primary disease.

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APPENDIX A: DATA ABSTRACT FORM

Study # 1296 : Secondary Diabetes In Children

Site:_____ **O Case O Control**
Patient Study #:_____
Gender (M/F):_____ **Ethnicity:_____**
Date of Birth (mth/day/yr):_____ Birth Weight:_____ Birth Length:_____

Date of Diagnosis for Underlying Disease (mth/day/yr)	Disease	Height (cm)	Weight (kg)

Date of Diagnosis Diabetes (mth/day/yr)	Date of Resolution Diabetes (mth/day/yr)	Insulin route (iv vs sc)	Insulin dose (units/kg/day)	Oral Hypoglycemic Agents	Height (cm)	Weight (kg)

Date of Diagnosis DKA (mth/day/yr)	Date of Resolution (mth/day/yr)	Presentation of DKA (new diagnosis, under treatment, non-compliance, etc)	Complications (cerebral edema, stroke, hypocalcemia, etc..)	Treatment (insulin infusion duration, boluses of fluid, mannitol, etc..)

Date of Last F/U (mth/day/yr)	Height (cm)	Weight (kg)

Date of Death (mth/day/year):_____

Cystic Fibrosis	**Mutation Type (delta F508?)**	**Prednisone**	**PFT**	
Thalassemia	**#Transufusions (units/kg/pRBC)**	**Chelation Therapy (yes/no)**	**Serum ferritin**	**Hepatitis (yes/no)**
ALL (Leukemia)	**L-asparaginase**	**Prednisone**		
Heart Transplant	**Cyclosporine**	**Tacrolimus**	**Prednisone**	
Kidney Transplant	**Cyclosporine**	**Tacrolimus**	**Prednisone**	
Liver Transplant	**Cyclosporine**	**Tacrolimus**	**Prednisone**	

Family History Type1 Diabetes	**Persons_____**	**Total Number of first degree relatives**
Family History Type 2 Diabetes	**Persons__**	**Total Number of first degree relatives**

APPENDIX B: OPERATIONAL DEFINITIONS

Study variables were defined so that relevant information could be collected accurately and consistently between participating centers in the study:

Date of Birth:

Date, recorded in hospital chart

Birth Weight:

Weight of newborn, expressed in kilograms, recorded in hospital chart

Birth Length:

Supine length of newborn, expressed in centimeters, recorded in hospital chart

Gender:

Sex of patient, recorded in hospital chart

Ethnicity:

As recorded on hospital chart: aboriginal, hispanic, asian, African-american, or caucasian

Height:

Standing height, expressed in centimetres, recorded in hospital chart at diagnosis

Weight:

Weight, expressed in kilograms, recorded in hospital chart at diagnosis

Body Mass Index:

Weight in kilograms divided by height squared in meters (kg/m^2) at diagnosis

Diagnosis of Diabetes:

Attending physician diagnosis based on Canadian Diabetes Association guidelines, recorded in hospital chart

Insulin Route:

Intravenous or subcutaneous, recorded in hospital chart

Insulin Dose:

Units of insulin per kilogram body weight per day

Family History of Diabetes:

First degree or second degree relative with either: type 1 diabetes, type 2 diabetes or gestational diabetes as recorded on the hospital chart

APPENDIX C: ETHICS APPROVAL - CALGARY

FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

OFFICE OF MEDICAL BIOETHICS
Room 93, Heritage Medical Research Bldg
3330 Hospital Drive NW
Calgary, AB, Canada T2N 4N1
Telephone: (403) 220-7990
Fax. (403) 283-8524
Email: omb@ucalgary.ca

December 6, 2005

Dr. D. Pacaud
Department of Paediatrics
Alberta Children's Hospital
Calgary, Alberta

Dear Dr. Pacaud:

RE: Assessment of Prevalence And Risk Factors For Secondary Diabetes In Canadian Children - Grant ID: 17627

Thank you very much for the progress report and the annual renewal, which you have provided on the above-named protocol on November 30, 2005. Please be advised that this report has been reviewed and approved.

The research protocol's ethical approval has been continued by the Conjoint Health Research Ethics Board of the Faculties of Medicine, Nursing and Kinesiology, University of Calgary, and the Affiliated Teaching Institutions. The Board conforms to the Tri-Council Guidelines, ICH Guidelines and amendments to regulations of the Food and Drug Act re clinical trials, including membership and requirements for a quorum.

The study continues to meet the requirements of the Health Information Act.

You and your co-investigators are not members of the CHREB and did not participate in review or voting on this study.

As Associate Chair of the Conjoint Health Research Ethics Board of the Faculty of Medicine, University of Calgary, and the Affiliated Teaching Institutions, I am pleased to advise you that ethical approval for this proposal has been extended to **2006-03-23**.

Please note that this approval is contingent upon strict adherence to the original protocol. Prior permission must be obtained from the Board for any contemplated modification(s) of the original protocol.

A progress report and annual renewal request concerning this study will be required by **2006-03-23**. This report should contain information concerning:

(i) the number of subjects recruited;
(ii) a description of any protocol modification;
(iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
(iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
(v) a copy of the current informed consent form;
(vi) the expected date of termination of this project;

Please accept the Board's best wishes for continued success in your research.

Yours sincerely,

Glenys Godlovitch, BA(Hons), LLB, PhD
Associate Chair, Conjoint Health Research Ethics Board

c.c. Child Health Research Committee Dr. B. Scott (information) Research Services

APPENDIX D: ETHICS APPROVAL - WINNIPEG

UNIVERSITY OF MANITOBA

BANNATYNE CAMPUS
Research Ethics Boards

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Tel: (204) 789-3255
Fax: (204) 789-3414

APPROVAL FORM

Principal Investigator: Dr. Elizabeth Sellers

Protocol Reference Number: H2005:033
Date of Approval: May 30, 2005

Protocol Title: "Assessment of Prevalence And Risk Factors For Secondary Diabetes In Canadian Children"

The following is/are approved for use:

- **Consent procedures (per letter dated May 27, 2005)**

The above was approved by Dr. Ken Brown, Chair, Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your letter dated May 27, 2005. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations*.

A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval should be sought from the relevant institution, if required.

Sincerely yours,

Ken Brown, MD, MBA
Chair,
Health Research Ethics Board
Bannatyne Campus

Please quote the above protocol reference number on all correspondence.
Inquiries should be directed to the REB Secretary · **Telephone:** (204) 789-3255 / Fax: (204) 789-3414

APPENDIX E: ETHICS APPROVAL - OTTAWA

CHEO Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

CHEO RESEARCH ETHICS BOARD APPROVAL NOTICE – EXPEDITED REVIEW

Principal Investigator:	Dr. Stasia Hadjiyannakis
Proposal Number:	#05/42X
Protocol Title:	Assessment of Prevalence and Risk Factors for Secondary Diabetes in Canadian Children
Department or PSU:	Endocrinology
Approval date:	March 29, 2005
Valid Until:	March 28, 2006
Documents reviewed and approved:	Research protocol dated March 21, 2005

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval to the above named research study on the date noted above. Research protocols that involve no more than minimal risk such as this one can be considered under the rubric of an expedited review. Accordingly, your above-mentioned project has been approved through expedited review.

Please submit a final study report when it becomes available. Wishing you success in your project.

Regards,

Dr. Carole Gentile, C.Psych.
Chair, Research Ethics Board

CG/smeh 29/03/05
c.c. Pat Brazeau, Manager, CHEO RI

- see email 31/03/05. SHaig

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APPENDIX F: ETHICS APPROVAL - HALIFAX

IWK Health Centre

August 28, 2006

RE: Study entitled "**Assessment of prevalence and associated risk factors for secondary diabetes in Canadian children**"

I am writing to confirm that the above study has received approval from the IWK research ethics board for the study to be carried out by myself as the collaborator at this site.

If you require any further information please do not hesitate to contact me.

Sincerely,

Arati S. Mokashi MD, FRCPC
Pediatric Endoorinologist
Ph (902) 470-8707
Email: Arati.Mokashi@iwk.nshealth.ca

APPENDIX G: DIABETES ASSOCIATION (BROOKS & DISTRICT) FUNDING

DA
(BROOKS & DISTRICT)
DIABETES ASSOCIATION

DIABETES ASSOCIATION
(Brooks & District)

Box 187 • (215 - 3rd St. W.)
Brooks, Alberta T1R 1B3
Ph. (403) 362-5914 Fax (403) 362-0336
e-mail: dabd@telusplanet.net

September 22, 2003

Alberta Children's Hospital
Department of Pediatric Endocrinology
1820 Richmond Road S.W.
Calgary, AB T2T 5C7

ATTENTION: DR. JOSEPHINE HO
Pediatric Endocrine Fellow

Dear Dr. Josephine Ho;

It is with great pleasure that the DIABETES ASSOCIATION (Brooks & District) grant $7000.00 towards your research project. It is alarming to hear that secondary diabetes is such a large problem. We sincerely hope that this grant will assist you to characterize the risk factors for developing secondary diabetes in pediatric patients and examine the prevalence of secondary diabetes in various pediatric populations. Please find enclosed our certified cheque in the amount of $7000.00.

From your letter that you emailed Lorraine Samis (on May 26th /03), it is apparent that you have been misdirected as to Who? the Diabetes Association (Brooks & District) is. We are not a Branch of the Canadian Diabetes Association and we are not associated with the CDA in anyway. We receive no financial assistance from the CDA , or any government funding. The Diabetes Association (Brooks & District) is an **independent, self-financing, non-government, not-for-profit charitable organization.** I have attached information sheets about us.

The Diabetes Association (Brooks & District) is very proud to partner with our Diabetes Education Center and Canada Safeway - Pharmacy on our annual **DIABETES EXPO**. This years 6th annual Diabetes Expo is scheduled for Saturday, April 3rd, 2004 at the Heritage Inn, in Brooks. The day starts at 1PM with Exhibitors, Ask-the -Expert tables and seminars running until 5PM. We respectfully request your presence at Diabetes Expo to present your findings from your very interesting project. We would be honored to announce your presentation in our media blitz and in our Diabetes Expo brochure. Please contact our Executive Director, Arlene Currie at(403-362-5914)or Lorraine Samis at 403-501-3298 to confirm your attendance.

The Diabetes Association (Brooks & District) will continue to support ongoing education programs and to grant monies to diabetes projects in Alberta. We are pleased that we could help your project, Dr. Ho, and wish you every success.

Sincerely,

Christie Waldner, President

Enclosures

APPENDIX H: PUBLISHED REVIEW ARTICLE

Ho, J. and Pacaud, D. Secondary Diabetes in Children.

Canadian Journal of Diabetes 2004; 28(4):400-405.

CANADIAN JOURNAL OF DIABETES
400

Secondary Diabetes in Children

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ABSTRACT

Secondary diabetes mellitus is a recognized complication of organ transplantation, some chemotherapy regimens, multiple blood transfusions, pancreatic injury and cystic fibrosis. To date, most studies have focused on secondary diabetes in the adult population with very little research on secondary diabetes specific to children. This paper reviews current concepts regarding causes, risk factors and diagnosis of secondary diabetes in the pediatric population, as well as management options.

RÉSUMÉ

Le diabète sucré secondaire est une complication reconnue de la greffe d'un organe, de certaines chimiothérapies, de transfusions sanguines multiples, de lésions pancréatiques et de la fibrose kystique. Jusqu'à maintenant, la plupart des études ont porté sur le diabète secondaire chez les adultes et très peu de recherche a été effectuée sur le diabète secondaire chez les enfants. Ce compte rendu passe en revue les concepts actuels sur les causes, les facteurs de risque et le diagnostic du diabète secondaire chez les enfants, ainsi que les moyens possibles de prise en charge.

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Keywords: cystic fibrosis, pediatric, post-transplant, secondary diabetes

INTRODUCTION

Secondary diabetes is a recognized complication of organ transplantation, some chemotherapy regimens, multiple blood transfusions, pancreatic injury and cystic fibrosis (CF) (1). It is becoming an increasingly important complication in children, since increased survival from life-threatening diseases can lead to the development of long-term complications. As new treatments and procedures have been developed for these childhood diseases, an increase in secondary diabetes has been noted. Furthermore, once diabetes has developed, the risk of long-term microvascular and macrovascular disease becomes yet another complication of the already complex underlying diseases. Early recognition and treatment of secondary diabetes are essential to prevent long-term complications of hyperglycemia.

POST-TRANSPLANT DIABETES

Multiple mechanisms are alleged to cause glucose intolerance and diabetes in patients who have undergone organ transplant. Both the underlying disease and the treatment modalities are involved. For example, disease infiltration in leukemia patients (2) or cytomegalovirus infection in immunocompromised patients (3,4) may cause direct damage to pancreatic beta cells. Cyclosporine A and L-asparaginase are known to have direct toxic effects on pancreatic beta cells, resulting in decreased insulin production and secretion (5-7). Corticosteroids induce insulin resistance (3,7) and may also decrease insulin secretion (8). The mechanisms causing the increased risks of glucose intolerance and diabetes in patients receiving the calcineurin inhibitors tacrolimus or FK506 are still unclear, as animal experimentation findings are discordant with human clinical data (7). Abdominal radiotherapy, which is often part of the pretreatment for bone marrow transplantation, can cause pancreatitis and secondary diabetes many years after treatment (9,10). Most patients requiring a transplant are exposed to more than 1 of these disease characteristics or agents, increasing the risk of secondary diabetes.

Renal transplant

Several studies have reported the incidence of and factors associated with post-transplant diabetes mellitus (PTDM) in adults following renal transplantation. Of 11 659 patients who received their first kidney transplant between 1996 and 2000 and registered with the United States (US) Renal Data System Coordinating Center, the cumulative incidence of PTDM was 9.1% at 3 months, 16% at 12 months and 24% at 36 months post-transplantation (11). A high incidence of PTDM was associated with tacrolimus used as an initial maintenance immunosuppressive medication, African-American race, Hispanic origin, body mass index >30 kg/m^2, increasing number of human leukocyte antigen (HLA) mismatches between donor and recipient, and hepatitis C infection (11). PTDM was found to be a strong independent predictor of graft failure and mortality. Cosio and colleagues (12) reviewed 2078 nondiabetic renal transplant recipients from 1 centre between 1982 and 1999. Patients had a mean age of 40.9 years. All patients received prednisone and cyclosporine post-transplantation. The incidence of PTDM increased from 7.1% after 1 year to 29.8% 15 years post-transplantation. Factors leading to an increased relative risk of developing PTDM included age >45 years, transplantation done after 1995, African-American race, and higher body weight at transplantation. While the rate of PTDM increased with time, despite use of lower cumulative doses of corticosteroids since 1995, the introduction of better-absorbed cyclosporine formulations resulted in higher blood levels and higher cumulative exposure to this diabetogenic drug. Johny and colleagues retrospectively reviewed 631 renal transplant recipients in Kuwait (13). Of this sample, 552 were nondiabetic pretransplantation; of these, 21.2% developed PTDM. There was no difference in the incidence of PTDM when prednisone and azathioprine were used together as a 2-drug regimen or in combination with cyclosporine (a 3-drug regimen). A higher incidence of PTDM was identified in patients >45 years of age or those of Arab descent. PTDM was also more likely to be associated with infections requiring hospitalization and coronary artery disease. In a small study by al Asfari and colleagues (14), 24% of 41 renal transplant patients age 18 to 64 years developed diabetes.

In contrast to adult studies, little information is available regarding the incidence of PTDM in pediatric renal transplant patients. Existing studies cite a wide range of occurrence. Greenspan and colleagues (15) reviewed 229 charts of pediatric renal transplant patients and found an incidence of 7%, a lower frequency than that found in adult studies. Risk factors identified included family history of type 2 diabetes, tacrolimus use and hyperglycemia in the 2 weeks post-transplant. Half of patients who presented with PTDM eventually became euglycemic and were able to discontinue taking all antihyperglycemic medications. Persistent PTDM was more likely if the diagnosis of diabetes occurred later after transplantation.

A retrospective analysis of 1365 children in the North American Pediatric Renal Transplant Cooperative Study (16) showed an incidence of PTDM (defined as >2 weeks of insulin therapy after transplantation) of <3%. African-American racial background and the use of tacrolimus were significant risk factors for the development of PTDM. Children with PTDM had a higher incidence of acute rejection; however, graft survival, kidney function and hospitalization rates were similar to selected controls.

Heart transplant

PTDM is a known complication of adult heart transplantation. A retrospective review by Depczynski and colleagues (17) showed that after a mean follow-up of 27 months, 15.7% of 97 adult heart transplant recipients developed PTDM. Risk factors associated with PTDM included family history of

diabetes and the requirement for insulin postoperatively on day 2. Nieuwenhuis and colleagues (18) followed 228 cardiac transplant recipients with a mean age of 50 years to see if oral glucose tolerance test (OGTT) values or pretransplantation maximal random glucose values and HLA-DR3 and/or DR4-phenotype would be predictive of PTDM. At a mean follow-up of 4.77 years, there was a cumulative incidence of PTDM of 19.6%. The risk of PTDM increased with the degree of pretransplantation glucose intolerance, yet the onset of secondary diabetes was considerably more frequent, even in patients with normal glucose tolerance. HLA-DR3 and/or -DR4 phenotype was not a predisposing factor.

Recently, Hathout and colleagues (19) reported the prevalence of diabetes in a cohort of 381 pediatric heart transplant recipients from Loma Linda University Children's Hospital, Loma Linda, California, US. The rate of PTDM was 1.8% overall and 3.8% for patients who survived for at least 7 years. The median time of onset of diabetes was 7 years post-transplant. In this series, risk factors associated with PTDM were mean and maximum tacrolimus blood levels, HLA-DR mismatch and older age at transplantation. Interestingly, the authors attribute the lower risk of PTDM (as compared with other pediatric solid organ recipients reported in the literature) to the decreased use of tacrolimus and/or steroids as primary immune suppressants.

Liver transplant

Liver transplantation has been shown to be associated with PTDM. Steinmuller and colleagues (20) studied 618 patients 1 year after liver transplantation. Although they found new-onset PTDM in 7.2% of patients, they did not find any significant risk factors (e.g. diagnosis leading to liver transplantation, age, gender, hepatitis B or C infection, steroid medication, treatment with tacrolimus or cyclosporine).

Hematopoietic cell transplant

Pediatric bone marrow transplantation and hematopoietic cell transplantation have contributed greatly to increased survival rates of patients with hematopoietic cell cancers. However, as survival rates increase, case reports and case series of secondary diabetes become more frequent (9,21,22). Traggiai and colleagues found the onset of diabetes occurred, on average, 9.8 years post-transplantation (range 1.2 to 21.1 years) (9). In general, onset was not associated with obesity, but could be associated with other evidence of insulin resistance such as lipid abnormality and hypertension (9,22). Taskinen and colleagues (23) reported a case-control series of 23 long-term survivors of bone marrow transplantation in childhood and 23 age- and gender-matched controls. Four of the survivors had type 2 diabetes compared to none of the controls. Furthermore, another 8 patients had insulin resistance. The frequency of insulin resistance increased with time elapsed since transplantation. Recently, Hoffmeister and colleagues (24) studied a cohort of 748 long-term survivors of pediatric hematopoietic cell transplantation (mean follow-up of 11 years) from the Fred Hutchinson Cancer Research Center, Seattle, Washington, US. Type 1 diabetes and type 2 diabetes developed in 4 and 34 patients, respectively. Type 1 diabetes developed between 8 and 14 years after transplantation, when patients were age 10 to 19 years. Type 2 diabetes was diagnosed on average 14.6 years (range 1.4 to 24.4 years) after transplantation, at an average age of 24.5 years (range 11.3 to 40.7 years). Diabetes was not associated with obesity in this population. Identified risk factors included diagnosis of leukemia, family history of diabetes, race (except Caucasians of non-Hispanic descent) and asparaginase toxicity.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) has been reported as an unusual consequence of PTDM in patients receiving calcineurin inhibitors. Yoshida and colleagues (25) described DKA in a 37-year-old renal transplant recipient on cyclosporine, a 50-year-old liver transplant recipient on tacrolimus and a 58-year-old liver transplant recipient on cyclosporine. Each of these patients was on maintenance immunosuppression at the time of DKA presentation and had not been receiving pharmacotherapy for hyperglycemia. Interestingly, both liver transplant recipients were found to have moderate to high serum levels of calcineurin inhibitors on presentation. The authors postulated that a combination of peripheral insulin resistance and pancreatic beta cell impairment by cyclosporine or tacrolimus resulted in the development of DKA.

CHEMOTHERAPY

In 1981, Pui and colleagues (6) studied various risk factors for the development of hyperglycemia with L-asparaginase and prednisone therapy. This study was a retrospective review of 421 children age 3 months to 20 years who had received L-asparaginase and prednisone for treatment of acute lymphoblastic leukemia from 1972 to 1980. The authors found that 9.7% of patients developed hyperglycemia, which resolved after discontinuation of the leukemia therapy. Significant risk factors identified for hyperglycemia were age >10 years, obesity, Down syndrome and family history of diabetes. When more than 1 factor was present, the risk of hyperglycemia increased significantly.

L-asparaginase has been implicated in DKA in pediatric patients receiving treatment for leukemia. In 1972, Gillette and colleagues (26) reported on a 10-year-old girl who developed DKA following treatment with L-asparaginase and prednisone for a relapse of leukemia. The patient required insulin therapy for 18 days and, following discontinuation of the L-asparaginase, subsequently had normal OGTT results. The authors hypothesized that their patient may have been hypoinsulinemic due to depletion of L-asparagines by the L-asparaginase, which could have resulted in an inhibition of insulin synthesis. Another possibility was that existing insulin might have been destroyed by the L-asparaginase.

CYSTIC FIBROSIS

CF has been identified as a cause of secondary diabetes. The primary mechanism is insulin deficiency caused by progressive damage of the pancreas by viscous secretions. Pancreatic islet cells are gradually destroyed and replaced by fibroadipose tissue. Insulin resistance also plays a role, particularly when patients are treated with glucocorticoids, or have acute or chronic infection with significant inflammation (27).

There has been a wide range of published prevalence of diabetes in both the adult and pediatric CF populations. This could be due to variable screening practices and age at investigation. In a retrospective review, Finkelstein et al (28) reported that 7.6% of 448 patients with CF between the ages of 1 and 49 years had diabetes, and the average age at diagnosis was 19.8 years. In 1994, Lanng and colleagues (29) published a cross sectional review of all Danish CF patients (age 3 to 40 years) systematically screened for glucose intolerance and diabetes and reported that 14.7% had diabetes. Mean age at diagnosis of diabetes was 20 years and the prevalence was found to increase with age. Microvascular complications of diabetes were found in 10% of patients who had a duration of diabetes of 1 to 17 years. Cucinotta and colleagues (30) showed in a 10-year prospective follow-up study of 28 selected patients age 6.1 to 22.6 years with CF that 42.8% developed diabetes. They also found that homozygosis for ΔF508 mutation was seen in 66.7% of the group that developed diabetes. Moran and colleagues followed 371 patients at the Minnesota Cystic Fibrosis Center, University of Minnesota, Minneapolis, Minnesota, US, and found that the prevalence of diabetes (based on OGTT screening) increased significantly with age: 9% for patients age 5 to 9 years, 26% for patients age 10 to 19 years, 35% for patients age 20 to 30 years, and 43% for patients >30 years old (31).

In 2003, in Toronto, Ontario, Canada, a study of pediatric patients with CF and no clinical symptoms of diabetes revealed that 4.3% had diabetes and 17% had impaired glucose tolerance (IGT) using a modified OGTT, despite having normal fasting glucose (32). No specific cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation was found to predict abnormal glucose tolerance, but all patients with diabetes or IGT had severe CFTR mutations (with at least one ΔF508 mutation) on both alleles as well as exocrine pancreatic insufficiency. Glycosylated hemoglobin (A1C) levels did not correlate with glucose tolerance results.

Table 1. Glucose levels for diagnosis of IFG, IGT and diabetes (36)

	FPG (mmol/L)		*2hPG in a 75-g OGTT (mmol/L)*
IFG	6.1–6.9		NA
IFG (isolated)	6.1–6.9	and	<7.8
IGT (isolated)	<6.1	and	7.8–11.0
IFG and IGT	6.1–6.9	and	7.8–11.0
Diabetes	≥7.0	or	≥11.1

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
NA = not applicable
OGTT = oral glucose tolerance test

THALASSEMIA

IGT and diabetes are seen in pediatric patients receiving multiple transfusions, such as those with thalassemia. The range of reported prevalence varies from 2 to 24%. Risk factors may include older age, a high number of blood transfusions, high serum ferritin, poor compliance with chelation therapy, family history of diabetes, hepatitis viruses and later pubertal stage (33). DKA has also been reported as a complication of transfusion-dependent thalassemia. In 1 study, 16 of 82 (19.5%) patients had diabetes; 31% of this group presented with DKA (33).

Chronic iron overload is hypothesized to cause insulin deficiency via toxic effects on pancreatic islet cells. It has also been suggested that insulin resistance plays a role in glucose intolerance and that chronic stimulation of insulin secretion may lead to secondary failure of the islet cells (34).

Merkel and colleagues (35) studied 12 children with thalassemia who required chelation therapy for multiple blood transfusions, and used euglycemic insulin clamp, hyperglycemic clamp and OGTT to determine if there was evidence of insulin resistance in this group. They found that when given a hyperglycemic stimulus, the pubertal children had impaired insulin-stimulated glucose metabolism and significantly elevated insulin levels. The authors posited that, before the development of diabetes, both insulin resistance and increased insulin secretion develop in older children with thalassemia treated with long-term hypertransfusion therapy. They further postulated that the insulin resistance may have been due to iron deposition in the liver or muscle, which interfered with the suppression of hepatic glucose production or glucose metabolism in muscle tissue.

DIAGNOSIS OF SECONDARY DIABETES

Detection of secondary diabetes and close monitoring of children at risk are necessary for the prevention of diabetes-related complications. Some symptoms suggestive of hyperglycemia include polyuria, polydipsia, weight loss, blurred vision and fatigue. A complete review of a child's medication regimen and past medical history may reveal risk factors for developing secondary diabetes.

The Canadian Diabetes Association (36) recommends screening for diabetes with a fasting plasma glucose (FPG) test (fasting is defined as no food or drink for at least 8 hours). A 75-g OGTT (or 1.75 g/kg in children who weigh

≤43 kg) may be necessary if the clinical suspicion of diabetes is high and the FPG is between 5.7 and 6.9 mmol/L. See Table 1 for diagnostic criteria.

Children with an increased risk of secondary diabetes because of treatment with chemotherapy agents or antirejection drugs could be screened annually. Children with CF or frequent red blood cell transfusions could be screened yearly after the age of 10 years (when diabetes is more likely to develop). A consensus statement developed in 1998 (37), recommends that, in patients with CF, random blood glucose (BG) levels should be measured annually. If the random BG is <7.0 mmol/L, it is unlikely that fasting hyperglycemia is present and there is no need for further work-up unless symptoms suggestive of diabetes in CF are present. An OGTT should be strongly considered to rule out diabetes in CF patients with a normal FPG but symptoms of hyperglycemia. Such symptoms would include unexplained polyuria and polydipsia, failure to gain or maintain weight, poor growth velocity, delayed progression of puberty or unexplained chronic decline in pulmonary function.

MANAGEMENT

Insulin therapy, with insulin infusion titrated to maintain euglycemia or subcutaneous insulin injections, is the main treatment option for the acute management of hyperglycemia. Dietary modification is also of benefit. Unfortunately, many oral antihyperglycemic agents used in adult patients with type 2 diabetes have not been licensed for use in the pediatric population and may be contraindicated in these complex patients. For example, use of metformin is contraindicated in the presence of liver, cardiac and renal insufficiency (36). Until the safety and efficacy of these medications are established, they cannot be recommended for routine clinical use in pediatric populations.

Treatment and follow-up of secondary diabetes in children is best accomplished through the combined efforts of a multidisciplinary pediatric diabetes healthcare team. Ideally, patients would have access to physicians, nurses, dietitians, psychologists and social workers. Secondary diabetes has a significant impact (combined with the stresses and constraints associated with the treatment of their primary disease) on the entire family and support should be offered, if required. There can be frustration and poor compliance with diabetes treatment plans because children often feel well and do not see the benefits of rigorous BG monitoring. Moreover, the long-term risks of hyperglycemia and the benefits of early treatment are often difficult for children to appreciate. Education and support are therefore essential in managing secondary diabetes and adapting diabetes care to coordinate with the rest of the patient's management.

CONCLUSION

There are few data describing risk factors and prevalence of secondary diabetes in the pediatric population. With changes in chemotherapeutic regimens, increasing numbers of transplants and more survivors of childhood diseases such as CF, it is imperative to evaluate the prevalence of secondary diabetes in the pediatric population.

Early recognition and treatment of secondary diabetes can help improve outcomes in children being treated for underlying diseases by optimizing nutrition, avoiding fluid imbalance and preventing metabolic derangements such as DKA. With the improved survival of children with chronic diseases, a focus on monitoring for secondary diabetes is necessary to prevent development of long-term complications associated with chronic hyperglycemia.

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