Prevention of Diabetic Ketoacidosis in Newfoundland and Labrador: Hospitalization Rates Pre and Post a Multiphase Provincial Knowledge Translation Program

By

© Georgia M. Darmonkow

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Faculty of Medicine

Memorial University of Newfoundland

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ABSTRACT

Background & Objectives: The province of Newfoundland and Labrador (NL) has one of the highest rates of type 1 diabetes mellitus globally. Diabetic ketoacidosis (DKA) is one of the major complications of this disease. The Newfoundland and Labrador Diabetic Ketoacidosis Project (NLdkaP) is a multiphase project aimed at lowering the rates of DKA in the province. In order to assess the effectiveness of this project, we studied hospitalization rates for type 1 diabetes over a six–year period.

Design, Setting & Measurements: This is a retrospective study carried out in NL using hospital administrative data covering the period January 1, 2009 – December 31, 2014 for patients aged ≤24 years. Data extracted for each patient included demographic factors (e.g., sex and age), location of treatment, length of stay, and whether the patient has had recurrent DKA.

Results: There were 412 patients admitted for DKA over the study period. DKA hospitalizations in the province decreased for the two years during the NLdkaP (2011 and 2012; n = 107). In the two years post project (2013 and 2014), DKA hospitalizations increased (n = 148) but rates did not increase to the initial rates measured before the project was implemented in (2009 and 2010; n = 157).

Conclusions: The NLdkaP was associated with a decrease in DKA hospitalization rates. This knowledge translation project could be adopted by other regions to reduce the rates of DKA hospitalizations. Ongoing efforts are needed to sustain this preventative effect.

ACKNOWLEDGEMENTS

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I would also like to acknowledge and thank my mother, Valerie Darmonkow, for her unwavering support, always listening to me talk about diabetic ketoacidosis (or "KDA" as she likes to call it) and her unmatched editorial assistance.

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LIST OF ABBREVIATIONS

ADA – American Diabetes Association
CDE – Certified diabetes educator
CDMS – Clinical database management system
CI – Confidence interval
CIHI – Canadian Institutes of Health Information
DKA – Diabetic ketoacidosis
IDDM – Insulin dependent diabetes mellitus
LOS – Length of stay
NADH – Nicotinamide adenine dinucleotide
NIDDM – Non–insulin dependent diabetes mellitus
NLCHI – Newfoundland and Labrador Center for Health Information
NL – Newfoundland and Labrador
NLdkaP – Newfoundland and Labrador Diabetic ketoacidosis Project
PHAC – Public Health Agency of Canada
P–Y – Person years
T1DM – Type 1 diabetes mellitus
T2DM – Type 2 diabetes mellitus
UK – United Kingdom
US – United States
WHO – World Health Organization

Chapter 1: Introduction

Diabetes mellitus is a global health problem with increasing incidence rates occurring worldwide. In Canada, 3.4 million people are estimated to have diabetes, which equates to approximately 9.4% of the population.[171] This is higher than the estimated global prevalence of 8.5%,[4] and the rate in Canada is forecast to rise to 5.0 million or approximately 12.1% of the population by 2025.[171] During the decade between 1998/99 and 2008/09, the prevalence of diagnosed diabetes in Canada increased by 70% (total prevalence changed from 3.3 – 5.6%).[5] This rise in prevalence but not incidence is explained by the Public Health Agency of Canada (PHAC) as an indication of longer disease duration in those diagnosed with diabetes.[5] PHAC further attributes this rise to improved care and treatment, but suggests it may also indicate earlier detection of those with undiagnosed diabetes or earlier age of onset.[5] The increase in diabetes cases cannot be explained by genetic susceptibility alone and it is hypothesized to be due to environmental, lifestyle or other epigenetic factors that are triggering or accelerating the onset and progression of the disease.[73] These factors point to the significant health burden that Canadians will face in relation to increasing rates of diabetes.

Diabetes is also one of the most common chronic diseases among children and youth.[5] Type 1 diabetes mellitus (T1DM) (previously known as juvenile–onset or insulin–dependent diabetes mellitus) is the most common form of the disease observed in the pediatric age group; however, Type 2 diabetes mellitus (T2DM) (historically known as adult onset or non–insulin dependent diabetes mellitus) is also on the rise in both the pediatric and adult populations. The majority of people with diabetes around the world

are affected by T2DM, and it is suggested that this is largely the result of excess body weight and physical inactivity.[158]

In NL, the incidence of T1DM from 1987 – 2010 was 37.7 per 100,000.[27] On average, one child or youth in NL is diagnosed with diabetes every week.[3] According to the Canadian Chronic Disease Surveillance System, the number of youth diagnosed with diabetes increased significantly during the period from 2001 – 2008.[3] This upward trend in incidence is alarming and calls for more focused investments in diabetes related research. In 2007/08, it was estimated that 600 children and youth in NL were living with diabetes.[3] Life expectancy can be decreased by as much as 15 years in those living with with T1DM and between five and ten years for those living with T2DM.[15] Thus, it is clear that efforts should be placed on better diabetes education and management as this has been shown to improve the health outcomes of individuals living with diabetes.

There are significant costs associated with diabetes. These costs include both direct treatment costs (e.g., hospitalizations, physician visits, medications) and indirect diabetes costs, including premature death and morbidity/disability related to diabetes and its complications.[5] In Canada, these costs were projected to rise from $6.3 billion dollars in 2000 to $36.9 billion in 2020[15] (Figure 1). In 2010, in NL, these costs were estimated to be $254 million, with a projected increase of 27% over the next decade to $322 million[17] (Figure 2). Most of these costs were for adult patients, but children with T1DM also have significant treatment costs. In NL, it is standard practice to hospitalize all newly diagnosed children and youth with T1DM, and it has been estimated that children and youth with diabetes are admitted to hospital 7.7 times more than those without

diabetes.[3] These admissions are costly for both the health care system and the patients' families.

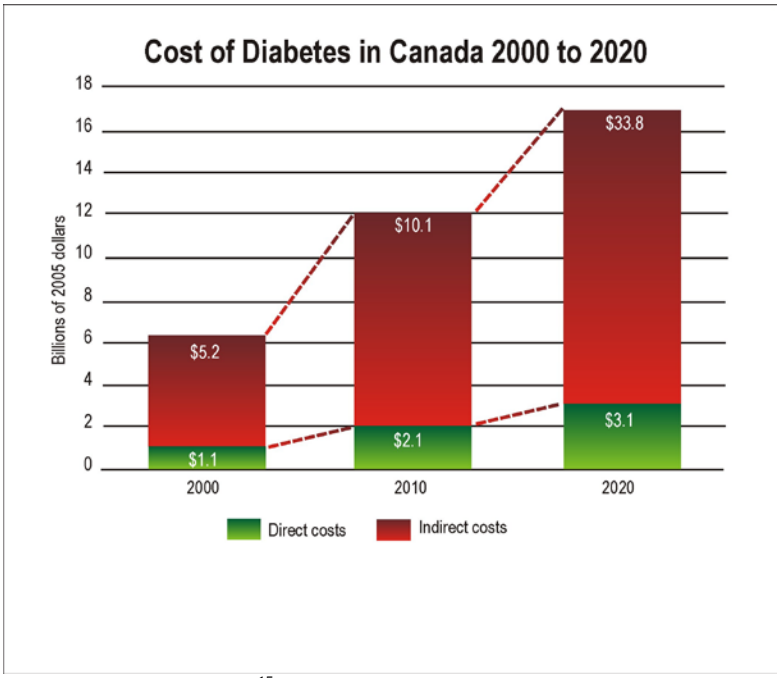

Figure 1: Cost of diabetes in Canada[15]

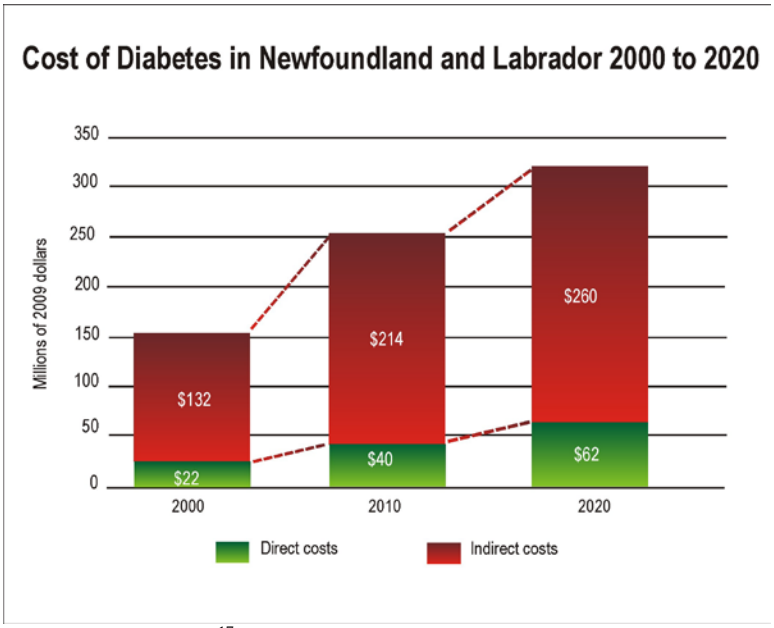

Figure 2: Cost of diabetes in NL[17]

Diabetes mellitus has many complications such as retinopathy, nephropathy, neuropathy and cardiovascular diseases. Complications are estimated to account for 80% of total diabetes costs.[15] One of the most serious and immediately life–threatening complications for patients with diabetes is diabetic ketoacidosis (DKA). In DKA, a lack of an anabolic hormone called insulin renders the body unable to use glucose for energy. This leads to unopposed fatty acid breakdown, which produces ketones in the blood. Ketones contribute to the metabolic acidosis present in DKA patients. DKA often requires hospital admission and intensive care management, and is associated with significant morbidity and increased mortality. If not properly diagnosed, pediatric DKA can lead to cerebral edema. Other possible complications of DKA are dehydration, myocardial infarction, necrosis of bowel tissue, kidney failure and even death, which occurs in less than 1% of patients in developed countries.[21,56,106] DKA is still the most common cause of morbidity and mortality in children with diabetes and a common cause of hospitalization.[6]

There are a number of different circumstances which can lead to DKA in a patient with diabetes. A patient with undiagnosed diabetes may present for the first time to their doctor or an emergency room with DKA. The diagnosis of DKA can initially be missed, especially in very young patients as the symptoms can mimic those of gastroenteritis or respiratory infection. Patients already diagnosed with T1DM can develop DKA either through improper management of diabetes during times of illness or significant stress, improper management of their insulin pump or infusion site problems, and by non–adherence and/or omission of insulin.[30] While patients can suffer significant morbidity and mortality, the majority of cases of DKA can be prevented through early diagnosis of

diabetes as well as proper insulin management.[132] Given the severity of DKA, emphasis should be placed on preventative efforts such as disease education and management.

The NL DKA project (NLdkaP) is a multiphase knowledge translation project aimed at lowering rates of DKA in the province. Launched in 2012, the NLdkaP provided information to educators, health care professionals, patients, their families and the general public on the significance of early detection and prevention of DKA. This included the development of a continuing medical education course for physicians, focus groups for youth and their families dealing with diabetes (rural & urban settings), distribution of updated clinical information, DKA treatment protocols for emergency rooms, and DKA prevention toolkits for families affected by T1DM, as well as a broad publicity campaign.

1.2 Study Rationale

The cornerstone of diabetes care is providing education to patients and families about the disease and supporting them to develop better diabetes self–management skills.[133] In the case of the NLdkaP, the education approach was multifaceted as it targeted healthcare professionals parallel to educating affected children, youth and their caregivers. The NLdkaP made it a priority to directly provide education to affected children and youth to equip them with the knowledge and tools to better understand and effectively manage their T1DM. The aim was to facilitate their T1DM management independence as they transition into older adolescence and adulthood and become increasingly less reliant on parental/caregiver support.

The ultimate goal of the NLdkaP was to reduce the number of DKA episodes in the province and decrease its burden. The current project aims to assess the effectiveness

of the NLdkaP and to determine whether DKA related pediatric hospitalizations varied before, during, and after the completion of the NLdkaP. Demonstrating the effectiveness of a multiphase educational intervention such as the NLdkaP holds the promise of generating new knowledge about effective interventions seeking to prevent diabetes complications locally and in other regions and jurisdictions.

1.3 Research objectives

The primary objective of this study is to analyze the effect of providing a multi–component DKA health education intervention to health care professionals and patients/caregivers on hospitalization rates for pediatric DKA in the province. This was accomplished by comparing hospitalization rates of children and youth diagnosed with DKA at three time periods over a six year period: two years before, during and after the intervention. Secondary objectives included measuring provincial and regional hospitalization rates of pediatric patients (age 0 – 18 years inclusive) presenting with diabetes and DKA and measuring provincial and regional hospitalization rates of patients aged 19 – 24 years (young adults) presenting with diabetes and DKA. The reason for including this older age group is that this group of patients may have indirectly received some components of the intervention. In addition, demographic factors of patients and multiple admissions for DKA were analyzed.

Chapter 2: Literature Review

2.1 Search Strategy

A literature search was conducted using PubMed, Embase, the Cochrane Library, and CINAHL, with search terms pertinent to studies on diabetes education, specifically diabetic ketoacidosis education and prevention, tailored to each search engine. Experts in the field of pediatric diabetes known to the author were also asked for their opinions regarding the search strategy and relevant literature. The literature search was limited to English language articles; however, it was not restricted by date to ensure the information for review would give a complete overview of the history of the prevention of DKA and the progress made over time. However, the main information sources for this paper were the most recent articles published in the period from 2000 to 2017. The literature review provides background information on diabetes with emphasis on T1DM and DKA, factors contributing to the development of DKA, and existing DKA prevention studies. While not part of the literature review, but to provide a context of this study, a more in–depth explanation of the NLdkaP will also be included in this chapter.

2.2 Diabetes Mellitus

Diabetes was first described in 1552 B.C. by the Egyptian physician Hesy–Ra of the 3rd Dynasty.[1] In the papyrus documents that were found, Hesy–Ra described the condition of "passing too much urine" and possible remedies for this. Throughout the centuries, scientists have written about their discoveries and understanding of diabetes, including its management, which, at a time, included using a starvation or fasting diet as treatment options. It was not until 1921 that Sir Frederick Banting and his colleagues co–discovered insulin and its therapeutic potential.[170] Since then, many improvements and

technological advancements have been made, including the availability of various types of insulin and insulin delivery devices, pancreatic cell transplants and glucose monitoring systems, all of which have revolutionized the management of diabetes. However, a cure remains elusive.

Diabetes mellitus is a chronic disease characterized by the body's inability to produce or effectively use insulin. Insulin is a naturally occurring peptide hormone produced by the beta cells in the Islets of Langerhan, which are a cluster of pancreatic cells. The various islet cells work together to regulate blood glucose levels. The primary function of insulin is to facilitate the entry of glucose from the bloodstream into cells. Glucose is then used in intracellular energy metabolism. It is produced and stored in the body as a hexamer, while the active form is a monomer. The hexamer form is useful for long–term sustainability. Since this form is less reactive than the monomer form, it keeps insulin protected while being readily available for use.[9] Human insulin is a peptide hormone composed of 51 amino acids with the chemical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808 Daltons.[14] It is a dimer of an alpha–chain and a beta–chain which are linked together by disulphide bonds.[13,14] The alpha chain has 21 amino acids and the beta chain has 30 amino acids.[13] A lack of glucose uptake from the bloodstream causes hyperglycemia, which can lead to a myriad of complications, including nerve and blood vessel damage.

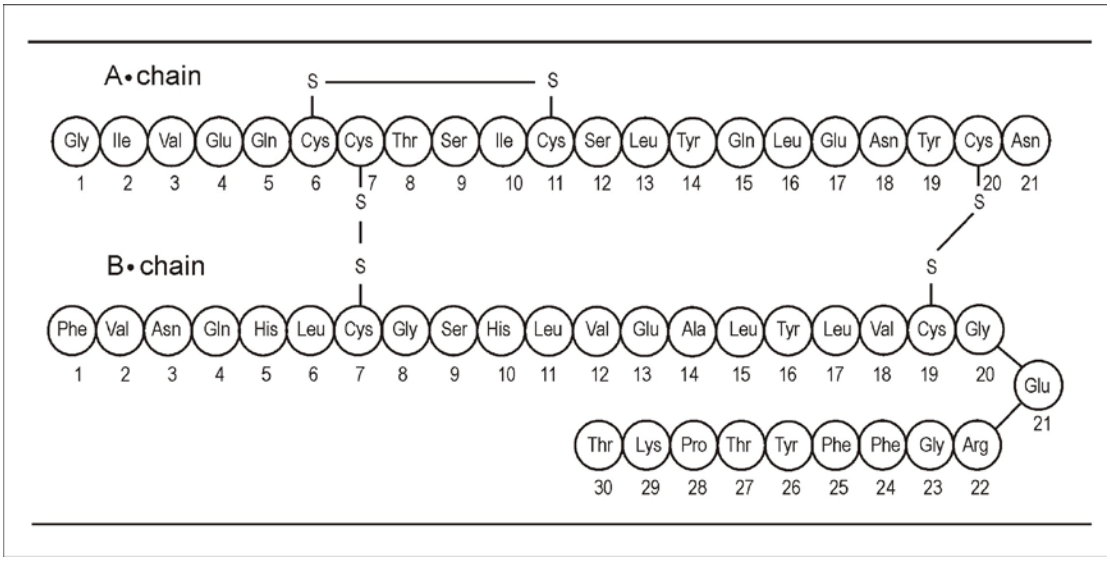

Figure 3: Primary amino acid sequence of human insulin[147]

There are two main types of diabetes mellitus in the pediatric and young adult population: Type 1 and Type 2. T1DM is characterized by the inability of beta cells to produce insulin. It was formerly called insulin–dependent diabetes, juvenile or childhood onset diabetes.[2] Its cause remains unknown and it is not preventable.[2] T1DM is a chronic autoimmune disease characterized largely by T cell–mediated destruction of insulin–producing pancreatic beta cells. Individuals become hyperglycemic and symptomatic when a critical amount of beta cell mass is lost and the residual beta cell mass is unable to match insulin demand.[3] T2DM is characterized by insulin insensitivity. Previously used terminology included non–insulin dependent (NIDDM) or adult–onset diabetes, and it is largely associated with excess body weight and physical inactivity.[2] The presenting symptoms of both types of diabetes are similar; however, those associated with T2DM often arise more gradually and, as a result, the disease is often not diagnosed until complications occur.[135] Common symptoms of diabetes mellitus include polydipsia, polyuria, weight change, extreme fatigue and lethargy, blurred vision, frequent or

recurring infections, cuts and bruises that are slow to heal and tingling or numbness in extremities.[1]

After decades of research involving over 160,000 individuals, the Juvenile Diabetes Research Foundation, the American Diabetes Association and the Endocrinology Society developed new guidelines for diagnosing T1DM, as a way to improve diagnostic timelines. The three distinct stages aid in a better understanding of how T1DM progresses in order to diagnose the disease in its earliest stages and provide prompt intervention.[143] T1DM progresses in the following three stages:[134]

Stage one: Individuals are screened for diabetes–related auto–antibodies. If an individual tests positive for two or more auto–antibodies, they are considered to be in stage one. This stage is indicative that the immune system has started attacking insulin–producing beta cells, although blood sugar levels remain normal and no symptoms are present.

Stage two: Individuals have tested positive for two or more diabetes–related auto–antibodies, but their blood sugar levels have become abnormal due to the increasing loss of beta cells. There are still no symptoms.

Stage three: At this stage, the immune system has already destroyed a very large number of beta cells. In addition to diabetes–related auto–antibodies and abnormal blood sugar levels, T1DM symptoms are usually present.

In contrast, the pathophysiology of pediatric T2DM is not completely understood; however, it is characterized by insulin insensitivity due to insulin resistance and a decline in insulin production, ultimately resulting in pancreatic beta–cell failure. This leads to a decrease in glucose transport into liver, muscle and fat cells.[134, 138]

On a global scale, in 2014, both T1DM and T2DM affected over 420 million people, accounting for 8.5% of the population over 18 years of age. This figure is almost quadruple from the 108 million affected in 1980.[4] In 2012, diabetes directly caused 1.5 million deaths and an additional 2.2 million deaths indirectly (by increasing the risk of cardiovascular and other diseases).[2] In Canada, diabetes affected over 3.4 million people in 2015.[171] According to the Public Health Agency of Canada, data obtained from blood samples showed that approximately 20% of cases remain undiagnosed.[5] It is estimated that when combined with undiagnosed diabetes and pre–diabetes, about one in three Canadians will be affected by 2025.[6] Newfoundland and Labrador (NL) has one of the highest rates of diabetes in the country, accounting for approximately 47,000 individuals in 2010 (9.3% prevalence rate) and estimated to rise to 73,000 in 2020 (14.4% prevalence rate).[6]

Diabetes and its complications bring about substantial economic loss to people with diabetes and their families. Further, the disease impacts health care systems and national economies through direct medical costs and loss of work and wages.[4] It is estimated that individuals with diabetes have 2.3 times the healthcare costs than individuals without diabetes, and that one in every ten healthcare dollars is spent on individuals with diabetes.[10] Globally, as of 2016, the cost of diabetes reached $825 billion per year, not including work days lost.[16] Nationally, the Canadian Diabetes Association reported that in 2010, diabetes–related costs impacting the healthcare system and the economy was $11.7 billion with projections rising to $16 billion by 2020.[15] In NL, the economic burden of diabetes was estimated to be $254 million in 2010. This cost

is expected to increase by a disquieting 27% over only one decade to $322 million by 2020.[17]

Given that currently there is no cure for diabetes, it is imperative that healthcare providers acquire sound knowledge and competencies for the diagnosis and treatment of the disease. Diabetes management can be strengthened through the use of standards and protocols.[4,7] However, to lower both the health and economic burden associated with the disease, diabetes education should extend to patients, their families and the general public.

2.3 T1DM in Canada and NL

Childhood T1DM is one of the most prevalent pediatric chronic diseases in the world.[29] The incidence of T1DM in children is well documented,[98,99] varying from 0.1/100,000 person–years (P–Y) in Venezuela and China to more than 36/100,000 P–Y in Finland and Italy from 1990 – 1994.[104] The latter two countries also reported rates of 45/100,000 P–Y in 1996.[99] There are a number of Canadian studies reporting the incidence of T1DM in children, including two studies based on urban tertiary hospital populations in Montreal[100] (10.1/100,000) and Toronto[101] (9/100,000), and three population–based studies using data collected from the provincial drug registry in Prince Edward Island[102] (24.5/100,000), the Manitoba Diabetes Database in Manitoba[103] (20.4/100,000) and Alberta[105] (20.4/100,000).

A 2004 population–based study carried out by Newhook et al. in NL reported that the province had the highest incidence rate of childhood T1DM in North America[28] and the third highest recorded worldwide.[28-30] Another study conducted in NL examined data

from 1987 – 2010 and found that the incidence of T1DM in the province rose during this time interval. A prospective study showed that from 1987 to 2005 the incidence rate was 37.7/100,000, but during the period 2007 – 2010 the incidence rate was found to be 49.9/100,000.[27] While T1DM is a genetically linked disease, this large rise cannot solely be attributed to heredity.[29] It is hypothesized that some environmental, epigenetic and lifestyle factors play a critical role.

Parallel to the rising rate of T1DM in NL, there is also a documented increase in hospitalization rates related to T1DM in the province. In the period 1995 – 1996, the hospitalization rate was 84.5/100,000. By 2001 – 2002, it had climbed to 103.8/100,000, a relative increase of 18%.[29] Investigating the hospitalization rates for T1DM is important in determining the overall burden of illness and the need for health services.[29] There is a large variation in diabetes hospitalization rates and length of stay between countries and different time periods, which may be attributed to differences among health care systems. In northern European countries, hospitalization rates among patients with diabetes were higher than those in the United States.[99] In comparison with other jurisdictions, the overall hospitalization rate of T1DM in NL is higher than Ontario (68.4/100,000)[106], California (31.9/100,000)[107] and The Netherlands (25.2/100,000)[108].

2.3.i Genetics and T1DM

As already discussed, T1DM is attributed to both genetic and environmental factors. In NL, the population is primarily comprised of descendants from approximately 20,000 English and Irish immigrants who settled in the province in the mid–1700s.[109] The immigration history of NL is well documented, concluding that approximately 96% of residents have ancestors from southeast Ireland or southwest England.[110] Most of the

settlers in NL were attracted to the cod fishery, which peaked in the late 18th and early 19th centuries. This was the last major in–migration, bringing the population of NL to around 75,000 in the mid–1830s. Since this time, natural growth has been the main source of population increase. The NL populace is considered to be relatively homogeneous due to geographic isolation, previous lack of roads, religious segregation, scarce intra–provincial migration and limited immigration and emigration; all of which kept related families together.[110,111,114] Interestingly, the incidence of T1DM is still high in ancestral England and Ireland, but is lower than in NL. For example, epidemiologic studies show that the incidence in the Republic of Ireland was (16.6/100, 000) in 1997,[112] and the incidence in Devon and Cornwall, England was (16.1/100, 000) from 1975 – 2001.[113] Several studies conducted in NL highlighted the link between genetic–based diseases and founder effects.[115,116] This association is hypothesized to be relevant in T1DM, potentially contributing to the high incidence rate in the province.[111] However, the steep incidence rise (37.7 to 49.9/100,000) over a relatively short period of time cannot be solely attributed to founder effects. Therefore, environmental factors are a reasonable assumption as contributing elements in an already genetically at–risk population.[111]

2.3.ii Environment and T1DM

A prospective and retrospective cohort study of the incidence of T1DM in NL in children aged 0–14 years from 1987 to 2005 determined a number of possible environmental factors related to T1DM.[111] First, the study noted that the development of T1DM may be related to the early infant diet. Studies have shown that infants who are breastfed are less likely to develop T1DM.[180] Most infants in NL are formula fed (cow's

milk protein–based) and breastfeeding initiation and duration rates are low, despite rising over the study period (36 – 64%).[123,124]

Second, there is a hypothesized correlation between vitamin D metabolism and various autoimmune diseases, including T1DM.[117-122] Given the northern geographic location of NL, sun exposure is minimal, resulting in less endogenously produced vitamin D.[125] Less hours spent outdoors and use of sunscreen on infants and toddlers are also suspected to affect vitamin D synthesis.[111] Further to this latitude–based hypothesis, the researchers compared incidence between geographic regions and found that the Northern Peninsula of NL had the highest incidence of T1DM (43.2/100, 000) while the South Coast of NL had the lowest incidence (18.3/100, 000).[111]

Another potential environmental influence identified in the literature is the association of T1DM and high rates of obesity.[126-128] The rates of being overweight and obese in NL are documented as the highest in Canada and rising.[129] Other studies suggest that high birth weight, increased height, weight and body mass index are likely risk factors in the development of T1DM, and are likely factors contributing to the high rates of T1DM in NL.[130,131]

2.4 Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute and life threatening complication of diabetes and is the leading cause of morbidity and mortality in children with diabetes.[22] It is the most common pediatric metabolic emergency.[23] It is defined as a blood glucose concentration of >11 mmol/L, with ketonemia/ketonuria and a venous pH <7.3 or bicarbonate <15 mmol/L.[26,148] Insulin deficiency is the primary defect, causing elevated serum glucose and lipolysis, which leads to ketone formation. Secondary defects such as

psychological stress caused by acidosis and progressive dehydration and coexistent infection or illness can stimulate the release of counter–regulatory hormones. These hormones include catecholamines, cortisol, growth hormone and glucagon and they contribute to increased serum glucose through increased hepatic glucose production and impair peripheral glucose uptake.[148] Epinephrine promotes lipolysis and free fatty acid release through the activation of adipose tissue hormone–sensitive lipase in adipocytes.[148] This mechanism results in the accumulation of acidic intermediate and end metabolites, which are toxic to the body at high levels. Ketone bodies are produced from acetyl coenzyme A mainly within hepatocytes in the mitochondria. High levels of acetyl coenzyme A present in the cell inhibit the pyruvate dehydrogenase complex, but activate pyruvate carboxylase. Thus, the generated oxaloacetate enters gluconeogenesis rather than the citric acid cycle, as the latter is also inhibited by the elevated level of nicotinamide adenine dinucleotide (NADH) resulting from excessive β–oxidation of fatty acids. The excess acetyl coenzyme A is therefore rerouted to ketogenesis.[34] There are three ketone bodies responsible for DKA, β–hydroxybutyrate (78% proportion in the blood), acetoacetate (20%) and acetone (2%).[26] It should be noted, however, that only acetone is a true ketone, while β–hydroxybutyrate is a hydroxy acid and acetoacetate is a ketoacid.[34] DKA is characterized by the triad of hyperglycemia, metabolic acidosis and increased total body ketone concentration; and stems from absolute or relative insulin deficiency.[7] The severity of DKA is defined by the degree of acidosis: mild, venous pH 7.2–7.3; moderate, pH 7.1–7.2; and severe, pH <7.1.[8]

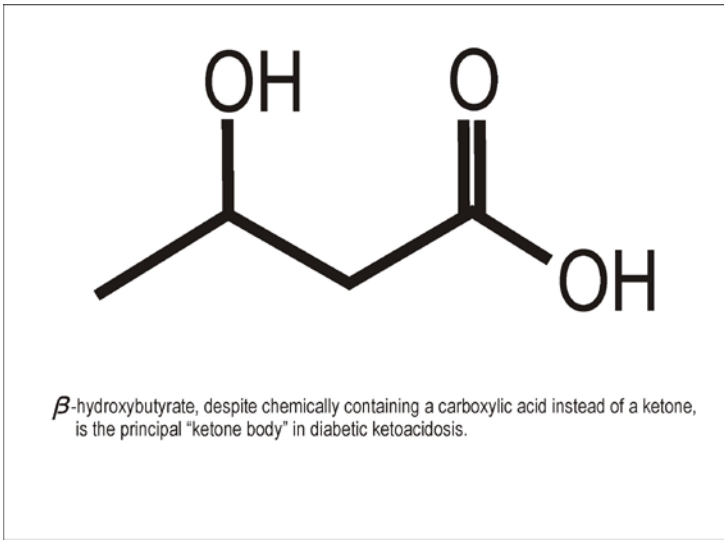

Figure 4: B-hydroxybutyrate, the main ketone in DKA[9]

As discussed above, DKA is the outcome of absolute or relative deficiency of circulating insulin combined with the effects of increased levels of the counter–regulatory hormones catecholamines, glucagon, cortisol and growth hormone.[31,32] Absolute insulin deficiency may occur in previously undiagnosed T1DM and/or when a patient undergoing insulin treatment deliberately or unknowingly fails to take insulin. This is especially the case if the long–acting insulin is omitted.[26] Patients who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason because only rapid-acting insulin is being used.[33] On the other hand, relative insulin deficiency arises when the concentrations of counter–regulatory hormones increase in response to stress in conditions such as sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting. The combination of low serum insulin and high counter–regulatory hormone concentrations results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), impaired peripheral glucose utilization resulting in hyperglycemia, hyperosmolality, increased lipolysis and

ketogenesis causing ketonemia and metabolic acidosis.[26] DKA causes severe water and electrolyte depletion from both the intra and extracellular fluid compartments.[26] Table 1 below depicts the range of fluid losses.

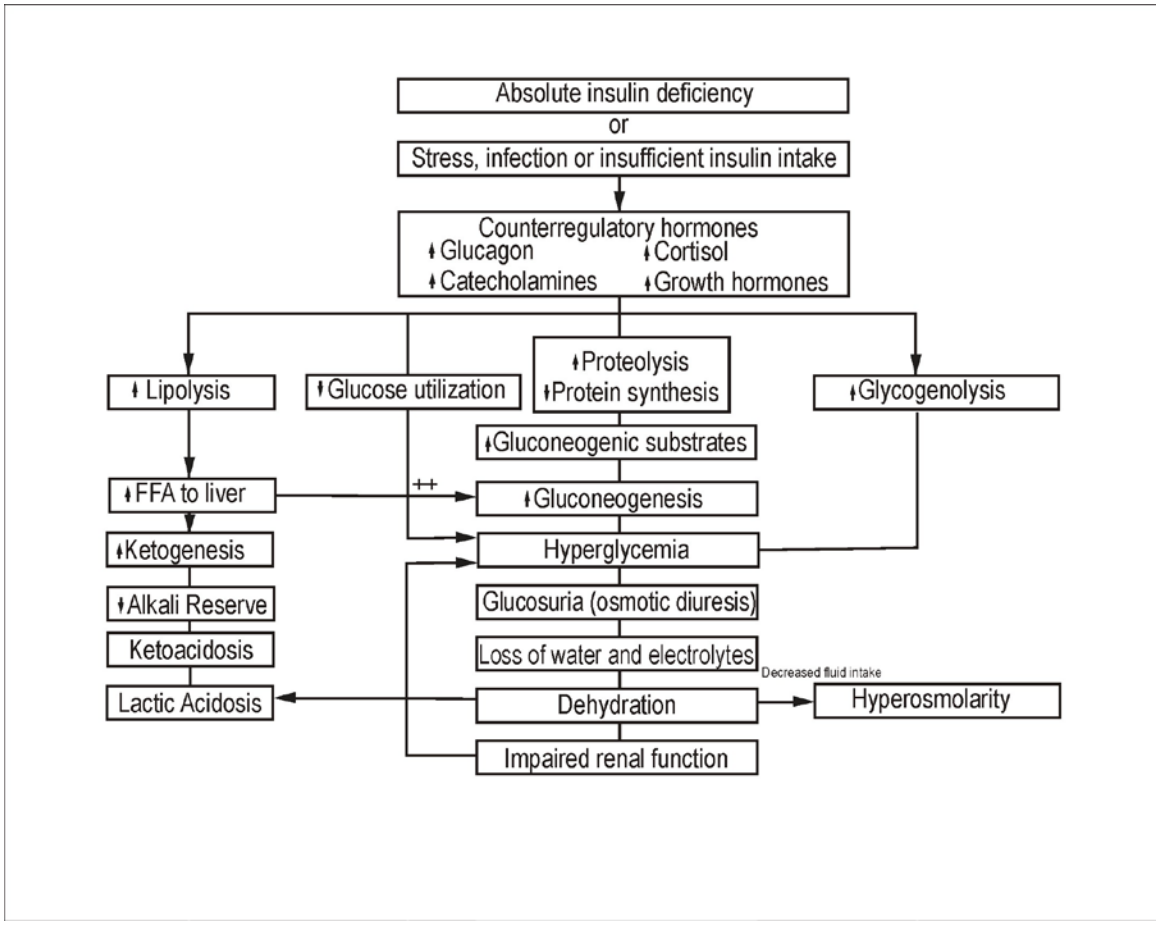

Figure 5: Pathophysiology of DKA[8]

Table 1: Fluid and electrolyte loss in DKA[26]

Losses of fluids and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg	24-hour maintenance requirements	
Water	70mL (30-100)	<10kg	100mL/kg/24hr
		>11-20kg	1000mL+50mL/kg/24 hr for each kg from 11-20
		>20kg	1500mL +20mL/kg/24hr for each kg > 20
Sodium	6mmol (5-13)		2-4 mmol
Potassium	5mmol (3-5)		2-3 mmol
vChloride	4mmol (3-9)		2-3 mmol
Phosphate	(0.5-2.5mmol)		1-2 mmol

In any individual patient, actual losses may be less or greater than the ranges shown.

In patients newly diagnosed with T1DM, the most common symptoms for DKA include polyuria, polydipsia, weight loss and nocturia as well as neurologic symptoms such as irritability and altered levels of consciousness. In previously diagnosed individuals, the most common symptoms of DKA are vomiting and abdominal pain.[30] If the presenting symptoms are left untreated, they can escalate into tachycardia, hyperventilation, vomiting, dizziness, confusion, fruity breath, drowsiness and unconsciousness.

Some complications of DKA can be exacerbated by inappropriate medical management such as giving too much or the wrong types of intravenous fluids.[38] Physicians must be judicious when restoring fluids along with the necessary electrolytes such as sodium, potassium and chloride and when administering insulin. For example, insulin infusions allow glucose to enter the cells, and if too much insulin is given, blood

glucose levels can drop too quickly and hypoglycemia may occur. Further, intravenous fluids and insulin infusion may cause potassium levels to drop, a condition called hypokalemia. Hypokalemia can impair the heart, muscle and nerve function. Finally, rapid changes in osmolarity can contribute to cerebral edema.[38] Despite these common and serious complications, leaving DKA untreated is fatal. To avoid the development of DKA, it is critical to understand and be able to detect the most common presenting symptoms of diabetes.[30]

2.4.i Differences in adult and pediatric DKA

While the fundamental pathophysiology of DKA is very similar in adults and children, there are a number of reasons why DKA is different in a pediatric population. Considering these differences is integral in developing DKA awareness and education programs tailored to health care personnel, patients and families. In 2006, Wolfsdorf and al[8] reported that it is challenging to detect a history of polyuria and polydipsia in young children. Consequently, the preschool age group are often misdiagnosed with pneumonia, bronchiolitis, gastroenteritis or other common childhood diseases. Sometimes they are treated with glucocorticoids, which further exacerbate metabolic imbalances that are present in DKA. Also, children have a higher basal metabolic rate and large surface area relative to total body mass. This requires greater precision in delivering fluids and electrolytes. Cerebral and other auto–regulatory mechanisms may not be as well developed in children. Hence, in a younger population, greater symptom severity at presentation in combination with less developed auto regulatory systems predispose children to cerebral edema, which occurs in approximately 0.5 – 1% of all episodes of pediatric DKA.[8] Cerebral edema is a very serious DKA complication.

Although its pathophysiology is related to dehydration and acidosis, its causes are multifactorial and not fully understood. Increased levels of inflammation and coagulation are hypothesized to lead to decreased blood flow to areas of the brain, which then swell once fluid replacement is initiated.[11] Cerebral edema is more likely to occur in patients with severe DKA, who are younger (<5 years of age), and are having their first episode of DKA at diagnosis.[11,12] It is estimated that it is three times more likely to occur in those with new onset diabetes.[20] Cerebral edema is the most common cause of mortality in children with DKA,[18-21] accounting for 60 – 90% of all DKA–related deaths in the pediatric population.[7,8] Preadolescent DKA occurs most often in children with previously unrecognized diabetes (delay in diagnosis), whereas omission of insulin is the leading cause of DKA and recurrent DKA amongst adolescents and young adults.[8]

2.5 Factors contributing to the development of DKA

DKA can be primary or secondary: 1) primary DKA is at initial diagnosis of T1DM and 2) secondary DKA which occurs in those with established diabetes as a result of accidental or deliberate insulin omissions, at times of stress such as intercurrent illness, and/ or inappropriate management.[38] DKA at initial presentation is common, however, rates vary greatly among countries, ranging from 15 – 70%.[7,9,34,35,36] Similar variability across jurisdictions applies to DKA in children with previously diagnosed T1DM.[36,37] DKA is mainly associated with T1DM however, it can also occur in individuals with T2DM.[136] An imperative point to know is that most, if not all, cases of DKA are preventable.[21,22] Prevention of DKA by proper insulin management and early detection of diabetes in new patients should reduce the severity and rates of DKA.

A systematic review conducted in 2011 identified 46 studies, including more than 24,000 children with T1DM from 31 countries.[23] It is unclear why some children present in DKA whereas others do not, and whether the development of DKA is a consequence of delayed diagnosis and treatment or whether it reflects a particularly aggressive form of diabetes.[164] Exploring the underlying factors associated with DKA is therefore integral to developing a better understanding of the disease and how to inform individuals, families and healthcare professionals.

A number of studies worldwide examined the risk factors leading up to an individual developing DKA. These factors have been grouped into the following categories: 1) Individual; 2) Family; 3) Physician–related; 4) Disease–related; 5) Other and 6) Protective. The ensuing paragraphs discuss these influences and are summarised in Table 2.

INDIVIDUAL FACTORS

1. Age

Previous research has shown that younger age at T1DM diagnosis is a significant risk factor in the development of DKA. Usher–Smith et al. found that children under two years of age had three times the risk of presenting with DKA than children older than two years of age (OR 3.41; 95% Confidence Interval (CI), 2.54 – 4.59) and this continued up to five years of age (OR 1.59; 95% CI, 1.38 – 1.84).[38] It has been determined that the frequency of DKA decreases with age from 37 – 40% (95% CI, 32.9% – 41.8%) in children up to four years of age, to 15 – 24% (95% CI, 11.7% – 17.7%) in children 15 to 19 years of age.[40,41] There are a number of suspected reasons for the higher rates of DKA

in younger age groups. First, the classic signs of T1DM may not be as obvious, therefore causing a delay in diagnosis. In addition, young children are unable to speak and verbalize their symptoms. Second, clinicians may have lower rates of suspicion of T1DM in younger children.[42,43] These conclusions could also be considered under the "Physician–related" heading. Third, younger children have less developed mechanisms of metabolic compensation, thus DKA manifests at a much faster rate.[40,44] Finally, in children < 2 years of age, β–cell destruction may be more aggressive as indicated by low serum levels of C–peptide found in younger versus older children.[44,46] In adolescents, factors associated with DKA occurrence may be attributed to the teen's growing independence and less time spent with parents/guardians and family. They may be more likely to ignore signs and symptoms and in those with T1DM there may be higher rates of non–adherence to medical treatment and insulin mismanagement. Other confounding factors in this older age group are psychological factors, such as intentional weight restriction and eating disorders, which can lead to poor glycemic control and higher risk of DKA.

2. Sex

Prior studies have shown the association between sex and DKA frequency. In particular, DKA occurrence was found to be higher in females.[29,30,50,64] Although these studies did not look at specific reasons as to why this may be, it is suggested that there are psychosocial factors involved, such as familial conflict, behavioral issues and intentional weight reduction associated with insulin omission.[74,75] As well, in one study, females were found to have a higher mean H_bA1C level.[30] H_bA1C levels are measured

by blood test and indicate the percentage of haemoglobin that is glycated.[149] The test result reflects blood glucose levels over the preceding few months, rather than at one point in time, thus shedding light on overall diabetes management. While H_bA1C levels can vary slightly between individuals, a higher level indicates poor glycemic control (ideal is $\leq$ 7.0).[142,149] Another study showed that being female was significantly associated with an increased chance of delayed diagnosis with a symptomatic period $\geq$4 weeks (OR 2.78 (1.09 – 7.14), P = 0.033).[59] Interestingly, in this study, delayed diagnosis was not associated with an increased risk of severe DKA (pH < 7.1; bicarbonate < 5 mmol/L, OR 0.68; 95% CI, 0.26 – 1.83, P = 0.450).[59]

3. Ethnic minority

Studies have demonstrated an increased risk of DKA among ethnic minorities. Most of the studies conducted had such a heterogeneous pool of patients that establishing whether the frequency of DKA was significantly different in any particular race or ethnic group was difficult. However, in studies comparing the frequency of DKA between two different ethnic groups, all showed a significant difference in the frequency of DKA, and further, in each case, the ethnic minority group experienced an increased risk of DKA.[38] A multicenter study conducted in the United States (US) found that independent of socioeconomic status and age, non–Caucasian youth were at higher risk of presenting with DKA at diagnosis when compared with non–Hispanic Caucasian youth (OR 1.21; 95% CI, 1.03 – 1.43).[47] A number of other US studies researched ethnic background and its relation to DKA risk. The results showed the DKA risk for non–Hispanic Caucasian people compared with others (OR 0.55; 95% CI, 0.32 – 0.96),[71] Caucasian people

compared with Hispanic (OR 0.33; 95% CI, 0.14 – 0.76)[72] and non–Hispanic Caucasian compared with Hispanic (OR 0.58; 95% CI, 0.37 – 0.89).[73] A study in the United Kingdom (UK) demonstrated more frequent DKA at diagnosis of T1DM among ethnic minorities compared with non–Hispanic Caucasian patients (41.3% vs. 21.4%, P = 0.03).[48] Finally, a study in New Zealand showed that non–Europeans were more likely to have DKA at diagnosis than Europeans (OR 1.52, P = 0.048).[49] Cultural differences, language barriers, lack of access to health care services and lack of awareness of T1DM are all factors that may contribute to the disparity that exists between minority and non–minority populations. Based on these observations, an effective DKA prevention program should be developed in a way to reflect considerations on ethnic minority and surrounding issues.

4. Body mass index (BMI)

Studies conducted in Austria and Finland both included BMI as a risk factor of DKA. Both of these studies concluded that a lower BMI is associated with a higher risk of developing DKA.[69,70] These findings are in line with the psychosocial/psychological factors discussed in the age and sex categories above, as weight loss due to insulin omission can lead to poor glycemic control and increased risk for DKA.

5. Psychological stress

When the body is under short or long term stress, the counter–regulatory hormones such as catecholamines, cortisol, growth hormone and glucagon are released.[30] A study conducted by MacGillivray et al. concluded that the rapid onset of DKA in

patients who reported emotional stress suggests that stress was the trigger for the release of large amounts of counter–regulatory hormones which overwhelmed and inhibited the physiologic action of insulin. While these hormones inhibit or overwhelm the action of insulin at one or more of its target tissues, it is also likely that the prescribed and usual dose of insulin in these patients was insufficient to offset the effects of these counter–regulatory hormones, and without increasing the dosage of insulin, DKA ensued.[173]

6. Non–adherence to insulin management

Insulin mismanagement can be deliberate or accidental. It has been shown to occur in youth, and more often females, who are restricting their weight (as mentioned in the age and sex sections). It has also been shown to occur in youth as they take on more responsibility for the management of their own condition, but falter on occasion. This could be in part due to immaturity or simply not having enough education and/or understanding about when and how to deal with issues that may arise (e.g., pump failures). As well, a lack of understanding regarding the consequences of not acting in a timely manner may be relevant. Finally, there is a higher risk of entering into DKA when children are under the temporary care of people other than their parents or guardians who may not know how to properly administer insulin (for example, when managing sick days[141,142]). It is imperative for proper education and re–education of both the individual with diabetes and those around them to ensure that issues of insulin mismanagement do not occur, and are quickly addressed if they do arise.

FAMILY FACTORS

1. Lower socioeconomic status

Socioeconomic status as measured by family income or neighbourhood income is associated with an increased risk of DKA at diagnosis.[47,50] An American study by Dabelea and colleagues found that the frequency of DKA was 70 – 80% higher in patients with family income below $50,000 when compared to those with family income above $50,000.[47] This finding applies to patients in Canada even in light of having universal access to healthcare. A Canadian study found that patients with low socioeconomic status, measured by neighbourhood quintiles, were more likely to present with DKA at diagnosis when compared with those living in higher income quintiles (OR 1.39; 95% CI, 1.17 – 1.63).[50]

2. Lack of private health insurance

Lack of private health insurance has consistently been found to be a significant risk factor for DKA at diagnosis.[51-53] A study in the United States concluded that patients with private health insurance were least likely to present with DKA.[51] King et al. found that patients without private health insurance were 60% more likely to present with DKA compared to those with private health insurance. When uninsured patients presented with DKA, they were more likely to present with severe DKA (venous pH < 7.10; serum bicarbonate < 5mmol/L).[53] The odds of uninsured patients presenting with severe DKA were six times greater than for insured patients (OR 6.09; 95% CI, 3.21 – 11.56).[52] Children in the US with no insurance also had a greater risk of presenting in DKA compared with those receiving Medicaid (OR 2.84; 95% CI, 1.16 – 6.93), but there was

no difference between those with private insurance and those receiving Medicaid (OR 0.54; 95% CI, 0.26 – 1.10).[71] These findings suggest that uninsured patients are more likely to delay a hospital visit, which is consistent with a delayed diagnosis that can lead to more severe cases of DKA.

3. Parental formal education

Several studies from Baltic countries found that if a child's mother had higher than secondary education, it was a protective factor against the occurrence of DKA (OR 0.4; 95% CI, 0.20 – 0.79).[95] As well, children from families that had at least one parent with an academic degree were found to have lower incidence of DKA at presentation than those without (16.9% (43/254) vs 24.4% (105/431), $P < 0.05$, OR 0.64; 95% CI, 0.43 – 0.94).[45] Finally, children from families in which parents had ≤9 years of education had a significantly increased risk of severe DKA (OR 3.54; 95% CI, 1.10 – 11.35, $P = 0.034$) compared with children whose parents had ≥ 12 years of education, even after adjustment for rates of delayed diagnosis.[59]

4. Family structure

A few studies considered family structure as a factor of DKA, including having a single parent and the number of children in the family. Neither of these considerations were found to be associated with an increased risk of DKA.[59,68,94]

5. Rural / urban residence

Various studies have found that there is no difference in DKA occurrence between living in an urban or rural setting.[95,139] However, in NL, it is thought that living in a rural area does increase the odds of DKA occurrence.[160] This can be attributed to lower T1DM incidence and/or less DKA education (both for the public and for physicians) and due to less access to resources, resulting in missed or delayed diagnosis. In some communities, limited access to health care workers such as social workers, psychologists, psychiatrists, diabetes educators and dietitians may be part of the cause.[160] In a recent 2015 study, despite the geographic isolation and lack of resources that rural NL residents reported, they responded positively to community supports that were available in their hometowns, such as support groups.[160] Further, some rural residents commented that living in a small place allows for stronger community ties and social support which helped their children with diabetes.[160]

PHYSICIAN–RELATED FACTORS

1. Delayed diagnosis

An NL study by Jackman et al. found that a delay in diabetes diagnosis is one of the leading causes of DKA in children. In this 2015 study, the rate of DKA on presentation for incident cases of diabetes in NL was 22.1% in the region's tertiary care hospital.[21] Based on other study findings, DKA diagnosis on initial presentation of new onset T1DM occurs between 15 – 70% of the time.[34,36] There are a number of factors which can lead to delays in diagnosing diabetes. A study from the UK reported that a delay of more than 24 hours between initial presentation to a primary or secondary care

provider and referral to a multidisciplinary diabetes team is associated with an increased risk of presenting with DKA (52.3% vs 20.5%, $P < .05$).[48] The most common reason for a delayed diagnosis was arranging a fasting blood sugar test prior to referral to a multidisciplinary team.[48] Regions having higher rates of T1DM generally have lower rates of DKA at the time of diagnosis, according to findings from a number of studies.[81,21] This may be related to heightened awareness of DKA in areas with higher prevalence of T1DM. Bui et al. reported that children with DKA at diabetes diagnosis were more likely to have visited a health care professional on one or more occasions in the weeks prior, at which time diagnosis of T1DM was missed.[30,50] Further, 39% of children and adolescents with new onset diabetes who present in DKA had seen a physician in the preceding week.[50]

2. Diagnostic error

Several studies have reported an increased risk of DKA in children not diagnosed with T1DM at first presentation to the health care system either due to misdiagnosis or lack of recognition of the symptoms of T1DM.[48,50] Independent of preceding infection, diagnostic error has been associated with a three–fold increased risk of presenting with DKA (OR 3.35; 95% CI, 2.35 – 5.79).[56] Patients with DKA in whom the diagnosis of diabetes was missed at initial presentation tended to be younger (mean age 5.4 ± 4.4 years) compared to those in whom the diagnosis was not missed (mean age 8.8 ± 4.0 years) ($P < 0.001$).[50] Overall, younger children tend to be misdiagnosed with urinary tract infections, upper respiratory tract infections, diarrhea/gastroenteritis and otitis media.[50, 55]

3. Change in diabetes team

It has been shown that a change in the diabetes management team can negatively impact disease control.[150] It is estimated that between 25 – 65% of young adults have no medical follow up during the transition from pediatric to adult diabetes care services.[151,152] In a retrospective Canadian study conducted in 2009, Nakhla et al. found that diabetes related hospitalizations rose from 7.6 to 9.5 cases per 100 P–Y in the two years following transition to adult care.[150] Interestingly, they also found that with controlling for all other factors, individuals who were transferred to a new allied health care team with no change in physician were 77% less likely (RR: 0.23, 95% CI: 0.05 – 0.79) to be hospitalized after the transition than were those transferred to a new physician with either a new or no allied health care team.[150] These findings are integral to future studies as patients' lack of trust and satisfaction with their health care providers can lead to poor glycemic control[162,163] and decreased treatment compliance.[161] It is important to understand that transitioning from pediatric to adult care is a vulnerable time for patients and that time is required to build a solid relationship with a new physician and healthcare team.

DISEASE–RELATED FACTORS

1. Duration of symptoms

A few studies found that children presenting in DKA at diabetes diagnosis compared with those not in DKA had similar mean symptom durations, though the symptoms in the group presenting in DKA were slightly shorter, at 16.5 days (standard deviation (S.D.) 6.2) versus 17.1 days (S.D. 6.0) respectively, $P < 0.001$).[64,91-93]

2. Pattern / frequency of symptoms

It has been found that children with DKA present most often with polyuria, vomiting, abdominal pain, dyspnea, weakness, anorexia, and changes in mental status.[91,94,96] The EURODIAB study reported that 96% of children displayed polyuria at the time of diagnosis of T1DM.[84] Two studies also showed that children with T1DM with DKA had significantly greater weight loss than those without DKA, 4.84% vs. 3.32% of body weight ($P < 0.0001$).[84,93] This is consistent with findings described earlier that children with known diabetes and lower BMI present in DKA more than those with higher BMI, likely due to poor glycemic control associated with restricted weight.[69,70]

3. Preceding infectious illness

Patients with diabetes are susceptible to DKA under stressful conditions, such as trauma, surgery, or infection. Worldwide, infection is the most common precipitating cause for DKA, occurring in 30 – 50% of cases.[30] The presence of a concomitant infection may mask the early symptoms of diabetes, resulting in delayed diagnosis and increased risk of DKA.[47] In addition, an infectious or febrile illness usually increases the counter–regulatory response, leading to insulin resistance and metabolic decompensation.[31]

4. Sick–day management

Both the Canadian and American Diabetes Associations have published Sick Day Management guidelines to help families dealing with diabetes to manage sick days.[141,142] When the body has an infection, it releases hormones that increase blood glucose levels. In addition, during a period of illness one may vomit and/or have diarrhea so monitoring fluids is essential. In addition to the child being ill, sometimes they are left in the care of a temporary guardian. It is crucial for this individual to have sick–day management knowledge so that proper care is provided and action can be taken if necessary to prevent DKA.

OTHER FACTORS

1. Time of year

Two studies found that more cases of T1DM were diagnosed in the winter than summer months, however, the rate of DKA cases remained constant (OR 1.07; CI 0.89 to 1.28, P = 0.49).[64,140] It is thought that H_bA1C levels are higher in the winter months for several reasons.[149,166] First, physical activity levels tend to be lower in winter and it is thought that physical activity reduces insulin resistance and improves insulin bioactivity. Second, people tend to have larger weight fluctuation in the winter, and plasma cortisol and tissue sensitivity to glucocorticoids are also higher during this season, which could contribute to increased body fat and insulin resistance.[167] Individuals with T1DM should be especially conscious of managing their disease during the winter to avoid preventable complications such as DKA.

PROTECTIVE FACTORS

1. Background incidence of T1DM

It is hypothesized that background incidence of T1DM has an inverse effect on the rate of DKA in newly diagnosed T1DM.[38,41,45] Background incidence refers to the rate of occurrence of T1DM in a given area. If the incidence is higher, disease awareness and healthcare provision will generally be higher.[23,37,84] These insights are thought to be attributed to earlier recognition of symptoms and diagnosis.

2. Family history of diabetes

It is thought that having a family member with diabetes is a preventive factor against DKA. It is assumed to be because there is heightened awareness of the signs and symptoms of diabetes, allowing patients to seek care earlier preventing an individual from entering into DKA.[41,45,47] According to a number of studies,[44,65-67] this seems to be conditional upon whether the child has existing or newly diagnosed T1DM. Having a first–degree relative with T1DM decreased the frequency of DKA in three studies.[44,65,66] However, having a first-degree relative with T1DM did not predict a diagnosis of new–onset diabetes before the progression to DKA.[67] Further, a small UK study (N=79) suggested that children who were the second diabetes-affected child in a family were less likely to present in DKA than the first child (OR 0.07; 95% CI, 0.003 – 1.51).[68] This is a noteworthy finding as it separates the effect of having an increased genetic risk of developing diabetes from the environmental effects of having a family member with diabetes at the time of diagnosis. Although high–risk genotypes are associated with increased DKA risk, this relationship is unlikely to be solely genetic because it has been

shown that having even one first–degree family member with T1DM, there is an associated reduced risk of DKA.[60] Furthermore, results from a long–term follow–up study showed a reduced risk of DKA associated with various environmental factors.[61] It appears as though this protective relationship is almost certainly due to greater family awareness of the symptoms of diabetes, allowing recognition early and prior to developing DKA.[55]

4. Involvement in T1DM prevention research

It has been shown that enrolment in T1DM prevention research decreases the risk of DKA at diagnosis from 30% to less than 4%.[134]

In conclusion, it is also possible that some of these protective effects could be due to clinicians displaying extra caution regarding individuals who have a family history of diabetes, as well as variations in access to healthcare, child supervision or schooling.[38] It is reasonable to consider that if teachers have smaller classes and thus are more involved with their students, then they are more likely to look out for the students they know have T1DM, resulting in better prevention of DKA.

Table 2: Factors influencing the development of DKA

Individual	Family	Physician	Disease	Other	Protective
Age	Lower socioeconomic status	Delayed diagnosis	Duration of symptoms	Time of year	Background incidence of TIDM
Gender	Lack of private health insurance	Diagnostic error	Pattern/ frequency of symptoms		Family history of diabetes
Ethnic minority	Parental education	Change in diabetes team	Preceding infectious illness		Involvement in TIDM prevention research
BMI	Family structure		Sick day management		
Psychological stress	Rural/urban residence				
Non-adherence to insulin management					

2.6 DKA prevention studies

A number of studies have been conducted to determine the effectiveness of education campaigns at reducing DKA in the pediatric population. While those studies have displayed mixed results, there is convincing evidence that improving both community and physician awareness of the presenting features of T1DM helps reduce the incidence of DKA. Planning and implementing effective community–based interventions requires accurate population–based data on the incidence, hospitalization, and

complications of diabetes.[29] In this next section, seven published studies on DKA prevention and their results will be described (summary provided in Table 6).

2.6.i Italy

A DKA prevention study, carried out over the course of eight years in Parma, Italy, involved displaying brightly colored posters showing a sleeping child along with some simple messages for parents and teachers.[76] The relevance of the sleeping child image is that the first symptom of diabetes is unusual bed–wetting as reported by 89% of parents.[77] One thousand posters were displayed in 177 primary and secondary public schools of the Italian province of Parma. During the eight–year study period, these schools were attended by a total of 144,736 children aged six to 14 years. At the beginning of each school year, a committee formed by members of the Parents' Association for Diabetic Children and Adolescents of Parma verified whether the posters were displayed. In addition, 60 posters were displayed in 52 pediatricians' offices working in the area and 104 cards with guidelines for the diagnosis of diabetes were distributed. On one side of the card, early symptoms (bed–wetting, nocturia, and thirst) and late symptoms (polyuria, polydipsia, weight loss, and fatigue) of emerging diabetes were listed and the reverse had the criteria for the diagnosis of T1DM according to the World Health Organization.[78] Pediatricians were also asked to refer children with the above clinical features to the diabetes unit of the department of pediatrics at the University of Parma. To facilitate contact with the diabetes unit, a toll–free number was provided to teachers, parents, and pediatricians.

Each pediatrician was also equipped with devices for the measurement of capillary blood glucose and glycosuria, supplies for finger pricking, reagent strips, and a

reflectance meter. Two brief meetings were organized to instruct pediatricians in the measurement of capillary blood glucose and to give them more information on the criteria for early diagnosis of T1DM and warning signs of the disease. Nurses and pediatricians with experience in managing diabetes oversaw these meetings.

Clinical features and laboratory values of children six to 14 years old who were diagnosed with diabetes in the province of Parma were compared with those of peers from the two nearby provinces of Piacenza and Reggio Emilia, where no campaign for the prevention of DKA was carried out. The three above–mentioned provinces are all part of Emilia Romagna and are similar in environment, health services, socioeconomic status and number of students < 14 years of age. According to the regional health care system, all T1DM patients aged six to 14 years within the areas of Piacenza, Parma, and Reggio Emilia must be referred to the diabetes unit of the Department of Pediatrics at the University of Parma. Thus, all newly diagnosed T1DM children six to 14 years old in the above–mentioned area were enrolled in the study.

From January 1, 1991 to December 31, 1997, 148 children aged 45 days to 18 years with new–onset T1DM were admitted to the department of pediatrics at the University of Parma. Fifty-four (36.4%) of them were six to 14 years old (29 boys, 25 girls; mean age +/- SD: 8.9 +/-1.4 years). Of these children, 24 (13 girls, 11 boys; 8.3 +/- 1.8 years old) came from the province of Parma (group one) and 30 (16 boys, 14 girls; 8.5 +/- 1.3 years old) came from the nearby provinces of Reggio Emilia and Piacenza (group two).[76]

DKA was present in three children from group one and in 25 children from group two, 12.5% (3/24) and 83.0% (25/30) respectively (X^2= 26.8; P = 0.0001). The three

cases of DKA in group one were observed in 1991 (n = 1) and 1992 (n = 2). Duration of symptoms was significantly less in group one than group two (mean five vs. 28 days) and impaired level of consciousness was found in only three patients from group two.[76]

The total cost of the eight–year campaign was $23,470. This included costs for the posters (26.2%), toll–free telephone line (27%), time spent by nurses and residents to answer the phone (34.8%) and educating teachers, parents, and pediatricians (12%). The cost to the national health care system for the treatment and education of inpatients with diabetes was $196,457 and $53,356 for children with and without DKA, respectively. [76]

Overall, the prevention program was found to be effective and the cumulative frequency of DKA in new–onset T1DM in this area decreased from 78% in the 1987 – 1991 period to 12.5% in the 1991 – 1997 period. Further, no newly diagnosed children with diabetes ages six to 14 years old from Parma were admitted to the diabetes unit with DKA after 1992 until the end of the study. This result is credited to the prevention program because in the two neighbouring provinces where the program was not carried out, the incidence of T1DM with DKA was higher and similar to the one observed in the province of Parma prior to 1991. However, despite the promising results, this study was limited by its small size, not including children under six and over 14 years of age and high baseline rate of DKA compared with typical European rates.

2.6.ii Australia

Another study was conducted in Australia during the two–year period between March 2010 and February 2012. The rate of DKA at initial diagnosis of T1DM in children <18 years old was determined by a retrospective chart review in Gosford,

Newcastle, and Sydney (the Sydney Children's Hospital and the Royal North Shore Hospital) for two years prior to the intervention, February 2008 until February 2010. [79] Gosford was chosen as the intervention site as the population demographics were similar to New Castle and Sydney and the practice is for all children presenting with T1DM to be admitted to hospitals in the area.

The campaign involved a mail out to all childcare centers (n=105), schools (n=103), and doctors (n=90) in the Gosford area. This included an explanatory letter, four posters and four postcards. The letter described the study and asked that the posters be displayed in plain view of children, parents, childcare workers, teachers and physicians. The letter also explained that the postcards included relevant information on common symptoms of T1DM and how to facilitate the timely transport of the child to the doctor or emergency department. The simple poster displayed common signs and symptoms of diabetes in children, advice of when to seek medical assistance, and a contact phone number. A diabetes educator offered all childcare centers (n=125), schools (n=103), and doctors' offices (n=90) a visit; however, these only occurred at 67 childcare centers, 32 schools, and 12 doctors' offices. Physicians were provided with a capillary blood glucose meter, a ketone meter and strips. All emergency departments in the area were made aware of the study, but were not visited or educated. In addition, each year the Gosford Division of General Practice included an image of the poster and an explanation of the study in a monthly e–mail sent to its members.

In the two years prior to the intervention (see Table 3 for summary of results), 40 children presented in Gosford with newly diagnosed T1DM, 15 of whom had DKA (37.5%). During the intervention, 29 children presented with newly diagnosed T1DM

and four had DKA (13.8%). This was a 64% reduction ($X^2 = 4.74$, $P < 0.03$).[79] The four children with DKA during the intervention were three males and one female, ages 2.6, 12.1, 12.9 and 3.5 respectively.[79] In the control centers, no contact of any form was made with childcare centers, schools, or doctors' offices. In these areas, prior to the intervention, 123 children presented with newly diagnosed T1DM and 46 had DKA (37.4%). During the intervention period, 127 children presented with newly diagnosed T1DM and 49 had DKA (38.6%).[79]

Table 3: Gosford campaign results [79]

Characteristics	Control baseline	Control intervention	Gosford baseline	Gosford intervention
Total number (DKA)	123 (46)	127 (49)	40 (15)	29 (4)
Male (DKA)	67 (23)	65 (21)	13 (5)	17 (3)
Female (DKA)	56 (23)	62 (28)	27 (10)	12 (1)
Average age	9 yr	9 yr 5 months	10 yr 4 months	9 yr 2 months
Age 0-5.9 yr (DKA)	34 (15)	29 (15)	5 (1)	9 (2)
Age 6-14.9 yr (DKA)	83 (27)	90 (31)	33 (13)	19 (2)
Age > 14.9-18yr (DKA)	6 (4)	8 (3)	2 (1)	1 (0)

The reduction in presentation of DKA with newly diagnosed T1DM before (n=15) and during (n=4) the campaign in Gosford and the consistent presentation in control centers before (n=46) and after (n=49) was attributed to the awareness campaign. While the authors did not report exact monetary costs, they did report that the campaign was feasible and concluded that it could be implemented in larger centers. This is the

first study to show a reduction in DKA in children aged 0–18 years at initial diagnosis of T1DM.[79]

Limitations of this study included that due to a lack of numbers, the authors were unable to determine if there was an effect on the rate of DKA in the preschool age category. Second, because of limitations imposed by the ethics committees in the region, no formal attempt was made to assess the role of each component of the intervention in the reduction of T1DM presentation with DKA. Further, the authors did not look at DKA rates once the intervention had ended.

2.6.iii UK

A third study from Wales was conducted by Lansdown et al. for the period 1991 – 2009.[80] The authors used the Brecon Group (The Welsh Paediatric Diabetes Interest Group) register to identify children developing T1DM before 15 years of age living in Wales, where all secondary care pediatric diabetes units in Wales contribute to this register. New cases of T1DM were reported, including presentation with polydipsia/polyuria or DKA. Ascertainment analysis showed that the register is > 95% complete in each calendar year from 1995 to 2006.[80] The proportion presenting with DKA were analyzed from 1991 to 2009 by calendar year and age. The publicity campaign was launched on November 15, 2008, based on the one conducted in Parma, Italy.[76] Posters were sent to every pharmacy (n = 700), school (n = 1833) and general practitioners' offices (n = 500) in Wales. The headline was "Could Your Child Have Diabetes?" and there were a list of key symptoms to detect early signs and symptoms associated with T1DM. The poster also indicated that a simple urine or blood test done

by a physician or nurse practitioner could make the diagnosis. In addition, several radio and television interviews were conducted to discuss the symptoms of T1DM and diagnosis of the disease. Over the six months following the launch of the campaign, the parents of all children with newly diagnosed T1DM in Gwent (southeast Wales) and their general practitioners were asked to complete a post–publicity campaign questionnaire. The questionnaire was designed to assess 1) how long the child had symptoms before diagnosis, 2) whether cases were admitted via their general practitioner and whether it happened immediately or following direct attendance at the emergency department, 3) parents' awareness of the symptoms of diabetes and 4) whether they recalled seeing the publicity campaign.[80]

The proportions of newly diagnosed patients presenting with DKA two years before and one year after the publicity campaign were calculated and comparisons of proportions were made by X^2 test. Comparisons were made with data from the Yorkshire Childhood Diabetes Register, which covers a population similar in socio – economic status but where there had been no such campaign and is sufficiently far enough from Wales to not have been influenced by the Welsh campaign.[80]

The results of the study showed that in the period two years before the campaign (November 2006 – 2007), 36/122 (30%) presented with DKA and one year prior to the campaign (November 2007 – 2008), 30/118 (25%) presented with DKA. In the year following the poster campaign (November 2008 – 2009), 30/117 (26%) presented with DKA. The campaign had no significant effect on the proportion of cases with DKA at presentation of diabetes ($X^2 = 0.65$, $P = 0.72$).[80] Similar proportions of cases with DKA at diagnosis of T1DM were seen in Yorkshire.

The data from this study showed that the mean annual proportion of children with newly diagnosed T1DM presenting with DKA in Wales between 1991 and 2009 was 25. The study (Table 4) demonstrated that DKA at presentation is more common when T1DM is diagnosed before five years of age. The authors suggested that this age group should be targeted in prevention campaigns designed to reduce the occurrence of DKA at diagnosis.[84,85] Overall, the results of this study show that a campaign with more direct engagement of families and health care professionals is likely more effective.

Table 4: Welsh campaign results[80]

Year	Age at onset diabetes (years)	Proportion presenting with ketoacidosis in Wales		Proportion presenting with ketoacidosis in Yorkshire (%)
		n	% (95%CI)	
1991-2009	Under 5	166/450	37 (32-41)	-
	5-9	148/738	20 (17-23)	-
	10-14	197/858	23 (20-26)	-
	Total	511/2046	25 (23-27)	-
November 2006-2007 (pre-campaign)	Under 5	8/21	38 (17-59)	-
	5-9	12/46	26 (13-39)	-
	10-14	16/55	29 (17-41)	-
	Total	36/122	30 (21-38)	50/185(27)
November 2007-2008 (pre-campaign)	Under 5	6/25	24 (8-40)	-
	5-9	5/27	19 (4-33)	-
	10-14	19/66	29 (18-39)	-
	Total	30/118	25 (18-33)	50/185(27)
November 2008-2009 (pre-campaign)	Under 5	7/23	30 (12-49)	-
	5-9	7/40	18 (6-29)	-
	10-14	16/54	30 (17-42)	-
	Total	30/117	26 (18-34)	48/162(30)

A higher proportion of new cases under 5 years presented with ketoacidosis (X^2= 45.2, P < 0.001).

2.6.iv Austria

Another study to determine the value of a publicity campaign surrounding T1DM and DKA was conducted in Austria over a 22–year period, from 1989 – 2011. All newly diagnosed patients with diabetes ≤15 years of age were prospectively registered by the Austrian Diabetes Incidence Study Group.[86] This registry covers all pediatric hospitals, wards and diabetologists, and case ascertainment is > 93%.[86] In September 2009, a poster campaign was launched similar to the one in Parma, Italy. Posters providing information on the early signs of hyperglycemia and glucosuria were created

for both adults and children. The posters and a letter explaining DKA prevention were distributed to all kindergartens (n = 4175), primary and secondary schools (n = 6268), and pharmacies (n = 1200). Further, all Austrian pediatricians and general practitioners (n = 15, 700) received posters for their offices along with an article on pediatric diabetes that highlighted the symptoms of DKA. Also, medical journals with articles on pediatric DKA were distributed to all medical offices. During the meetings of the Austrian Diabetes Society (fall 2009 and spring 2010) and the Austrian Pediatric Society (fall 2009), the posters were mounted for all to see. Another facet of the campaign was the education of school medical officers, which occurred twice in 2010. These education sessions included information on the early clinical signs of T1DM and information about the DKA prevention program. As well, in fall 2009, a television broadcast was dedicated to the DKA–prevention campaign. Finally, 18 articles about dealing with the symptoms of pediatric diabetes were published in Austrian newspapers between September 2009 and March 2010, with a theoretical reach of 2,601,500 people.[86]

The frequency of DKA at onset of T1DM in the years prior to the campaign (2005 – 2009) and after the campaign (2010 and 2011) were compared. Differences in the prevalence of DKA between these time periods as well as time trends were tested with the X^2 test and logistic regression. During the 22–year observation period 1989 – 2011, 4038 children (male, n = 2186, females, n = 1852) younger than 15 years of age were registered in the Austrian Diabetes Incidence database.[86] The incidence rate of T1DM in Austria almost doubled, from 9/100, 000 in 1989 to 17.5/100, 000 in 2011.[86] Prior to the campaign in 2005 – 2006, 25.9% (95% CI 23.1 – 27.6) of children presented with mild DKA, and 12% (95% CI 10.1 – 14.8) with severe DKA.[86] Post–campaign in 2010 –

2011, a total of 27.5% (95% CI 27.1 – 27.7) had mild DKA and 9.4% (95% CI 9.0 – 9.9) had severe DKA. The frequency of onset of DKA and age at onset were negatively associated, ($P < 0.01$).[86]

Table 5: Austrian campaign results [86]

Prevalence of DKA onset in Austrian children 5 years (2005-2009) before and 2 years (2010-2011) after the poster information campaign

Period	No DKA			Mild DKA			Severe DKA		
Total group	n	%	Range	n	%	Range	n	%	Range
2005-2009	711	62.2	57.6-64.7	296	25.9	23.1-27.6	137	12.0	10.1-14.8
2010-2011	301	63.2	62.9-63.3	131	27.5	27.1-27.7	45	9.4	9.0-9.9
Age group <5 years									
2005-2009	148	51.6	42-57.7	99	34.5	31-38	40	13.9	7.7-20.0
2010-2011	60	53.6	50-57.6	40	36.0	34.6-37.3	11	9.9	5.1-15.4
Age group 5-<10 years									
2005-2009	272	70.7	64.9-80.3	76	19.7	9.2-26	37	9.6	7.8-12.3
2010-2011	110	67.5	64.8-96.7	43	26.2	25-27.3	11	6.7	5.3-8.0
Age group 10-<15 years									
2005-2009	291	61.7	54.7-69.1	121	25.6	22.7-28.4	60	12.7	8.3-19.0
2010-2011	131	64.8	64.5-65.1	48	23.8	22.9-24.7	23	11.4	10.8-11.9

All comparisons are non-significant.
Mild DKA=pH < 7.3-7.1; severe DKA=pH < 7.1

Similar to the study conducted in Wales, the Austrian study also showed no effect associated with community education. The authors stated a number of possible reasons for this: 1) posters are not as effective for health care messaging, as compared to when

the Parma study was conducted, 2) high baseline DKA prevalence in Parma in comparison with the rest of Europe, 3) large geographic region in which the study was conducted, 4) short duration of the campaign, and 5) the way in which pediatric care is conducted in both countries. In Austria, primary pediatric care is covered by family practitioners who in general have less training in pediatrics, whereas Italy has a nationwide primary pediatric network, which allows for a more focused intervention program via primary care pediatricians.[86]

2.6.v US study

This study was conducted in Bronx, New York, during 2011.[177] Hospital admissions at the Children's Hospital at Montefiore were used to determine DKA rates before and after an education campaign. The paper is a bit unclear as to when the program was launched, however, they state that 2007 – 2010 were pre-intervention years and 2012 – July 2014 were considered post-intervention years. The mean age for the pre-intervention group was 13.7 years and post-intervention was 14.2 years.

This study involved both healthcare professionals and patient/public education. For the portion of the campaign educating healthcare professionals, the authors aimed to have as many certified diabetes educators (CDEs) on the team as possible, including nurse practitioners, registered nurses, nurse managers and registered dietitians. Certification as a CDE requires that the health care provider have standardized knowledge, understanding and experience in diabetes prevention and diabetes care.[176] The teams would meet weekly to discuss patients and each team members' role in the patients' care. They created revised criteria for DKA admissions and patients were

transitioned from rapid-acting insulin sliding scales to basal-bolus regimens and insulin pump use. The authors concluded that while the initial cost and time commitment for this type of therapy is high, its cost-benefit supports its use.[174,175]

The next aspect of their campaign was a cross between physician and patient objectives. They increased access for patients by offering more diabetes sessions per week, and changed clinic visits from 15 to 30 minutes. Further, they alternated appointments between a nurse practitioner and a physician so a patient's total diabetes visits were at least four per year. This allowed for patients to see a CDE at different times during the day and at sites closer to home. As well, they offered quarterly education sessions for school and home registered nurses.

The public campaign started with the goal of becoming an American Diabetes Association (ADA) recognized program, which promotes the use of diabetes self-management educations and support. The diabetes team also used an electronic database for tracking individual patients and their specific clinical goals. Educational materials were developed in both English and Spanish. In addition to patients and their families, the campaign also targeted general community education. There were two annual events planned, a Family Diabetes Day and the Candy Exchange. The diabetes day included information on global and local diabetes programs, health lifestyles, insurance and legal rights of patients with diabetes. There were people with diabetes including both public figures and other patients that shared their success stories. The candy exchange event involved children exchanging their candy for a toy, and therefore promoted healthy eating.

DKA admissions decreased from 222 to 120, a 44% reduction post-intervention (16.7 vs. 9.3 per 100 P–Y, P = 0.006). Mean length of stay also decreased from 2 (range 1 – 47) to 2 (1 – 38), P < 0.0001). Finally, the authors reported unique patient readmissions reduced from 17 (pre-intervention) to 5 (post-intervention), (P = 0.001). Overall, the results of this study demonstrated that implementing a multidisciplinary clinical and educational diabetes program for both healthcare professionals and patients led to a reduction in DKA admission rates.

2.6.vi France

A national DKA information campaign for health professionals and families with the objective of reducing time to diagnosis was launched in France.[179] The article is only available in French, however, a summary available in English reported positive results, hence its inclusion. The authors compared frequency and severity of DKA at diagnosis of T1DM for one year before the campaign started and for the first year after the campaign was implemented. They only included patients <15 years of age, and found that overall DKA rates decreased from 43.9% to 40.5% (P = 0.08) exclusively due to the decrease in severe DKA rates from 14.8% to 11.4% (P = 0.01). Similar to the other studies, this group also found a higher rate of severe DKA in the youngest age group (<5 years).

2.6.vii Australia

There was another diabetes and DKA education campaign offered in Australia between April 2007 and February 2012.[178] The authors created a structured five–day training program for patients on diabetes self-management. The program was designed to be completed in five consecutive days or one day per week for five weeks. They

reported a reduction in DKA admissions from 4.1% - 1.2%. However, the study participants were all older than 18 years of age so this study was not examined further.

Table 6: Summary of DKA prevention studies

Study location	Duration	Intervention	Results
Parma, Italy	8 years	-Posters -Guideline cards -Toll-free 24 hour phone line -Glucose meters (for physicians) -T1DM information sessions (for physicians) -Physicians were asked to refer patients to diabetes unit if they displayed certain symptoms	DKA in new onset T1DM changed from 78% prior to the intervention to 12.5% post-intervention. *No newly diagnosed T1DM patients were ever admitted with DKA from 1992 to 1997 (study end)
Gosford, Australia	2 years	-Letters -Postcards -Posters -Diabetes educators went to schools, childcare centers and physicians' offices -Glucose meters (for physicians) -Monthly DKA newsletter to members of general practice subscription	DKA in new onset T1DM changed from 37.5% prior to the intervention to 13.8% post-intervention
Wales, UK	18 years	-Posters -Radio interviews -TV interviews -Post-publicity campaign questionnaires for physicians and parents	DKA in new onset T1DM changed from 30% two years prior to the intervention to 25% one year prior to the intervention to 26% one year post-intervention
Austria	22 years	-Posters -Letters -Articles about DKA sent to physicians -Education of school medical officers -DKA articles published in newspapers for general public	DKA in new onset T1DM changed from 25.9% (mild) and 12% (severe) prior to the intervention and 27.5% (mild) and 9.4% (severe) post-intervention
Bronx, New York	7 years	-Certified diabetes educators on teams -Weekly team meetings -Revised DKA admission criteria -Electronic database for tracking patients and their goals -Increased visit duration & frequency -Quarterly education sessions -Public awareness events	DKA admissions reduced from 222 to 120 post-intervention (44% reduction)
France (22 metropolitan regions)	2 years	-Specific interventions are unknown however the campaign was for health professionals and families	DKA in newly diagnosed T1DM decreased from 43.9% to 40.5% exclusively due to the reduction in severe DKA from 14.8% to 11.4%
Australia	4 years, 10 months	-Structured five day training program on diabetes self-management	DKA admissions decreased from 4.1% to 1.2%

2.6 Newfoundland and Labrador DKA Project (NLdkaP)

The NLdkaP was conducted from 2011 to 2012 and involved a series of community–based knowledge translation interventions carried out in an attempt to reduce the incidence of DKA in NL (Table 7). In a 2015 NL study, it was reported that 22% of new T1DM cases had DKA upon presentation.[30] The main objective of the NLdkaP was to improve the education of healthcare personnel in NL regarding the early detection of T1DM in children, and early detection and proper treatment of pediatric DKA, as well as differentiating how the treatment differs from adult DKA. The second objective was to improve the education of families with children and teens with T1DM with the aim of preventing DKA. The third objective was to mobilize a provincial multidisciplinary, intersectoral team which included health care leaders, community groups and families with the common interest of improving pediatric diabetes care and reducing the burden and suffering from pediatric DKA.

The project had an advisory committee, which included a teenage patient with T1DM, a parent of a youth with T1DM, two diabetes nurse educators, a pediatric endocrinologist and diabetologist, and other researchers. The study aims were reviewed and confirmed by the committee. To educate healthcare personnel and provide them with an introduction to early recognition of pediatric diabetes as well as DKA management tips and techniques, a continuing education curriculum was developed. Its aims were to allow providers to:

1. Recognize the signs and symptoms of T1DM and DKA in children and adolescents.
2. Identify patients most at risk for DKA.

3. Describe the existing clinical practice guidelines, statements, and treatment protocols related to pediatric DKA.

4. Explain the risk of cerebral edema and how to prevent and treat its occurrence.

5. Summarize and disseminate the national and provincial initiatives to prevent development of DKA in pediatric diabetes.

A course was developed and offered by Professional Development & Conferencing Services at Memorial University of Newfoundland (MUN). Physicians that completed the course were eligible for continuing medical education credits.

The program began with a pre–test, which included questions to establish baseline knowledge about pediatric diabetes and DKA. After these questions, **Unit 1: Introduction to T1DM** was given. The main points discussed that T1DM is an autoimmune disease characterized by the destruction of insulin producing beta–cells of the pancreas, it is one of the most common chronic diseases of childhood, some regions of Canada have very high rates of T1DM and that its underlying causes are unknown but thought to be related to complex genetic and environmental triggers. Common signs and symptoms were described, accompanied by the mnemonic STAT (Figure 6), which was developed by the Canadian Diabetes Association.

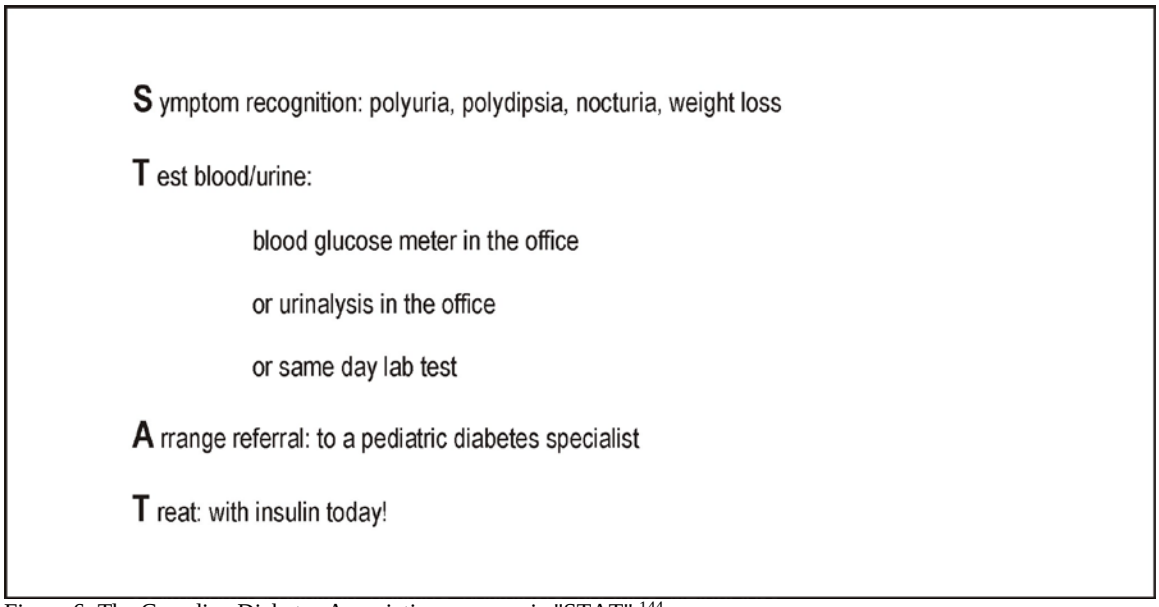

Figure 6: The Canadian Diabetes Association mnemonic "STAT" [144]

The next portion of the program was a case study, accompanied by a discussion forum and the opportunity to read a sample expert answer. The take away information from the case was that young children with symptoms of diabetes should be investigated on the same day by glucose testing in the blood or urine and that the diagnosis of diabetes is often not made on initial presentation, which is a missed opportunity for DKA prevention. **Unit 2: Diabetic Ketoacidosis** discussed the triad of uncontrolled hyperglycemia, metabolic acidosis and increased total body ketone concentration which characterize DKA, and highlighted the definitions of DKA (mild when the body's pH level is <7.3, moderate when the body's pH level is <7.2 and severe when the body's level pH is <7.1). It included information on DKA, how it is preventable in many cases, and that it can occur in patients presenting with diabetes for the first time, or in patients with pre–existing diabetes. Reasons for DKA were discussed, e.g., that patients with pre–existing diabetes are more likely to develop DKA if there is insulin omission, insulin mismanagement and psychosocial factors. Finally, this unit discussed that younger

patients (<5 years of age) are at higher risk to present with DKA upon diagnosis of diabetes. This unit was also followed by a case study, discussion question and expert answer. **Unit 3: Management of DKA** covered the fact that those presenting with DKA require constant and usually intensive care. Often times, seeking advice from a pediatric intensivist, emergentologist, or diabetologist may also be required and most tertiary care pediatric centres in Canada have 24–hour on call advice available. Managing pediatric DKA is not that same as adult DKA, as different complications can occur, namely cerebral edema. It is important to start intravenous (IV) insulin 1 – 2 hours after initiation of IV rehydration and avoid giving boluses of bicarbonate and insulin.

Clinical practice guidelines were created so that physicians who infrequently diagnose DKA would be able to easily recognize the signs and symptoms (Figure 7).

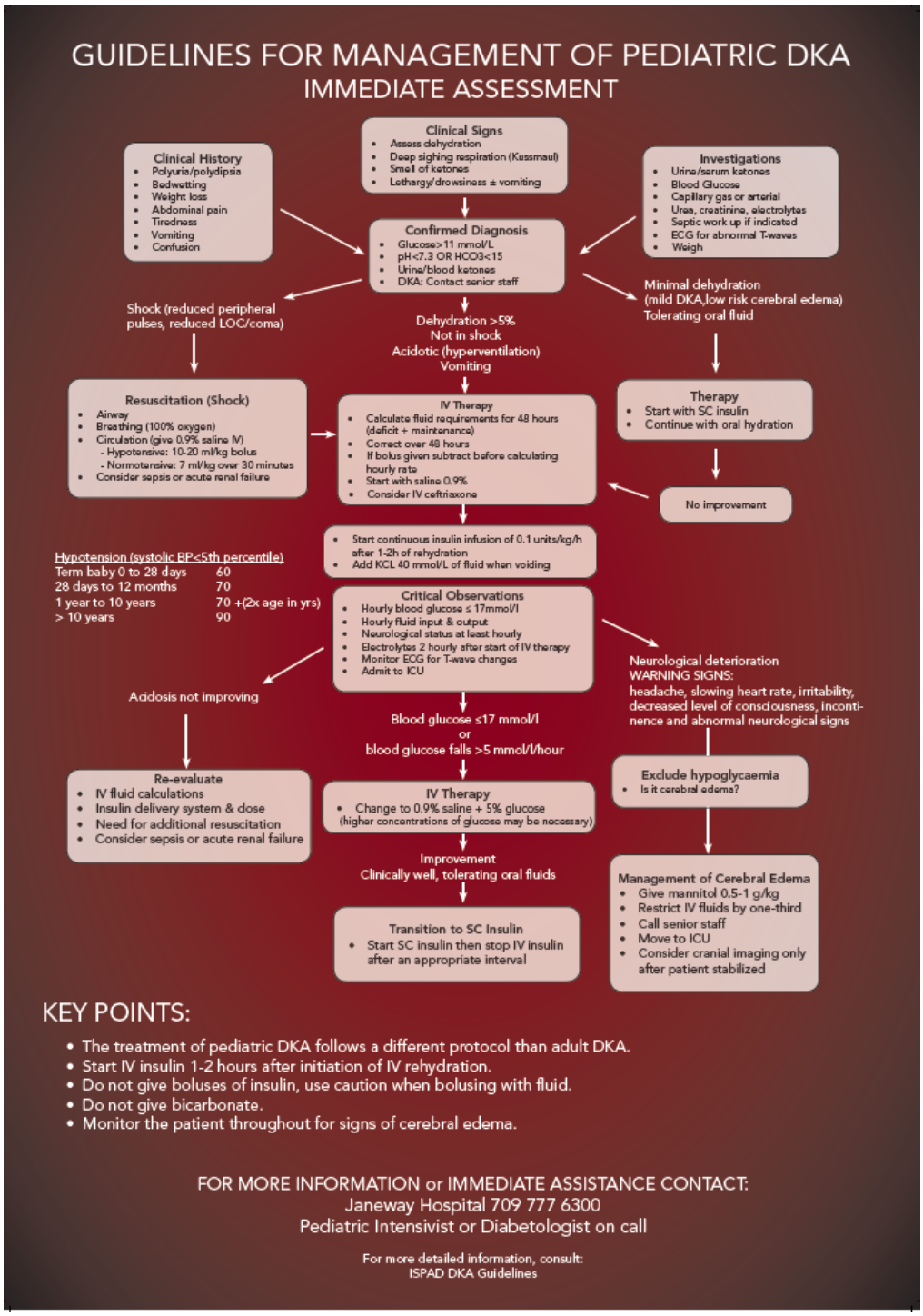

Figure 7: Guidelines for DKA management

Assess Level of Consciuosness

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to speech	Opens eyes spontaneously	N/A	N/A
Verbal	No verbal response	Inconsolable, agitated	Inconsistently inconsolable, moaning	Cries but consolable, inappropriate interactions	Smiles, orients to sounds, follows objects, interacts	N/A
Motor	No motor response	Extension to pain (decerebrate response)	Abnormal flexion to pain for an infant (decorticate response)	Infant withdraws from pain	Infant withdraws from touch	Infant moves spontaneously or purposefully

Figure 8: Merck Manual's Pediatric Glasgow Coma scale [153]

The guidelines outlined initial investigations to perform, including important calculations to be conducted. Two of these calculations are determining the anion gap and serum osmolality.

Anion Gap

The anion gap is the difference in the measured cations (positively charged ions) and the measured anions (negatively charged ions) in serum.

Anion Gap = Na − (Cl + HCO3)

Normal = 12 ± 2 mmol/L

Pseudohyponatremia

Pseudohyponatremia occurs because of a shift of water from the intracellular to the extracellular compartment secondary to hyperglycemia and increased plasma osmolality. There is evidence that hyponatremia may increase the risk of developing cerebral edema if blood glucose level declines too rapidly during therapy.

Corrected sodium[11] = measured Na + 2([plasma glucose −5.6]/5.6) (mmol/L) [145]

Serum osmolality

Patients who develop cerebral edema have a larger drop in plasma osmolality early during therapy. The changes in plasma osmolality are most prominent during the first eight hours after the start of therapy, which appears to be the time window with a large risk for the development of cerebral edema.[146] Effective osmolality[11] = (mOsm/kg) 2x(Na + K) + glucose (mmol/L)

The main goals of treatment are to correct dehydration over 48 hours, slowly restore blood glucose to close to normal (aim to decrease blood glucose by 3 – 5 mmol/L every hour), identify and treat any precipitating event including infection, avoid complications of therapy, correct acidosis and reverse ketosis, and minimize the risk of complications, especially cerebral edema. These are achieved through careful fluid and salt replacement, insulin therapy and potassium replacement.

Unit 4: Complications of DKA described the numerous complications that are associated with DKA and that these complications are the reason for high DKA morbidity and mortality rates. Reported mortality rates for DKA range from 0.15 to 0.51 percent in population studies in Canada, the United Kingdom, and the United States.[24,145]

Unit 5: Prevention Initiatives reiterated that most cases of DKA can be prevented, provided the symptoms are not misinterpreted or misdiagnosed. The unit highlighted that tools such as 24 hour telephone advice for families, home ketone monitoring (blood or urine), sick day education (e.g. never omit insulin), and insulin pump troubleshooting education are effective in reducing the frequency of DKA in patients diagnosed with diabetes. An overview of insulin pumps was described, as they are a method of insulin

treatment using only rapid acting insulin. In comparison to delivering insulin subcutaneously or via meals, if interruption of an insulin pump occurs, deficiency can occur within several hours. There are a number of issues that may occur with this type of insulin therapy, such as problems with the infusion site or set, the catheter being occluded/bent at insertion site, blocked, torn or leaky tubing, air in the tubing, patient not checking sugars to detect hyperglycemia, pump suspended too long, and very rarely, pump malfunction. In addition, not changing the catheter/cannula every two to three days can lead to scarring and infection. Therefore, it is crucial to monitor the pump as well as the injection site for these occurrences. While it is important for health professionals to be aware of these possibilities, they also need to continuously educate the families that come in with diabetic children so that they can monitor the pump in their home settings. Another prevention technique is education regarding appropriate sick day management. Infections that occur during childhood can sometimes be difficult to manage in those with diabetes. It is essential to have a plan in place for what to do during times of intercurrent illness. Finally, this section concluded with some clinical pearls about DKA;

1. Since most patients develop DKA over days, slow metabolic repair is safest as over–hydration may contribute to cerebral edema.
2. DKA risk factors include younger age, new onset diabetes, children with poor metabolic control and/or psychosocial difficulties, infection, and insulin delivery issues with insulin pump therapy.

3. The goal is to treat dehydration, acidosis and hyperglycemia over 48 hours and continually re–evaluate status of hydration, glycemia, acidosis, vital signs and mental status.
4. Large fluid boluses are potentially dangerous: IV fluids should be administered slowly and with caution, unless the patient is in shock. Only very rarely will a larger (>20 cc/kg) fluid bolus will be required to maintain perfusion.
5. Insulin Treatment: do not give bolus of insulin and start IV insulin 1 – 2 hours after IV fluid initiation
6. Cerebral Edema: subclinical brain swelling is common in children with DKA. Cerebral edema accounts for more than half of the mortality rate of DKA in children and risk factors for mortality and DKA include new onset diabetes, age < 5 years old, severe acidosis and dehydration, rapid rehydration with hypotonic fluids (> 50cc/ kg in first 4 hours), insulin given as bolus or in the first hour of fluid administration and bicarbonate administration.
7. With early diagnosis of pediatric diabetes and education of pre–existing diabetes families regarding sick–day management and DKA prevention, most cases of DKA can be prevented.

The continuing medical education program concluded with ten post–course questions.

Another component of the NLdkaP included a qualitative study, which involved focus groups with families of children with diabetes. These focus groups were an effective starting point to better understand the issues families face as families have unique perspectives that can aid in the information dissemination process. Since they personally have diabetes or live with an individual with diabetes, participants are likely

more aware of what is suitable and efficient in a real–world setting. There were four focus groups held in three communities in NL, two rural and one urban with adolescents and parents of children/youth with diabetes. The discussion topics focused on general diabetes education, barriers to diabetes self–management, DKA awareness and knowledge, personal experiences with DKA and resources that could be developed to aid youth in preventing DKA. The discussions were completed in a semi–structured format, leaving room to deliberate on other issues if and as they arose. Participants were recruited through diabetes clinics or diabetes support groups, and the first eight in each rural and urban location that met the inclusion criteria were invited to partake. Written consent was obtained from all participants prior to the focus group sessions and written assent was obtained from minor participants. Ethics approval for the project was obtained from the *Newfoundland and Labrador Health Research Ethics Authority*.

During the focus groups, a number of barriers were identified. One of the first issues that arose was that people found it difficult to determine if the condition was DKA or something else. Many times the patient had to experience DKA once to know when it was occurring for a subsequent time. Families also commented that some health professionals did not identify that their child was experiencing DKA right away either. The next theme was diabetes education. It is inevitable that diabetes education will vary in different regions, most likely due to the prevalence in that area. Regardless, more efforts should be placed on ensuring that everyone receives and has access to the same or at least comparable information. It was also stated that the level of information at first diagnosis of diabetes could be overwhelming. Many parents forgot all the details about DKA that were given at initial diabetes diagnosis, and just read about it in pamphlets or

other materials provided to them. Another facet of this information overload at the time of initial diagnosis is that often times the child is too young to retain any of the information or is not included in the information sessions at all; therefore some type of subsequent information sessions when the child is older is necessary.

The next discussion question addressed when children were in the care of guardians other than parents. Parents described episodes of insulin mismanagement occurring while the child was in the care of other temporary guardians such as a babysitter or grandparent. Another concern was regarding school time. Several participants reported that their teachers were quite compassionate and understanding, however, many students, especially the older ones have multiple teachers per day. Educating every single one of them about diabetes care proves to be a very difficult task. The next concern was the overall stress of experiencing DKA. Most of this fell on the parents/guardians and was mainly due to lack of understanding/education on the issue and some felt they were to blame for the episode. A lack of resources, specialist care and supplies was a barrier that mostly concerned the rural participants, but was a concern that the urban participants understood and empathized with.

Many of the issues were common amongst all participants, and the following are the conclusions from the focus groups.

1. Diabetes education needs to continue after initial diagnosis. Often, too much information is given at once and not enough is retained. It would be beneficial to have periodic re–education, especially about complications such as DKA.
2. Some guidelines or quick facts should be available to distinguish between an episode of DKA and another illness, e.g. gastroenteritis.

3. Youth should have available education tools once they reach an age where they begin to separate from their parents/guardians and become more independent. A child with diabetes should have full knowledge of management techniques when they are away from their parents/guardians.
4. Some resources should be available to teachers or other temporary caregivers so that the uncertainty of a child's wellbeing is diminished.
5. An at–home toolkit for management of blood sugars would be beneficial for lowering chance of DKA episodes.

Overall, it was concluded that DKA is a stressful and traumatic event for both youth and their parents. With the information collected in these focus groups, the second objective of the NLdkaP was continued. An information campaign was developed and implemented in all the schools across NL. This included posters (Appendix A) to remind teachers and students of diabetes symptoms, as well as other resources just for teachers. These posters were also distributed to all family doctors' offices, public health offices and pharmacies. There were also information sessions held about DKA with families, primary care physicians and hospitals across the province, which covered DKA prevention practices. For example, members of the NLdkaP team visited hospitals throughout NL and met with health care professionals during in-person presentations. The aim was to provide opportunities for enhanced competencies on early diabetes detection, as well as prevention and management of DKA. These learning opportunities and the lessons learned through them laid the foundation of the continuing medical education course for healthcare professionals, offered through the Faculty of Medicine's Office of Professional Development and Conferencing Services, MUN. Treatment

protocols were established to help medical staff more efficiently diagnose diabetes and manage DKA. As suggested, a DKA toolkit was created by a local diabetes nurse educator, Donna Hagerty. The toolkits (Figure 9) were available for all families with a child with diabetes and the kits included insulin syringes as back up for the pumps, ketone strips and instructions for parents if their child has high blood sugar.

Figure 9: DKA prevention toolkits

Another undertaking of the NLdkaP was visits to the NL branch of the Canadian Diabetes Association camp called "Douwanna." Further, a calendar depicting artwork created by children at this camp was made (Figure 10). Each month is marked by the artwork produced by a child with diabetes, along with a quick diabetes tip.

Figure 10: Calendar artwork from camp Douwanna

The third facet of the NLdkaP was the development of videos about DKA made by youth with diabetes as a means to share their experiences with the disease. These videos were developed but not widely distributed. It is believed that this type of education will be effective, especially for the adolescent age group that may be more receptive to advice and stories from others their own age (peer–to–peer) rather than from an adult.

Table 7: NLdkaP knowledge translation interventions

Objective	Educate healthcare professionals	Educate family/teens
Intervention	Continuing education course	Focus groups
	Clinical pearls	Calendars with diabetes tips
	Information sessions	Posters to schools, physician offices, pharmacies and public health offices
	Grand rounds	Videos for peer education
		DKA toolkits
		Information sessions
		Visits to camp for patients

Chapter 3: Methodology

The primary objective of this research is to study the effect of a multifaceted knowledge translation DKA project aimed at educating healthcare professionals, families/patients, and the public on the hospitalization rates of children diagnosed with DKA in NL. To achieve this objective, the following research aims were identified:

1. Measure and compare provincial and regional hospitalization rates of pediatric patients (aged ≤ 18 years) and young adult patients (aged 19 – 24 years) presenting with DKA;
2. Analyze and compare demographic factors of pediatric and young adult patients with DKA;
3. Analyze regional patterns of DKA hospitalizations;
4. Determine hospitalization rates and patterns for two years prior, during and two years post the NLdkaP.

This chapter will discuss how data were collected, processed and analyzed. It will also discuss the rationale for the assumptions made.

3.1 Ethical/Administrative Approval

The Health Research Ethics Authority of Newfoundland approved this study (HREB# 2015.270). Approval for the extraction and use of record–level information for secondary uses was obtained from the Newfoundland and Labrador Center for Health Information (NLCHI).

3.2 Study Design

This is a pre-post design study. Patient data was initially collected by their respective health care centers and submitted to NLCHI, as per the standard practice in this province.[29] Patients were stratified by age and sex to determine demographic factors

in pediatric and young adult DKA admissions. The NLdkaP project was aimed at the pediatric population. The young adult age group was used as the control–group.

3.3 Patient Ascertainment

3.3.i Setting

This study took place in the province of NL, which consists of two major geographical areas, the island of Newfoundland and a mainland section, Labrador. The island of Newfoundland is the easternmost part of Canada and Labrador is a coastal region of the Canadian mainland and the most north-eastern part of continental North America. Patients were assigned to regional health authorities - Eastern, Central, Western and Labrador–Grenfell based on the hospital in which they were admitted. This assignment was used to determine regional patterns of DKA.[169]

3.3.ii Diagnostic Criteria

NLCHI reviewed data on all patients aged 0 – 24 years during the study period, January 1, 2009 – December 31, 2014. Using the International Classification of Diseases 10th Revision (ICD–10) diagnosis codes, NLCHI identified those patients with a hospitalization for DKA during that period. Hospitalizations for diabetic ketoacidosis were defined by ICD–10 codes E1.10 Type ~ diabetes mellitus with ketoacidosis, (ketotic) hyperglycemia, ketoacidosis (DKA), ketone formation with acidosis, E1.11 Type ~ diabetes mellitus with lactic acidosis and E1–.12 Type ~ diabetes mellitus with ketoacidosis with lactic acidosis. These codes were decided upon with the help of NLCHI to ensure all relevant patients were included in the study.

3.4 Data Collection

The present study includes T1DM subjects, 0 – 24 years of age residing in NL during the six–year period, January 1, 2009 – December 31, 2014. The standard practice in NL is to hospitalize all newly diagnosed children with T1DM for initial medical treatment, including insulin therapy and family training.[29] Also, all patients with moderate to severe DKA are admitted, and almost all cases of mild DKA are admitted, although a small number of mild DKA may be treated in the emergency department and discharged home without admission. All patients with an admission for DKA during the six–year study period, January 1, 2009 – December 31, 2014 were included in the analysis for this study. The data was obtained from NLCHI as they collect and store hospitalization data that is contained in the clinical database management system (CDMS). The CDMS incudes primary and all other discharge codes of the ICD–10. It is mandatory for all health care facilities in NL to submit discharge abstract data that describes inpatient services to the Canadian Institute for Health Information (CIHI). This practice applies to all other Canadian provinces and territories as well. The data are subsequently sent to the provincial Department of Health and Community Services. NLCHI maintains the CDMS on behalf of the provincial Department of Health and Community Services. The reliability and validity of this database has been documented.[168]

Prior to performing any analysis on the dataset, it was reviewed to ensure completeness and accuracy. After running the analysis with the ICD codes described above, a total of 831 hospitalizations were identified over the six year period for 0-24 year olds living in NL. It was found that amongst the data provided, many patients were

diagnosed for other conditions in addition to DKA. After duplications and hospitalizations for other conditions were removed, the revised data had 412 patients aged 0 – 24 years of age diagnosed with DKA between January 1, 2009 and December 31, 2014.

3.5 Analysis

SPSS Statistics v20 was used. Poisson distribution was used to calculate 95% confidence intervals. Poisson regression with a linear term for time was used to assess the increasing or decreasing trend of hospitalization rates over the study period. The estimated slope from the regression model with a P–value < 0.05 was considered statistically significant. Chi–squared analysis was used for comparison of hospitalization rates between sex and hospitalization rates between age groups.

3.5.i Crude DKA Hospitalization Rate per year during 2009 – 2014, NL

In order to calculate the crude hospitalization rate for each year,[154,155] the total number of hospitalizations per year for individuals ages 0 – 24 were totalled and used as the numerator. The mid–year total population was calculated by summing the mid–year populations as per the NL Statistics Agency[156] for each age group per year of the study period and then divided by five to find the average general population for that year. The mid–year population sum was divided by five as there are five different age groups. This number served as the denominator. The rate was then multiplied by 100,000 to find the rate per 100,000. The hospitalization rates were combined to look at the two years before, during and after the NLdkaP.

$$\text{Rate} = \frac{\text{Total Number of DKA Hospitalizations per year}}{\text{Mid–Year Total Population 0 – 24yrs}} \times 100{,}000$$

3.5.ii Age specific hospitalization rates due to DKA per year during 2009 – 2014, NL

The number of hospitalizations for each of the five age groups were totalled by year. The mid–year population for each year during the six–year study period was taken from the NL Statistics Agency[156]. The calculated rate was then multiplied by 100,000 to obtain the number of hospitalizations per 100,000.

Age-specific Hospitalization Rate per year[154,155] =

$$= \frac{\text{Total Number of DKA Hospitalizations per age group per year X 100,000}}{\text{Mid–Year Total Population stratified by age group}}$$

3.5.iii Age/Sex Specific Hospitalization Rates due to DKA during 2009 – 2014, NL

In order to calculate the age and sex specific hospitalization rates during the entire study period (2009 – 2014), the number of hospitalizations for each age group was totalled.

The average total population for each age group and sex was calculated by using the mid–year population for each of the six years during the study period as procured from the NL Statistics Agency.[156] The mid–year populations for each age group for both males and females during each year of the study period were summed and then divided by six to get the average population stratified by age group and sex over the study time period. A similar procedure was followed to obtain the average total population. The summed population value was divided by six as the study period was six years long and using an average provides more precise population estimates.[157] There was no reported mid–year population data found for the year 2009. As a result, an estimate for the 2009 population was extrapolated from the population data from 2010.

Age/Sex Specific Hospitalization Rate[154,155] =

$$\frac{\text{Number of hospitalizations stratified by age group and sex}}{\text{Mid–year population average stratified by age group and sex}} \times 100{,}000$$

The numerator is the number of hospitalizations for each age group and sex reported separately and then a total number of hospitalizations for each age group with males and females together. The denominator is the average mid–year population for each age group and sex separately and then each age group with males and females together. The resulting calculated value was multiplied by 100,000 to determine the rate per 100,000.

Chapter 4: Results

This chapter presents the results from the analysis of hospitalizations during the study period.

4.1 Descriptive Analysis

A total of 412 hospitalizations were included in the study: 244 females and 168 males (59.2% and 40.8%, respectively).

Table 8: Age at admission to hospital for DKA

Age at admission	Frequency	Percent
1	3	,7
2	5	1.3
3	7	1.7
4	4	1.0
5	9	2.2
6	8	1.9
7	2	,5
8	8	1.9
9	5	1.2
10	5	1.2
11	21	5.1
12	30	7.3
13	17	4.1
14	18	4.4
15	15	3.6
16	14	3.4
17	17	4.1
18	26	6.3
19	37	9.0
20	38	9.2
21	30	7.3
22	25	6.1
23	29	7.0
24	33	8.0
25	6	1.5
T O T A L	412	100

Table 8 illustrates that the largest percentage of DKA hospitalizations were amongst those aged 19 and 20 (N = 37 (9.0%) and N = 38 (9.2%), respectively). The smallest percentage of DKA hospitalizations were amongst those aged 7 and 1 (N=2 (.5%) and N=3 (.7%), respectively).

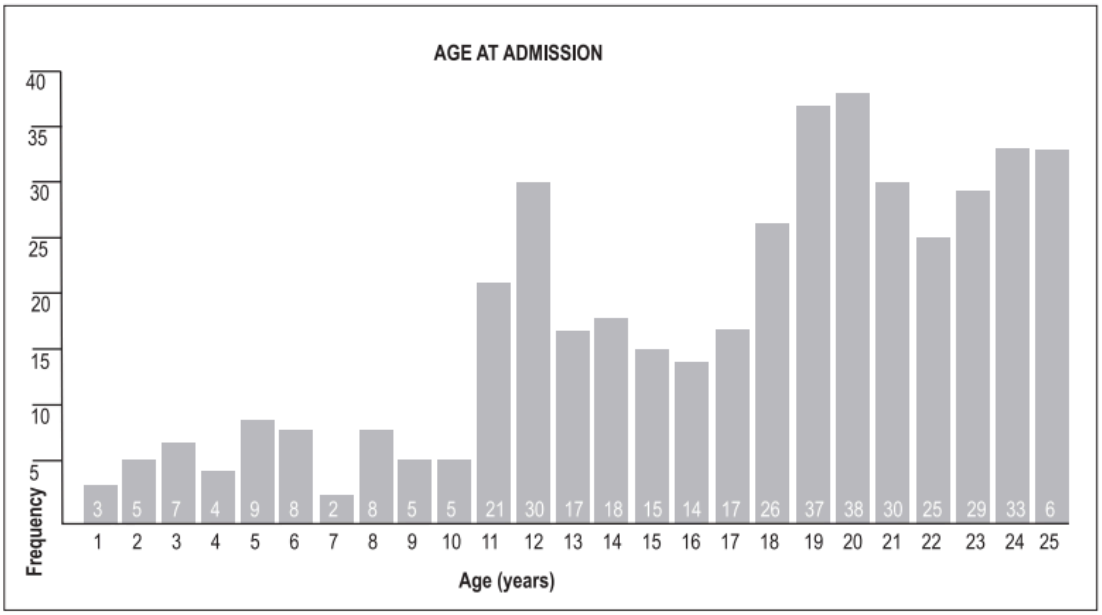

Figure 11: Age at admission to hospital for DKA

Table 9: Number of DKA hospitalizations per age category

Age Category	# of Hospitalizations	Percentage
0-4	19	4.6%
5-9	32	7.7%
10-14	91	22.1%
15-19	109	26.4%
20-24	161	39.1%

The largest percentage of individuals diagnosed with DKA are those in the 20 – 24 years of age category followed by the 15 – 19 years of age category.

The data were categorized into two age categories, 0 – 19 years and 20 – 24 years as the 20 – 24 year olds were not the target of the NLdkaP intervention, and would have only indirectly received components of this intervention. There were 251 DKA hospitalizations (60.9%) in the 0 – 19 years of age category and 161 DKA hospitalizations (39.1%) in the 20 – 24 years of age category.

Table 10: Number and % of DKA admissions per healthcare facility

Healthcare facility	City/Town	# of admissions	Percent
Bonavista Community Health Center	Bonavista	2	.5
Burin Peninsula Health Care Center	Burin	6	1.5
Captain William Jackman Memorial Hospital	Labrador City	6	1.5
Carbonear General Hospital	Carbonear	13	3.2
Central Newfoundland Regional Health Center	Grand Falls-Windsor	37	9.0
Charles S. Curtis Memorial Hospital	St. Anthony	6	1.5
Connaigre Peninsula Health Center	Harbour Breton	2	.5
Dr. Charles L. Legrow Health Center	Grand Bay East	3	.7
Dr. G. B. Cross Memorial Hospital	Clarenville	7	1.7
Health Sciences Center, including Janeway Children's Hospital	St. John's	231	56.1
James Paton Memorial Hospital	Gander	18	4.4
Labrador Health Center	Happy Valley Goose Bay	5	1.2
Labrador South Health Center	Forteau	1	.2
Sir Thomas Roddick Hospital	Stephenville	7	1.7
St. Claire's Mercy Hospital	St. John's	12	2.9
Western Memorial Regional Hospital	Corner Brook	56	13.6
T O T A L	412	412	100

As per Table 10, the healthcare facilities throughout the province which had DKA hospitalizations include: Bonavista Community Health Centre, Burin Peninsula Health Care Centre, Captain William Jackman Memorial Hospital, Carbonear General Hospital, Central Newfoundland Regional Health Center, Charles S. Curtis Memorial Hospital, Connaigre Peninsula Health Centre, Dr. Charles Legrow Health Centre, Dr. G.B. Cross Memorial Hospital, General Hospital – Health Sciences Centre (including the Janeway Children's Hospital), James Paton Memorial Hospital, Labrador Health Centre, Labrador South Health Centre, Sir Thomas Roddick Hospital, St. Clare's Mercy Hospital and Western Memorial Regional Hospital.

Table 11: Names of hospitals in each region

Region	East	Central	West	Labrador
	Bonavista Community Health Center	Central Newfoundland Regional Health Center	Dr. Charles Legrow Health Centre	Captain William Jackman Memorial Hospital
	Burin Peninsula Health Care Centre	James Paton Memorial Hospital	Sir Thomas Roddick Hospital	Charles S. Curtis Memorial Hospital
	Carbonear General Hospital			Labrador Health Centre
	Connaigre Peninsula Health Centre			Labrador South Health Centre
	Dr. G.B. Cross Memorial Hospital			
	Health Sciences Centre - including Janeway Children's Hospital			
	St. Claire's Mercy Hospital			

The hospitals were divided into four regions: East, Central, West and Labrador-Grenfell (Table 11) as per the Government of NL Regional Health Authorities.[169]

Table 12: Number of hospitalizations in each region

Region	# of Hospitalizations	Percentage
East	273	66.3%
Central	55	13.3%
West	66	16.0%
Labrador	18	4.4%
TOTAL	412	100%

The largest absolute number of DKA hospitalizations occurred in the Eastern region (Table 12).

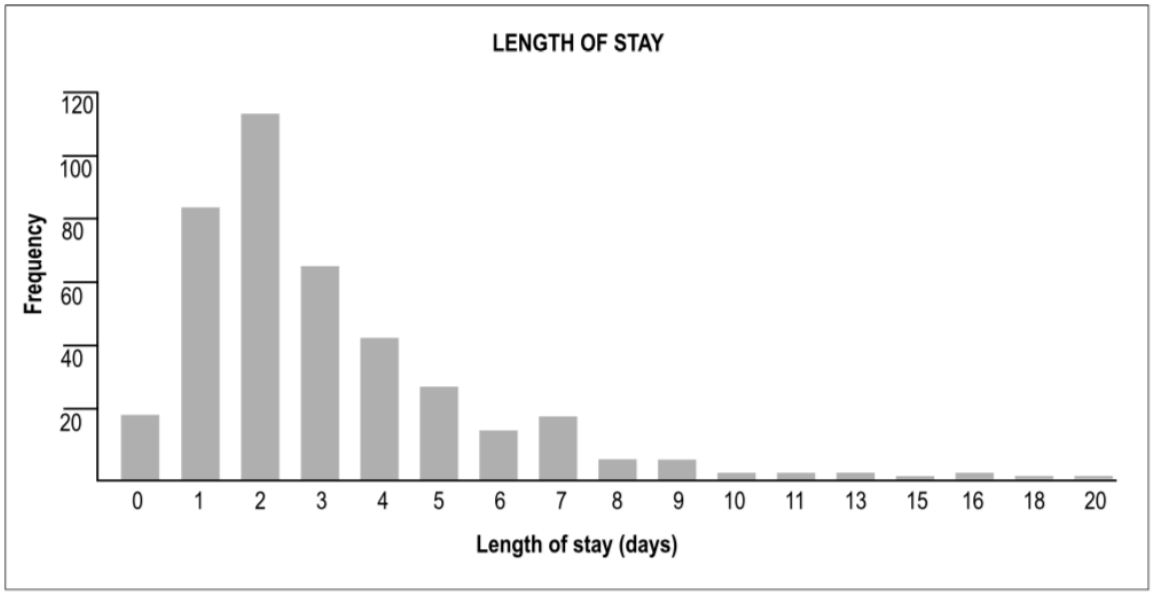

Figure 12: Length of stay (days) of hospital admission for DKA

In Figure 12, the majority of patients had a length of stay of two nights (n = 116, 28.2%), followed by those with a one–night length of stay (n = 82, 19.9%). Sixty patients (14.5%) had a hospitalization length of stay of over one week.

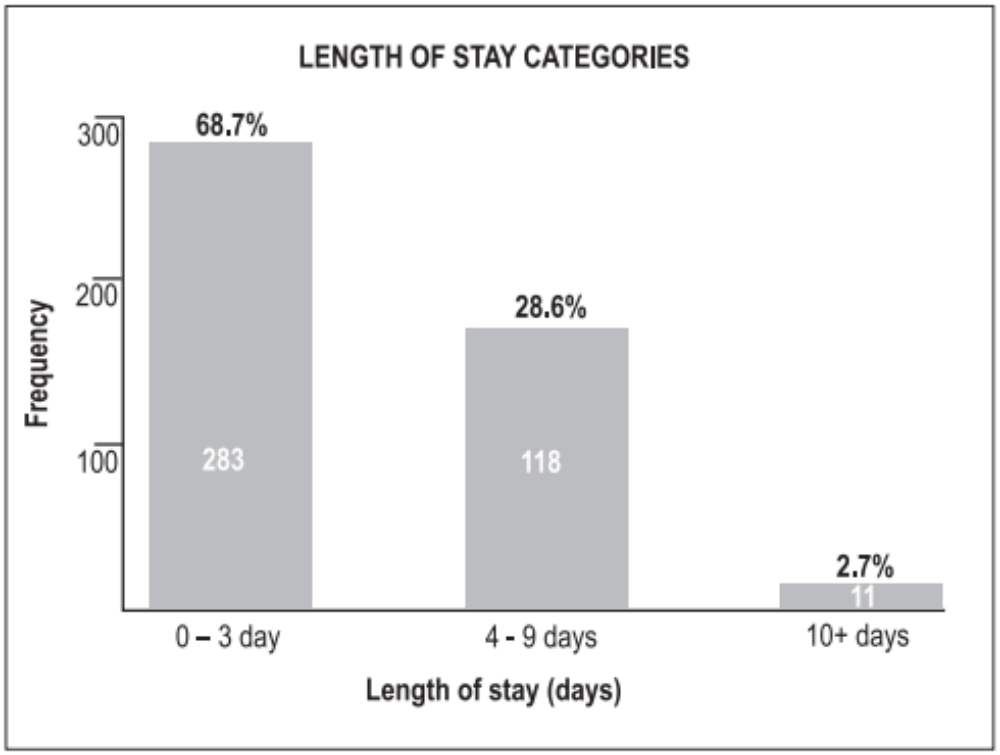

Figure 13: Length of stay categories

Dividing the patients into categories based on their length of stay (Figure 13) was helpful in order to visualize the hospital utilization for DKA admissions. 283 patients (68.7%) spent up to three days in hospital, 118 patients (28.6%) spent between four – nine days, and 11 patients (2.7%) were hospitalized for over ten days.

Table 13: Season of hospitalization

Season of hospitalization	# of admissions	Percent
Winter (Dec - Feb)	94	22.8
Spring (Mar - May)	92	22.3
Summer (June - Aug)	126	30.6
Fall (Sep - Nov)	100	24.3
T O T A L	412	100

There was no statistically significant seasonal variability in DKA hospitalizations (P=.109) (Table 13). There were 94 hospitalizations during winter (December – February), 92 hospitalizations during spring (March – May), 126 hospitalizations during summer (June – August) and 100 hospitalizations during fall (September – November).

Table 14: Recurrent DKA hospitalizations

# of DKA hospitalizations during study period	# of patients hospitalized
1	159
2	38
3	18
4	5
6	3
7	2
8	2
9	3
14	2

The majority of patients were hospitalized once (n = 159, 68.5%), followed by patients hospitalized twice (n = 38, 16.4%) then three times (n = 18, 7.8%) then four times (n = 5, 2.2%) then six times and nine times (N = 3, 1.3% each, respectively) then seven, eight and 14 times (N = 2, .86% each, respectively). Overall, 31.5% patients had recurrent DKA admissions (Table 14).

4.2 Statistical Analysis

4.2.i Crude DKA hospitalizations per year during 2009 – 2014, NL

Since the project was implemented for a two-year period, for ease of comparison and consistency, DKA admissions reported in two-year periods before, during and after the project were used.

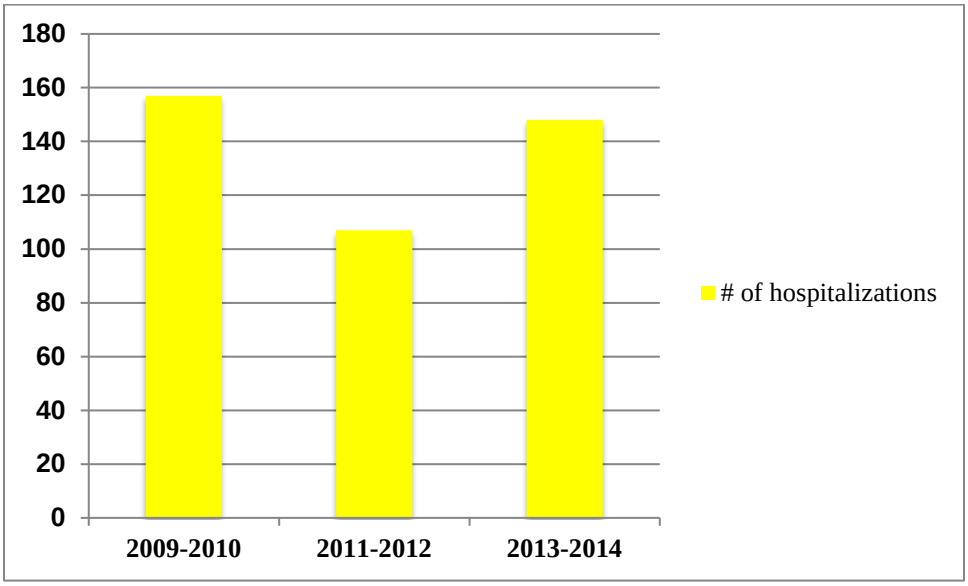

Figure 14: Crude DKA hospitalizations by two year periods during 2009 - 2014, NL

Table 15: Number of DKA hospitalizations per year during 2009 - 2014, NL

Year	# of admissions	Proportion of total DKA hospitalizations (2009-2014)
2009	90	21.8
2010	67	16.3
2011	51	12.4
2012	56	13.6
2013	79	19.2
2014	69	16.7
TOTAL	412	100.0

In 2011 and 2012, when the project was ongoing, the province of NL had the least number of DKA admissions N=51 (12.4% of total DKA admissions during study period) and N=56 (13.6%), respectively. Compared to 2009/2010 DKA admissions (157/412 = 38.1%), 2011/2012 DKA admissions (107/412 = 26%) showed a 12.1% decrease. Overall, the number of hospitalizations prior to the NLdkaP in 2009 and 2010 were the highest, N=90 (21.8%) and N=67 (16.3%). In the two years post – NLdkaP, 2013 and 2014, the hospitalizations were slightly lower than before the project N=79 (19.2%) and N=69 (16.7%) respectively, but were higher than during the project N=51 (12.4%) and N=56 (13.6%).

The cumulative hospitalizations for the two years after the project showed an overall 38.1% – 35.9% = 2.2% decrease from 2009/2010, but a 35.9% – 26% = 9.9% increase from the hospitalizations while the project was ongoing.

4.2.ii Age specific DKA hospitalizations per year during 2009 – 2014, NL

Two age categories were compared (0 – 19 years and 20 – 24 years) as the 0 – 19 year olds were directly targeted by the NLdkaP.

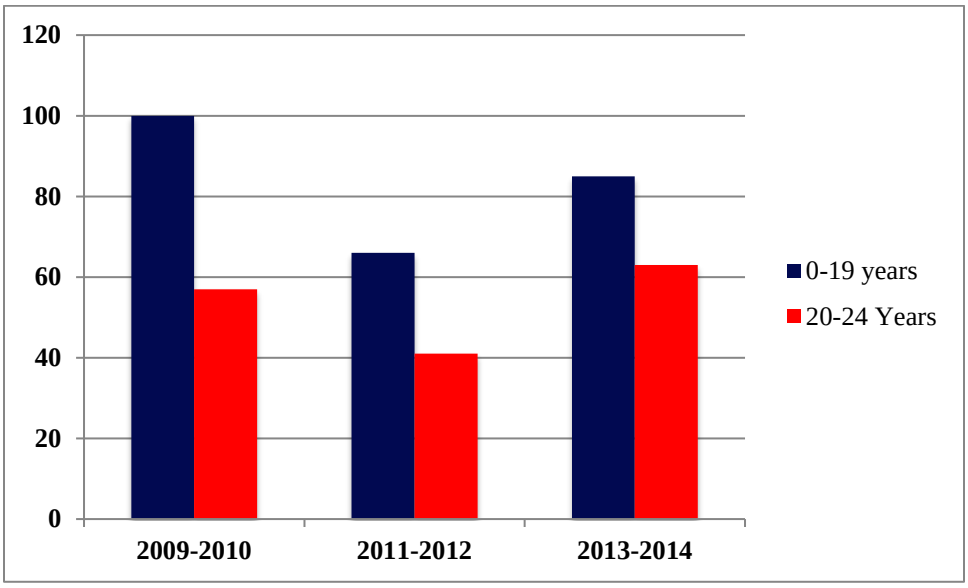

Figure 15: Age specific hospitalizations for age groups 0 – 19yrs and 20 – 24yrs in two-year periods during 2009 – 2014 in NL

Table 16: Hospitalization rates between 0 – 19 and 20 – 24 year age groups in two year periods during 2009 – 2014 in NL

Hospitalization Rates (95%CI) per 100,000

Year	0-19 years (N, 95% CI)	20-24 years (N, 95% CI)	*P*-value
2009 - 2010	50 (40, 50)	90 (70, 120)	<0.001
2011 - 2012	30 (20, 40)	70 (50, 90)	<0.001
2013 - 2014	40 (30, 50)	110 (80, 140)	<0.001

Table 17: Age specific DKA hospitalization rates per year during 2009 - 2014, NL (per 100,000 population)

Yearly DKA hospitalization rates by age group for 2009-2014 in NL

Year	0-4 years		5-9 years		10-14 years		15-19 years		20-24 years	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
2009	4 / 26078	15.34	6 / 24811	24.18	19 / 27940	68	28 / 31144	89.9	33 / 30830	107.04
2010	2 / 24320	8.22	1 / 25110	3.98	18 / 27445	65.59	22 / 30755	71.53	24 / 29985	80.04
2011	5 / 24495	20.41	6 / 25100	23.90	12 / 27030	44.4	12 / 29585	40.56	16 / 30050	53.24
2012	5 / 24075	20.77	4 / 24875	16.08	11 / 26575	41.39	11 / 29000	37.93	25 / 29430	84.95
2013	2 / 23755	8.42	6 / 24875	24.12	15 / 25655	58.47	20 / 28180	70.97	36 / 29870	120.52
2014	2 / 22740	8.90	8 / 25295	31.63	16 / 25505	62.73	16 / 27705	57.75	27 / 29035	92.99
P-value for trend test		0.5867		0.3082		0.6453		0.3819		0.7178

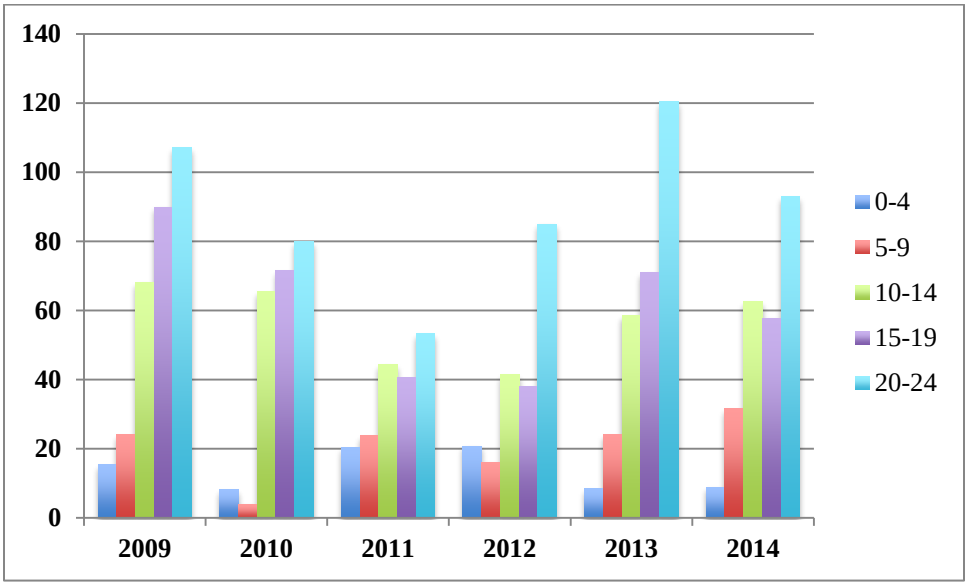

Figure 16: Age specific DKA hospitalization rates per year during 2009 - 2014, NL

The above figures and table show the variation in hospitalization rates for the six-year study period. Figure 15 demonstrates a reduction in DKA rates for both age groups (0 - 19 and 20 - 24) during the NLdkaP. In the two years post-project, there is a slight increase in DKA rates for the 0 - 19 year age group (40 vs. 30) and a larger increase in DKA rates for the 20 - 24 year age group (110 vs. 70). The 20 - 24 year age group shows a significant increase in DKA hospitalization rates in 2012. Table 16 depicts significant

hospitalization rates for both age groups, 0 – 19 years and 20 - 24 years, during all time intervals of the project.

4.2.iii Age/sex specific DKA hospitalization rates during 2009 – 2014, NL

Table 18: Age/sex specific DKA hospitalization rates during 2009 - 2014, NL

DKA hospitalization rates by age group and gender for 2009-2014, Newfoundland & Labrador

Age group (years) and sex	Hospitalization (numbers)	Average population	Hospitalization rate per 100,000	95% CI	*P*-value
0-4					
Male	12	13451	89	(40, 140)	0.4510
Female	8	12627	63	(20, 110)	
Total	20	26078	77	(40, 110)	
5-9					
Male	18	12658	142	(80, 210)	0.4322
Female	13	12153	107	(50, 170)	
Total	31	24811	125	(80, 170)	
10-14					
Male	23	14238	162	(100, 230)	<0.001
Female	68	13702	496	(380, 610)	
Total	91	27940	325	(260, 390)	
15-19					
Male	47	15922	295	(210, 380)	0.0940
Female	62	15222	407	(310, 510)	
Total	109	31144	350	(280, 420)	
20-24					
Male	68	15343	443	(340, 550)	0.0554
Female	93	15487	600	(480, 720)	
Total	161	30830	522	(440, 600)	
0-24					
Male	168	71612	235	(200, 270)	<0.001
Female	244	69191	352	(310, 400)	
Total	412	140803	293	(260, 320)	

When all ages are combined, there are more female than male DKA hospitalizations (P<0.001). In sub-group analysis of females, there are more female DKA hospitalizations in the 10-14 year old age category (P<0.001).

Chapter 5: Discussion

DKA is an acute and life-threatening complication of diabetes and is the leading cause of morbidity and mortality in children with diabetes. It is defined as a blood glucose concentration of >200mg/dL, with ketonemia/ketonuria and a venous pH <7.3 or bicarbonate <15 Eq/L. The NLdkaP was conducted from 2011 to 2012 and involved a series of community–based knowledge translation dissemination activities carried out in an attempt to reduce the occurrence of DKA in NL. The main findings of this study demonstrated that hospitalizations for DKA decreased during the intervention phase of the project, and the most hospitalized age group was 20–24 years of age. The results from this study will be compared to the published literature as described below.

The DKA prevention studies identified in the literature review were all developed to address physician, patient, family and other caregiver gaps in knowledge.[76,79,80,86,177-179] The studies were multifaceted and incorporated active and passive ways of educating. The studies that leaned towards the passive forms of knowledge translation such as posters, radio and television advertisements found little to no impact on DKA hospitalization rates.[80,86] This demonstrates, that perhaps, more integrative methods such as education sessions, longer clinic appointments and telephone help lines are more effective at relaying information with the goal of reducing DKA rates.[76,79,177,178] Most of the studies analyzed DKA rates before and after intervention programs, while two (including the NLdkaP) looked at DKA rates during the intervention period. The study conducted in Australia monitored DKA rates before and during their intervention but did not include any post-intervention analysis. The lack of consistency across program

components such as duration of interventions, follow up periods and ages of participants makes it difficult to compare studies and draw conclusions.

In discussing the individual factor of age, the literature review concluded that the largest proportion of DKA hospitalizations were seen in children less than five years of age and rates of DKA decreased with increasing age. Our analysis of the NLdkaP did not support this trend. The studies included in the literature review did not include individuals up to 24 years old; the oldest age was 18 years old in the study conducted in Australia. In the NLdkaP analysis, the highest rates of DKA were in the 20 – 24 year old category (522 per 100,000) followed by the 15 –19 year olds (350 per 100,000). It is reasonable to conclude that since the NLdkaP was predominantly geared towards the pediatric population, this could explain why the rates of DKA were significantly lower for this age group. This may suggest that its impacts were greater in increasing the surveillance of new cases of T1DM than addressing the issues of noncompliance with insulin management in the older population.

Adolescence is a time when individuals become more independent from their parents/caregivers and many move out to begin university, college, or fulltime work. This change in supervisory structure could be accompanied with less insulin regulation and may provide an explanation for such a high occurrence of DKA in this age group. Further, a number of studies have reported that a change in diabetes management team can severely impact disease control.[150-152,161-163] A large number of patients develop DKA when transitioning from pediatric to adult care so this may also explain the higher rates of DKA in the 20 – 24 year old age group during the NLdkaP. Further, the high

rates of DKA hospitalizations in the 20 – 24 year age category are consistent with a previous study done in the province by Alaghehbandan et al.[29]

A number of the reviewed studies focused on sex and DKA frequencies.[29,30,50,64] These studies determined that females have higher DKA occurrence than males, which agrees with the findings from the current study. Although the reasons for this phenomenon are not clear, it is hypothesized that females may be more affected by psychosocial issues such as familial conflict, behavioural issues and intentional weight loss through insulin omission.[74,75] The NLdkaP analysis showed that for all ages (0 – 24 years of age) there were significantly more females than males hospitalized (244 vs. 168, P – value < 0.001), thus concurring with the literature. In addition, the only separate age category to show a significant difference between female and male DKA hospitalization was the 10 – 14 years of age (68 vs. 24, P – value <0.001). This finding is consistent with other published literature. During 10 – 14 years of age, puberty occurs, which is associated with hormones that may cause cause insulin resistance leading to poor metabolic control. In addition to this, females are more likely to be affected by eating disorders and to omit insulin, which leads to weight loss but also is associated with poor metabolic control.[74,75]

A number of studies report that more cases of T1DM are diagnosed in the winter months compared to other months;[64,140] however, in the current study DKA hospitalizations remained stable during the year with no seasonal peaks. The NLdkaP yielded slightly more DKA hospitalizations during the summer months, although this was not statistically significant. This could perhaps be attributed to the fact that during the summer children spend more time away from their parents and with temporary guardians.

Whether it is with a temporary caregiver, playing outdoors, or attending a summer camp, it is likely that children are not monitoring their blood glucose levels closely, nor do the temporary guardians have all the pertinent information to recognize and attend to the symptoms of DKA.

The reviewed literature concluded that there are no differences between urban and rural settings for occurrence of DKA hospitalizations.[95,139] The NLdkaP analysis determined that the majority of DKA hospitalizations were on the Avalon Peninsula (East). This was an expected occurrence as the majority of the province's population lives on the Avalon Peninsula and it is the location of the Janeway Children's Hospital, the only pediatric tertiary care center in the province.

5.1 Strengths and Limitations

This pre-post design study helped shed light on a prevalent condition in our population in a relatively inexpensive and time-efficient manner.

There were several notable limitations of the current study. First, the information collected was not specific to the current project, so some pertinent information was not collected that could have been useful. Retrospective studies are subject to confounding since other risk factors may have been present that were not measured, and we cannot make direct cause-effect assumptions. Further, we used hospitalization data, which has its limitations as well. This type of data could be subject to incomplete and unstandardized information.

Other limitations of the present study include that information was collected from hospitalization data and information like BMI, ethnicity, DKA background knowledge,

parental education level, socioeconomic status, family history of diabetes and preceding infectious illness were not recorded. Differentiation between hospitalizations of an individual presenting in DKA at diagnosis or not could not be made. As well, incidence could not be calculated from the data, as we were not able to determine if the patient had been previously hospitalized for DKA or not. During the six–year study period, multiple DKA diagnoses per individual were recorded as per Table 10. There may have been other factors apart from the NLdkaP affecting reduced DKA rates during the study period, such as changes in disease incidence or changes in the population. Further, there may have been cases of prevented DKA that were not measured, as families may have managed sick days and insulin delivery problems at home and avoided hospitalization. Since it was de–identified data, it was impossible to determine (or ask) if people had indeed received information directly from the NLdkaP through a focus group or information session, or indirectly through seeing posters, word of mouth, etc. It would have also been helpful to have an idea of how many individuals were reached through the knowledge translation project. There were a number of individuals with greater lengths of stay and their files could not be reviewed to determine if they were in hospital for that length of time solely for DKA, or because of comorbidity. As well, there were patients with multiple DKA diagnoses during the study period. With the information collected, it could not be determined why these individuals were outliers from the majority that were only hospitalized once. Finally, our analysis was conducted on the impact of the NLdkaP program as a whole. We could not determine if certain parts of the knowledge translation program were more effective than others.

5.2 Recommendations

Overall, the study findings demonstrate that the NLdkaP was associated with a reduction of hospitalization rates province-wide in pediatric DKA during intervention years. In order to sustain these positive results, ongoing educational campaigns are needed as during non-intervention years post NLdkaP, rates of pediatric DKA increased. The methods utilized during the project could be implemented longer–term to reduce DKA rates and be shared with the young adult age group that have the highest rates of hospitalization for DKA. It would be beneficial to adapt or add in another facet to the NLdkaP targeted at the older age groups. Specifically, arranging organized transition services from pediatric to adult care may significantly reduce DKA admissions. Given the advancements in technology since the launch of the NLdkaP, it may also be advantageous to discuss the project on the radio, television, and through social media. Further, adding a post–publicity campaign survey for both physicians and patients and their families would be helpful in determining the efficacy of the intervention and could provide insight for methods that were well received and those that could be adjusted.

Chapter 6: Conclusions

The alarming rates of T1DM in the province of NL have implications for the families living with diabetes and the health care system. DKA is one of the most serious and life–threatening but preventable complications of diabetes. The high rates of DKA place a significant financial burden on the health care system and individual families and there is a need for targeted health services for patients and their families. Continued research is warranted to understand the etiology and pathogenesis of T1DM and to determine the reasons for such a high disease incidence. As well, efforts should be placed on diabetes education and management.

The NLdkaP was launched as a knowledge translation project to better educate healthcare professionals and others involved in the circle of care. The results of the analysis show that there was a reduction in provincial rates of DKA during the two years the project was ongoing, with an increase in DKA rates after the NLdkaP. These promising results suggest that this type of knowledge translation project was effective and could be shared nationally and internationally as a model for DKA awareness and prevention. Future research to examine and ensure program sustainability and to evaluate its cost-effectiveness is recommended.

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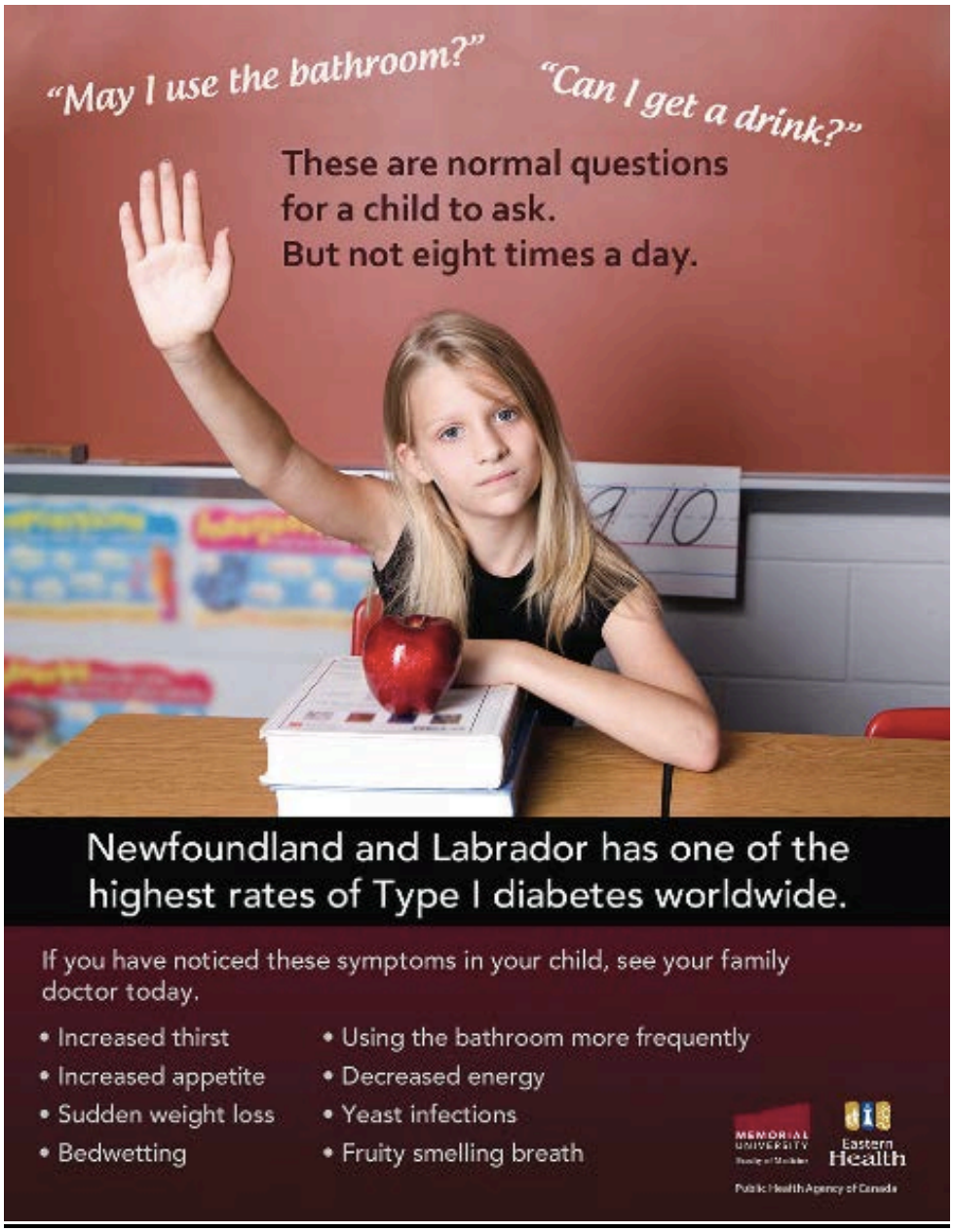
Appendix A


"May I use the bathroom?"
"Can I get a drink?"
These are normal questions
for a child to ask.
But not eight times a day.
Newfoundland and Labrador has one of the
highest rates of Type I diabetes worldwide.
If you have noticed these symptoms in your child, see your family doctor today.
• Increased thirst
• Increased appetite
• Sudden weight loss
• Bedwetting
• Using the bathroom more frequently
• Decreased energy
• Yeast infections
• Fruity smelling breath
Eastern Health
Public Health Agency of Canada