EPIDEMIOLOGY OF TYPE 1 DIABETES: HIGH INCIDENCE OF CHILDHOOD TYPE 1 DIABETES MELLITUS IN THE AVALON PENINSULA, NEWFOUNDLAND, CANADA

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EPIDEMIOLOGY OF TYPE 1 DIABETES:

HIGH INCIDENCE OF CHILDHOOD TYPE 1 DIABETES MELLITUS IN THE AVALON PENINSULA, NEWFOUNDLAND, CANADA

By

© Leigh Anne Newhook

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ABSTRACT

Objective: To determine the incidence of type 1 diabetes mellitus among children aged 0 –14 years in the Avalon Peninsula in the Canadian Province of Newfoundland and Labrador.

Research Design: Prospective cohort study.

Participants/Setting: Children aged 0-14 years who were diagnosed with type 1 diabetes mellitus from 1987 to 2002, on the Avalon Peninsula of Newfoundland.

Methods: The primary objective was to determine the incidence of childhood type 1 diabetes mellitus (T1DM). Identified cases during this time period were ascertained from several sources and verified using the capture-recapture technique. Data were obtained from the only pediatric diabetes treatment center for children living on the Avalon Peninsula.

Results: Over the study period 294 children aged 0-14 years from the Avalon Peninsula were diagnosed with T1DM. The incidence of T1DM in this population over the period 1987 – 2002 inclusive was 35.93 per 100,000 per year. The incidence over this period increased linearly at the rate of 1.25 per 100,000 per year.

Conclusion: The Avalon Peninsula of Newfoundland has one of the highest incidences of T1DM reported worldwide. The incidence is increasing over the 16-year study period.

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In memory of my brother, Carl Robert Allwood (1970-1991).

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1 Chapter 1: Introduction

Diabetes mellitus is a severe metabolic disturbance that results from insulin deficiency, impairment of insulin action, or both. Diabetes is characterized by classic symptoms caused by hyperglycemia. Type 1 diabetes mellitus (T1DM) is a T-cell mediated autoimmune disease in which both genetic and environmental factors play roles in the etiology(1). T1DM is the most common form of diabetes in childhood and it is characterized by the destruction of pancreatic beta cells resulting in the absence of insulin secretion requiring exogenous insulin for survival. T1DM accounts for about 10% of all diabetes and it is one of the most common severe chronic diseases of childhood.

Acute complications of T1DM include diabetic ketoacidosis (DKA), hypoglycemia and infections. Deficiency of insulin and acute hyperglycemia can be life-threatening leading to diabetic ketoacidosis (DKA) and its complications including electrolyte disturbances and cerebral edema. Over-treatment of hyperglycemia leads to hypoglycemia, which also has significant morbidity and even mortality. An estimated 26% of the patients have at least one episode of severe hypoglycemia within the initial 4 years of diagnosis (2). Severe hypoglycemia is associated with short-term risks that can arise while a person is hypoglycemic (e.g. driving, working). Other complications of severe hypoglycemia include intellectual impairment, convulsions, coma, paresis, pontine dysfunction, encephalopathy and death (3).

Chronic elevation of blood glucose values results in long-term damage to blood vessels and organs (retinopathy, nephropathy, neuropathy, and cardiovascular disease), leading to high degrees of morbidity and increased mortality. Diabetes is the most common cause of new cases of blindness. After 15+ years of T1DM, 80% of the patients have diabetic retinopathy and 25% have vision-threatening proliferative diabetic retinopathy (PDR)(4). Diabetic nephropathy is the most common cause of renal failure in the western world(5). The cumulative incidence of diabetic nephropathy from European registry data appears to indicate an cumulative risk of 20% to 30%(6). Neuropathies are an important complication of diabetes and can lead to sensory loss, pain and weakness. In patients with diabetes but no evidence of retinopathy, polyneuropathy develops in up to 10% of individuals within 5 years. In patients who already have

retinopathy, polyneuropathy develops in up to 16% of individuals within 16 years. These consequences along with the high costs of treating diabetes have made it a major health care problem.

Coronary heart disease (CAD) is the main cause of death in persons with T1DM and accounts for a large proportion of premature morbidity and mortality. Heart disease in T1DM patients occurs earlier in life, affects women as often as men, and associated mortality is dramatically higher than that in the general population. In T1DM patients, arteriosclerosis is more diffuse, leading to higher case fatality, higher cardiac failure, and shorter survival, compared to the general population (7).

Although the absolute mortality at onset and within the first 20 years of type 1 diabetes is low (3-6%), it is 5 times higher for males and 12 times higher for females with T1DM, compared to the general population (8).

Epidemiologic studies of T1DM have been important in providing clues directing study into the possible genetic and environmental causes of the disease. Despite a tremendous amount of scientific research into the etiology of T1DM, its specific causes remain elusive.

This Chapter will review the definition, description and classification of diabetes. Subsequent to this will be a review of the epidemiologic research of T1DM including summaries of the incidence and prevalence, demographic characteristics, genetics, autoimmune associations, and hypothesized environmental factors. This information will lay the background for the purpose of this thesis; to study T1DM in the Avalon Peninsula, Newfoundland. A paper entitled "High Incidence of Childhood Type 1 Diabetes in the Avalon Peninsula, Newfoundland, Canada" has been published(9).

1.1 Literature Review

Classification of diabetes mellitus and disease definition

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs-especially the kidneys, eyes, nerves, heart and blood vessels.

Diabetes mellitus describes a heterogeneous group of disorders. It can be classified into two primary types: type 1 diabetes mellitus (previously referred as juvenile-onset or insulin dependant diabetes mellitus) and type 2 (previously called adult-onset or non-insulin dependent diabetes mellitus). There are several other types of diabetes mellitus related to pancreatic or hormonal diseases, drug or chemical exposure, and certain genetic syndromes.

Type 1 diabetes mellitus encompasses diabetes that is primarily a result of pancreatic beta cell destruction and that is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.

Type 1 diabetes mellitus in childhood and adolescence is characterized by four phases. The state preceding the clinical onset (pre-diabetes) of diabetes by months or even years, is characterized by the presence of antibodies to several islet cell antigens which are often, but not always predictive of the development of T1DM. The antibodies have been used as markers of identifying persons at risk for the disease. During this period beta cell destruction progresses and insulin secretion diminishes (10).

The second phase is the presentation of the disease, usually symptomatic with polyuria, polydipsia, weight loss, and ketosis (10).

The third phase may occur after the initiation of insulin treatment, when there may be a partial remission (or Honeymoon) phase. Approximately 30-60% of children and adolescents demonstrate a partial remission phase during the first 1-6 months after starting insulin (10).

After a period of months there is permanent exogenous insulin dependency (phase 4), and beta-cell function becomes almost immeasurable in the great majority of children by 1-2 years after diagnosis. Established diabetes is associated with acute and chronic complications and premature death (10). Retinopathy, nephropathy, accelerated cardiovascular disease, neuropathy, and peripheral vascular diseases are serious long-term complications of this disease(11).

Type 2 diabetes mellitus may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance. Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder with both genetic and environmental determinants. Individuals with T2DM may or may not have symptoms of hyperglycemia, and up to one-half of all cases may be undiagnosed. Risk factors for T2DM include advancing age, increased body mass index, central fat distribution, ethnicity, family history of T2DM, low birth weight, sedentary lifestyle, higher systolic blood pressure, impaired glucose tolerance and history of gestational diabetes(12).

The specific genetic defects implicated in most cases of T2DM are unknown. Studies suggest that insulin resistance is a primary inherited defect that occurs early in the course of T2DM(13). Eventually persons who develop T2DM have a failure of insulin secretion, hyperglycemia and symptoms of clinical diabetes ensue. Obesity contributes to the development of diabetes by further increasing insulin resistance which may be more pronounced in those with a family history of diabetes(14).

In the past, the vast majority of children and adolescents were diagnosed as having T1DM. New research, however, supports the rising incidence of T2DM in the pediatric population, specifically among adolescents in high risk

groups, such as First Nations, Hispanics, African-Americans, and Asian –Americans (15). Data from the United States suggest a 10-30-fold increase in the number of children with T2DM over the past 10 to 15 years(16).

Risk factors for the development of T2DM in children and adolescents include a history of T2DM in a first or second-degree family member, being a member of a high-risk population (e.g. people of Aboriginal, Hispanic, South Asian, Asian or African descent), overweight, impaired glucose tolerance testing, polycystic ovarian syndrome, exposure to diabetes in-utero, acanthosis nigricans, hypertension, and dyslipidemia (3).

Gestational diabetes mellitus refers to glucose intolerance with first onset or recognition during pregnancy. Gestational diabetes occurs in 2 to 4% of the pregnant population and is due to a combination of the insulin resistance of pregnancy and an insulin secretory defect. It is associated with neonatal macrosomia and hypoglycemia and, in the mother there is an increased long-term risk of diabetes (17).

There are a group of conditions caused by genetic defects of beta-cell function (formerly known as maturity-onset diabetes in the young, MODY subtypes). These are associated with early-onset hyperglycemia before age 25 years, with a monogenic, autosomal dominant mode of inheritance. These individuals are usually non-insulin-dependant for at least five years after diagnosis of diabetes, have impaired insulin secretion and absence of severe ketosis.

A wide variety of relatively uncommon conditions are listed in Table 1. This list also includes genetically defined forms of diabetes or diabetes associated with other diseases or drug use.

Table 1. Etiologic classification of diabetes mellitus (3)

Type 1 diabetes mellitus Beta cell destruction, usually leading to absolute insulin deficiency • Immune mediated • Idiopathic	
Type 2 diabetes mellitus May range from predominant insulin resistance with relative insulin deficiency to predominant secretory defect with insulin resistance	
Gestational diabetes mellitus Onset or recognition of glucose intolerance in pregnancy	
Other specific types	
Genetic defects of beta cell function Chromosome 20, HNF-4alpha (formerly MODY1) Chromosome 7, glucokinase (formerly MODY2) Chromosome 12, HNF-1alpha (formerly MODY3) Mitochondrial DNA Others *Genetic defects in insulin action* Alstrom syndrome Leprechaunism Lipoatrophic diabetes Rabson-Mendenhall syndrome Type A insulin resistance Others *Diseases of the pancreas* Cystic fibrosis Fibrocalculous pancreatopathy Hemochromatosis Neoplasia Pancreatitis Trauma/pancreatectomy Others *Endocrinopathies* Acromegaly Aldosteronoma Cushing syndrome Glucagonoma Hyperthyroidism Pheochromocytoma Somatostatinoma Others	*Infections* Congenital rubella Cytomegalovirus Others *Uncommon forms of immune-mediated diabetes* Anti-insulin receptor antibodies 'Stiff-man' syndrome Others *Drug or chemical induced* Atypical antipsychotics Beta-adrenergic agonists Diazoxide Glucocorticoids Interferon alfa Nicotinic acid Pentamidine Phenytoin Protease inhibitors Thiazide diuretics Cyclosporine Tacrolimus Others *Other genetic syndromes sometimes associated with diabetes* Down syndrome Friedreich's ataxia Huntington's chorea Klinefelter syndrome Laurence-Moon-Bardet-Biedl syndrome Myotonic dystrophy Porphyria Prader-Willi syndrome Turner syndrome Wolfram syndrome Others

Diagnostic Criteria

The diagnostic criteria for diabetes includes a fasting (no caloric intake for at least 8 hours) glucose >7.0 mmol/L or a casual plasma glucose ≥ 11.1 mmol/L with the classic symptoms of diabetes which are polyuria, polydipsia and unexplained weight loss. Also an elevated 2-hour plasma glucose ≥ 11.1 mmol/L in a 75-gram oral glucose tolerance test is diagnostic(3).

Table 2. Diagnosis of diabetes (3)

FPG ≥7.0 mmol/L

Fasting = no caloric intake for at least 8 hours

Or

Casual PG ≥11.1 mmol/L + symptoms of diabetes

Casual = any time of the day, without regard to the interval since the last meal

Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss

Or

2hPG in a 75-g OGTT ≥11.1 mmol/L

A confirmatory laboratory glucose test (an FPG, casual PG, or a 2hPG in a 75-g OGTT) must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation.

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
OGTT = oral glucose tolerance test
PG = plasma glucose

1.2 Epidemiology of Type 1 Diabetes Mellitus

Introduction

The incidence of childhood T1DM is known to vary widely between and within countries. The incidence of T1DM (≤ 14 years) varies from 0.1/ 100,000 per year in China (1990-1994) and Venezuela (1992) to 36.8/ 100,000 per year in Sardinia (1990-1994) and 36.5/100,000 per year in Finland (1990-1994) (18). In most populations the incidence has been increasing (19).

Incidence refers to the number of people who develop T1DM during a period of time, usually expressed as the number of cases per 100,00 population per year. Incidence studies most often define the onset of T1DM as the date of the first insulin injection, because of the variable time between the onset of symptoms and diagnosis. New case incidence varies greatly between different countries, within countries, and between different ethnic populations (18).

In countries with higher incidence, the age of onset indicates that T1DM under the age of 1 year is extremely uncommon, incidence increases with age, and there is a minor peak at age 4-6 years and a major peak at 10-14 years. In many countries the total incidence of T1DM is increasing, especially in the under-five age group (20).

There is no clear pattern of inheritance although there is familial aggregation due to the association of T1DM with certain genetic markers. In higher incidence countries the familial risks of developing the disease are ~7% if the father has T1DM, ~2% if the mother has T1DM, ~35% for an identical twin with T1DM, and ~3-6% for a sibling with T1DM (10).

Measures of Disease Frequency

1.2.1.1 Incidence

Incidence is the number of new cases of a disease, which come into existence within a certain period of time per specified unit of population. Incidence provides a picture of the movement of disease through a population; the rate at which people without a disease develop the disease during a specified period of time(21).

The role of the numerator in incidence is to provide specific information about the occurrences of a disease. The numerator is the exact number of new cases starting within a time period(21).

The denominator should accurately set forth the numbers at risk or under study in the population. Usually the population numbers at a midpoint in the time period is used to represent the average population at risk. Since incidence is used to study new cases of a disease, only those individuals at risk of developing the disease, i.e. the population at risk, should be included in the denominator. In large population studies it is recommended not to try and correct the data in the denominator by excluding those not at risk. When census data are used the diseased cases data should not be removed from the denominator(21).

1.2.1.2 Prevalence

Prevalence is the number of cases of disease present at a particular time (point prevalence), or during a period of time (period prevalence) divided by the population at risk at or during the time of the outcome ascertainment. (21). In general, incidence provides a more accurate assessment of the activity of a particular disease in a given population and is the preferred measure.

1.2.1.3 Ascertainment Bias

Ascertainment bias refers to a systematic distortion in measuring the true frequency of a disease due to the way in which the data is obtained. Sampling or ascertainment bias is important to consider and avoid. One type of bias is visibility bias, whereby only those cases that are easily accessible or identifiable are included in the analysis. This could occur in a disease like type 1 diabetes mellitus if there are multiple treatment centers, uncoordinated services, or few cases treated by multiple physicians.

Ascertainment bias for T1DM is less of an issue in North America because it is an easily diagnosed disease, which eventually requires the patient to seek medical attention because of the severity of its symptoms. It is standard practice in Canada that all children with T1DM, whenever possible should be followed by a multidisciplinary diabetes team that has expertise in treating children with the disease(3).

Ascertainment bias when collecting information such as family histories and pedigrees can be problematic. Loss to follow-up can be a major source of bias, due to factors like emigration. Families may be non-responders, incomplete responders or refuse to participate. Information collected on family members may be inaccurate (recall bias) unless the information can be verified by other means. There may be a self-selection bias for families more heavily affected by a disease to participate in genetic studies.

1.2.1.4 Childhood diabetes before insulin

There is very little known about the incidence of type 1 diabetes during the early 20th century, however the information which is available suggests that it was an uncommon disease. Before the discovery of insulin, young patients with diabetes usually died from diabetic ketoacidosis, often within three years of diagnosis. Joslin in 1923 wrote that 86% of persons with diabetes died from diabetic ketoacidosis, the younger the patient with diabetes the quicker the death, and those with a hereditary form (likely genetic beta-cell abnormality MODY) lived a long time (22).

Earliest reports on prevalence of diabetes were from the Massachusetts General Hospital (1824-1898). During this time period, 172 out of a total of 47,899 patients were diagnosed with diabetes. Eighteen of the 172 patients with diabetes were less than 20 years of age, and 3 patients were less than 10 years of age. In 1884 laboratory urine screening became available. Previous to this the diagnosis was based on clinical features and sweet urine. In 1913 Morse (professor of pediatrics Harvard Medical School) assembled 989 cases of diabetes. 162 patients were less than 5 years, 302 were between 5 and 9 years and 525 were greater than 10 years of age. In 1915 laboratory blood glucose measurement became available. There was near uniform mortality for children with hyperglycemia before insulin treatment existed. The death rate from diabetes in 1890 for children under-15 years of age in the U.S. was 1.3/100,000 and in 1920 it was 3.1/100,000. During this same period the death rate from diabetes in Denmark was estimated as 2/100,000 (1905-1909) and 4/100,000 (1915-1919). Overall early 20th century incidence can be estimated based on mortality rates in the US, Denmark and Norway for children less than 15 years to be 2-7 per 100,000 (1900-1920) (22).

1.2.1.5 Post-Insulin Era

Insulin was discovered at the University of Toronto, Canada, in the summer of 1921. Frederick Grant Banting and Charles Herbert Best discovered it. During the discovery phase, Dr. Banting and Charles Best worked alone in the lab to produce and test the drug on dogs. Dr. Bertram Collip and John J. R. MacLeod joined the team when insulin tests

worked and the purification stage started(23). The discovery of insulin changed childhood diabetes from a fatal illness to a condition where prolonged survival was possible.

A landmark U.S. National Health Survey from 1935-36 estimated the prevalence to be 0.35/1000 for males and 0.41/1000 for females less than 15 years of age. In Norway (1925-1954) the average incidence was 4.1/100,000 and between 1938-1949 the incidence in Northern Sweden was 10.2/100,000. In 1953 the incidence in Finland was 12.5/100,000, around one third of the number affected by the end of the century(22).

The incidence seems to have increased during the latter part of the 20th century. Since the 1950's there has been a linear increase in many parts of the world (19). Type 1 diabetes mellitus in children is one of the most extensively studied childhood diseases with respect to epidemiology. From 1960 onward there have been over 50 studies reporting type 1 diabetes incidence in over 27 countries.

Modern Prevalence Studies of T1DM

Prevalence refers to the number of people who actually have the disease at a point in time. It is usually expressed as the number of cases per 1,000 persons. Prevalence data are often less precise than incidence data, because it can be difficult to track the population of interest after the development of disease.

Estimates of T1DM prevalence in different populations with at least 90% ascertainment of cases are shown in Table 3. The prevalence of T1DM in children aged less than 15 years ranges from 0.5 to 3 per 1000 in most European and North American populations (24). Varying age ranges are identified for each study, which may affect the prevalence.

Table 3. Prevalence of childhood type 1 diabetes (7)

Location	Year of Study	Age (y)	Prevalence (per 1000)
United States			
Rochester, MD	1970	0-14	0.57
Kentucky	1978-79	0-17	2.08
Erie County, PA	1961	0-15	0.61
Europe			
Denmark	1973	0-14	0.83
Finland	1979	0-14	1.91
Sweden	1977	0-14	3.00
Leicester	1984-85	0-14	0.99
Estonia	1988	0-14	0.60
Oceania			
Canterbury, NZ	1986	0-19	1.05
Tasmania, Australia	1984	0-14	0.57

Modern Incidence studies of T1DM

1.2.1.6 Worldwide Incidence Studies

There is a wide global variation in the incidence of diabetes. Most of the information regarding type 1 diabetes incidence thus far has come from regions with a high or intermediate incidence. There have been several registries in Europe and North America but the information from Africa, Asia and South America remains sparse. It is much more difficult to set up and maintain stable registries for larger populations with low incidence (18).

Registries have advantages and disadvantages. Registries are expensive to develop, require the cooperation of many health care providers and entities, and need excellent management. Disease registry systems are of value if the disease has a good prospect for intervention, control, prevention, and for research that can lead to these ends (25).

The World Health Organization (WHO) began a Multinational Project for Childhood Diabetes (DiaMOND) in 1990 to investigate and monitor patterns in the incidence of type 1 diabetes worldwide. Incidence data on T1DM has been collected and published from 1990-1994 (18). Another large-scale study on the epidemiology of T1DM is the EURODIAB ACE study, which included 26 centres in Europe and Israel(26).

The WHO DiaMOND Study as mentioned, found a wide variation of T1DM incidence worldwide. This study included 100 centres, including 50 countries, totaling 19,164 cases of children with T1DM aged less than 15 years. The total population of children was 75.1 million. Cases were ascertained using standardized methods established by the WHO study group. To be eligible for the study each centre was required to have a well-defined population-based registry, and incidence data was collected using the framework provided by the WHO Diamond incidence study. Participating centres had submitted annual incidence data to the WHO DiaMOND data centre in Helsinki using standardized forms. Data on sex, ethnic group, date of birth, date of first insulin administration, source of data on family history of diabetes (the diabetes status of siblings, parents, and children of registered cases) were included in their database(18).

1.2.1.7 Capture-Recapture Method

Ascertainment was confirmed using "capture-recapture" methods in most centers. The "capture-recapture" approach to counting T1DM was published by Laporte and coworkers(27). New cases of T1DM are identified using numerous sources (hospital lists, pediatricians clinic lists, diabetes clinic lists etc.), the sources are aggregated and duplicates are sorted out. The aggregated list (number of new cases) is used for determining the numerator (to calculate the incidence), however is considered a crude rate because of possible undercounting of missing cases. An independent secondary source is used (records from local diabetes association, diabetes camp lists, school health records, social assistance schemes etc.), and duplicate/missing cases are recorded. "Recaptured" cases can determine the degree of undercounting and the percent ascertainment can be calculated. Authors felt that under-ascertainment may have been a problem in "low incidence" areas. Setting up and maintaining population-based registries in very low-incidence areas such as South America, Asia, and Africa is very difficult as pediatric diabetes services may be fragmented (18).

The denominator for the analysis was children ≤ 14 years of age with residency in the study area, which was defined geographically to correspond with administrative and census boundaries. Cases were classified and defined as having diabetes based on 1985 WHO diagnostic criteria of diabetes. Eligible individual were placed on daily insulin injections before their 15th birthdays and were residents in their area of registration at the time of their first insulin administration(18).

Overall results revealed **low incidence** (**1-4.99/100/000**) in Asia and parts of South and Central America, **intermediate incidence** (**5-9.99/100,000**) in Africa (except Mauritius), Israel, and parts of Europe, South America and Central America (except Puerto Rico and Virgin Islands). **High incidence** (**10-19.99/100,000**) was confirmed in Kuwait, parts of Europe and North America, Portugal (Portalegre), Puerto Rico, Virgin Islands, Australia and New Zealand (except Canterbury). **Very high incidence (>20/100,000**) was confirmed in Finland, Sardinia, Sweden, Norway, Alberta, and Prince Edward Island. (Figure 2)

There is a wide variation within countries as well. For example Sardinia, an island south of Italy with the second highest reported incidence (36.8/100,000) worldwide, has an incidence 3 to 5 times that of mainland Italy. Portugal has a much higher incidence in Portalegre (21.1/100,000) as compared to the Madeira Island (7.2/100,000). Within New Zealand there is a difference between Canterbury (21.9/100,000) and Auckland (12.3/100,000) (18).

1.2.1.8 Canadian Incidence Studies

The incidence of T1DM in Canada is available from only a few studies, which were carried out over the past 25 years (18),(28), (29),(30). Two Canadian Provinces have also reported a very high incidence of the disease. A six-year study (1990-1995) reported a mean incidence of 25.7/100,000 in children less than 15 years of age who lived in the city of Edmonton (28). Manitoba has reported an incidence of 20.4/100,000 in children less than 15 years of age from 1985-1993(31). A four-year study from the province of Prince Edward Island reported a mean incidence of 24.5/100,000 in children less than 15 years of age (1990 –1993) (18). The reported mean incidence for Montreal (1971-1985) among

children 0-14 years was 10.1/100,000. (29) The lowest reported incidence was from Toronto (1976-1978) with a mean incidence of 9.0/100,000 per year in children under 19 years of age (30). Comparing studies of different age ranges must be interpreted carefully however as the incidence may appear lower when higher age-range is studied because the peak of T1DM occurs in early childhood.

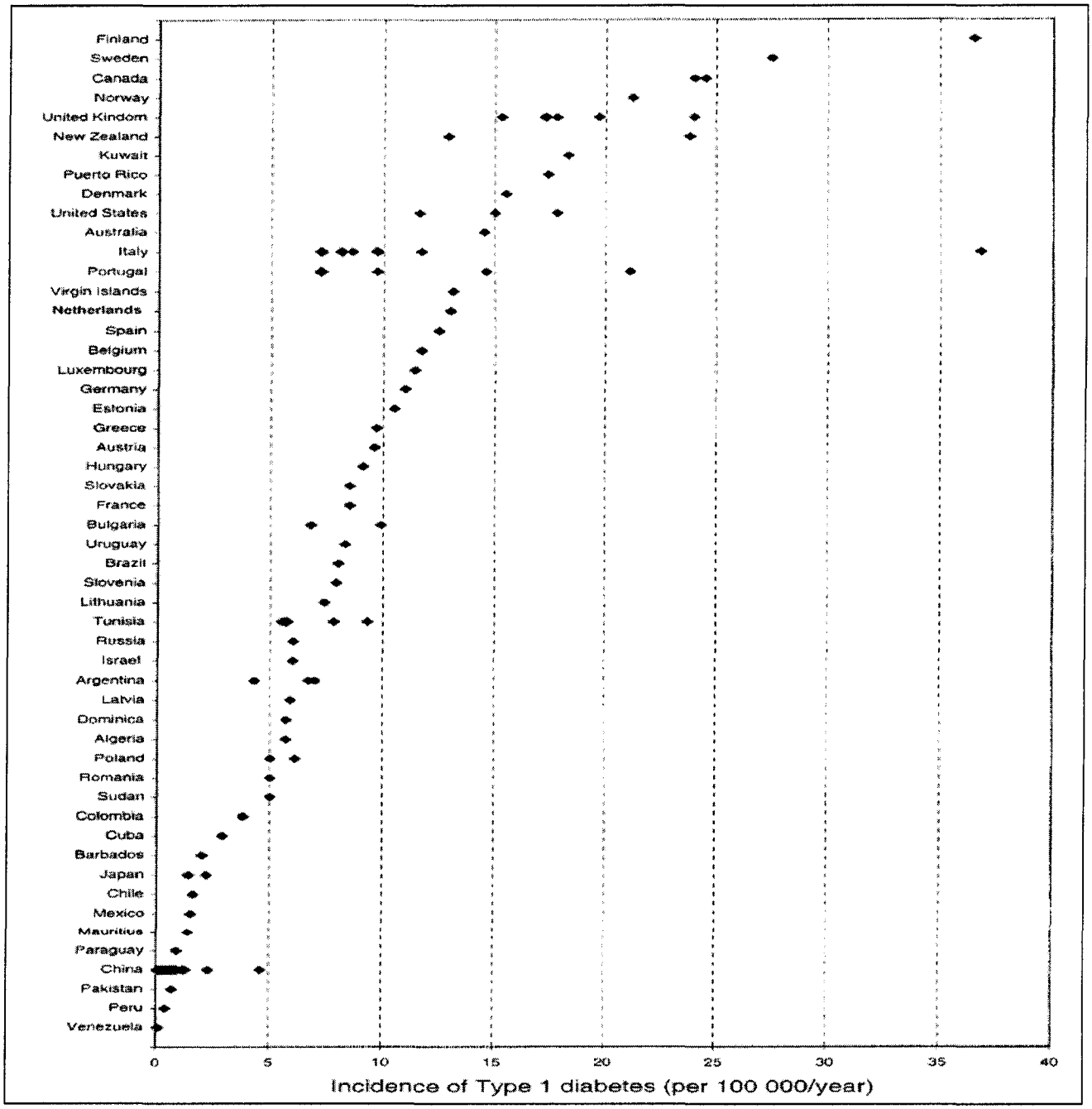

Figure 1. Worldwide Incidence of Type 1 Diabetes (18)

Increasing Incidence of T1DM

The incidence of T1DM appears to be increasing in many parts of the world. Most population-based registries have shown an increase in type 1 diabetes incidence over time (26;32-36). Periodic outbreaks, sometimes of pandemic proportion, e.g., during 1984-86 (33) appear to be superimposed on a steady secular increase in incidence. While the increase in type 1 diabetes incidence has affected all age groups, several studies have reported particular increase among the o-4 year age group (18;37-40).

A recent study covering the period from 1984 to 1996 found a linear increase of 2.3% per year(41). Importantly, the increase in incidence was seen in the age group 0 to 14 years and also in the age group of 15-29 years. The incidence is increasing both in low and high incidence populations. A recent analysis of data on published incidence trends showed that the incidence of type 1 diabetes is globally increasing by 3.0% per year, and that the incidence of type 1 diabetes will be 40% higher in 2010 than in 1998 (42).

1.3 Demographic Characteristics

Age at onset

A number of studies have documented a peak onset around the time of puberty in both males and females. There is a minor peak located around age 5 years. The highest incidence is in the 10-14 age group(18). Type 1 diabetes is extremely uncommon before the age of one.

It is felt by some that the total incidence of type 1 diabetes is not increasing but the age of onset is earlier, with fewer adults being diagnosed but more children (43).

Incidence of T1DM in adults has not been well documented mainly because of the difficulty distinguishing T1DM from insulin-requiring T2DM in older adults, but there may be a peak at around age 50 years (44).

Sex ratio

In general males and females have a similar risk for developing T1DM. The male to female incidence was calculated in 98 populations. Three areas showed a statistically significant male to female excess (Sardinia, Oxford, and Santafe de Bogotá). No populations showed a female excess in incidence (18).

Racial/Ethnic and Geographic Differences

Type 1 diabetes mellitus occurs most commonly in Caucasians throughout the world. In general the highest rates are found among Caucasians living in Northern Europe and the lowest for Japanese living in Japan.

Migrant studies are useful to help determine if populations maintain or change their risk for a disease when they immigrate to a new area with either a lower or higher incidence of the disease. Migrant populations may retain their ranking of risk for diabetes; it may be increased or decreased. If the incidence changes for a particular migrant population, environmental factors may be implicated in the change in incidence. Unfortunately there are few migrant studies on Type 1 diabetes (18). In a study reported from Montreal, Canada, local residents of French descent had lower incidence of T1DM than British descendents, but higher than the rates reported from French residents in France. (29)

Socioeconomic Status

The incidence of type 1 diabetes mellitus may be slightly higher in the upper socioeconomic classes (29;45-47).

Seasonality

In the Northern Hemisphere, the incidence declines during the warm summer months; similarly in the Southern Hemisphere, the seasonal pattern exhibits a decline during the warm months of December and January, suggesting a climatic factor (48). Due to the long prodrome of type 1 diabetes before the diagnosis of the disease, the seasonal pattern is usually interpreted to mean that a precipitating factor may be increased during these seasons. Thus any number of factors may be involved; possible infectious agents more common in cooler months, changes in diets, exercise and hormonal levels. This seasonal pattern appears to occur only in older children (49;50), suggesting that factors triggering diabetes may be related to school attendance (7).

A study by Helgason and Jonasson also looked at seasonality of birth and found that Icelandic males with an onset in childhood were more likely to have been born in October. They surmised that this might be due to parental consumption of mutton in the New Year, which is rich in nitrosamines(51).

1.4 Genetics and T1DM

The importance of genetic factors has long been identified in type 1 diabetes. Numerous twin and family studies have confirmed that genetic factors are very important in the etiology of T1DM. As mentioned previously, in higher incidence countries the familial risks of developing the disease are ~7% if the father has T1DM, ~2% if the mother has T1DM, and ~3-6% for a sibling with T1DM (10).

Identical twins of patients with T1DM have an overall risk of ~50% of developing T1DM. The risk varies dramatically with the twin's age of onset of development of diabetes. If the twin develops diabetes before age five, the identical twin's risk is greater than 50% however if the twin develops diabetes after age 25 the risk is around 10%(52).

At least 20 different chromosomal regions have been linked to T1DM susceptibility in humans, using genome screening, candidate gene testing, and studies of human homologues of mouse susceptibility genes. The largest contribution from a single locus (IDDM1) comes from several genes located in the MHC complex on chromosome 6p21.3, accounting for at least 40% of the familial aggregation of this disease (53;54). Approximately 30% of T1DM patients are heterozygous for HLA-DQ2/DQ8 (HLA-DQA1*0501-DQB1*0201/DQA1*0301-DQB1*0302)(55). A particular HLA-DQ6 molecule (HLA-DQA1*0102-DQB1*0602) is associated with dominant protection from the disease. Less than 1% of children with T1DM have this molecule(56) (57-59).

Independent confirmation of IDDM2, located on the insulin gene (chromosome 11p15.5) has been achieved in both case-control and family-based studies whereas associations with the other potential IDDM loci have not always been replicated (60-63).

1.5 Autoimmune Associations and T1DM

Insulin autoantibodies (IAA) are usually the first autoantibody to appear in children followed from birth, and they can appear in the first six months of life (64;65). Once insulin autoantibodies appear in such young children there is a high risk of development of additional anti-islet autoantibodies (ICA) and progression to diabetes. More than 90% of children developing T1DM prior to age 5 have insulin autoantibodies while less than 50% of children developing diabetes after age 12 have such autoantibodies (66). Insulin therapy with human insulin can also induce insulin antibodies that cannot be distinguished from insulin autoantibodies. Autoantibodies measured in the first 9 months of life may be trans-placental in origin (66).

A single autoantibody is associated with only a modest risk of progression to diabetes. When two or more anti-islet autoantibodies are present (of GAD, ICA, or IAA) the risk of progression to diabetes is very high, exceeding 75% with a 10-year follow up (67;68). Following the development of diabetes, ICA and GAD autoantibodies decrease over time.

Following islet or pancreatic transplantation autoantibodies can resurge (69). Not all individuals with two or more autoantibodies are destined to progress to T1DM (67;68).

It has been well documented that patients with T1DM and their relatives have an increased risk of autoimmune disease especially autoimmune thyroid disease (Hashimoto thyroiditis, Grave Disease), Celiac Disease (gluten enteropathy), Addison Disease, pernicious anemia, vitiligo and myasthenia gravis(3). Patients with T1DM are routinely screened for thyroid disease, and are investigated for other autoimmune disorders when clinically indicated.

1.6 Environmental factors and T1DM

Foods and Food Additives

1.6.1.1 Cow Milk Proteins and Duration of Breast Feeding

It has been hypothesized that cow's milk exposure in early infancy is associated with the development of T1DM. Countries that consume large amounts of cow's milk per capita also tend to have higher incidence of T1DM(70;71).

Experiments in the Biobreeding (BB) rats and Non-obese diabetic (NOD) mouse have shown cow's milk protein to be harmful to beta cells. These studies have shown that by removing the protein from the animals diet the risk of diabetes was reduced (72).

Newly diagnosed children with T1DM have higher levels of IgA antibodies to bovine serum albumin (BSA), beta-lactoglobulin and IgG antibodies to beta-lactoglobulin (73;74). The bovine serum albumin hypothesis is interesting. BSA is similar to islet protein p69. It is hypothesized that there is a misdirected immune response targeted at the BSA but re-directed towards the islet cells (74).

Some studies, but not others, have suggested a dose-response relationship between the duration of breast-feeding and protection from type 1 diabetes (75). Breast-feeding may be associated with a delay in the introduction of

diabetogenic substances present in formula, or early childhood diet. Two meta-analyse including 13 case control studies have reported a higher incidence of T1DM if breastfed less than 3 months (OR 1.37, 95% CI 1.22 to 1.53) and if supplemented cow's milk less than 3 months of age (OR 1.57, 95% CI 1.19 to 2.07) (70;76;77), but a subsequent meta-analysis reported much lower risk estimates (77). To resolve this controversy, a dietary intervention trial to prevent T1DM by a short-term elimination of cow's milk from infant diet (TRIGR study) is underway (78).

1.6.1.2 Nitrosamines and Nitrates in Drinking Water

Experimental animal research has shown that nitrosamine compounds are toxic to the beta cell, probably through the reduction of nicotinamide adenine dinucleotide (NAD+) content of cells (79;80). Also, streptozotocin, which is a nitrosourea compound, is beta-cell toxic and produces insulitis in mice (81);(82).

A descriptive study from Iceland showed a clustering of birth dates indicating a possible association between the incidence of T1DM and the consumption of nitrosamines rich food by pregnant mothers(51). A case-control study showed a dose-response relationship between the risk of T1DM and the frequency of intake of food containing nitrosamines (83).

As well an ecological study from Colorado showed a correlation between the incidence of T1DM and the content of nitrate in drinking water(84). A Finnish study found an association with maternal and children's consumption of nitrites but no association with dietary nitrates. They concluded that higher consumption of dietary nitrites during childhood is associated with a 2.3-fold increased risk of developing T1DM (85).

Viral Infections

Viral infections have been implicated in the etiology of T1DM for over one hundred years. It is hypothesized that a virus may cause a cytolytic effect on the pancreatic beta cell or that the virus triggers an autoimmune process and by "molecular mimicry," antibodies that are triggered by the virus may bind to similar structures on the beta cell, allowing the immune system to attack the pancreatic cells. Viral infections may also be related to the onset of clinical symptoms of diabetes. An acute infection may stress the remaining islet cells of a child in the prodromal stage of the disease, thereby hastening the onset of overt diabetes.

Congenital rubella infection is associated with an increased risk of T1DM, and can also lead to other autoimmune disorders (e.g. Thyroid autoimmunity). While Congenital Rubella Syndrome (CRS) is responsible for a minute proportion of T1DM it provides an example of viral persistence leading to type 1 diabetes. The incubation period of T1DM in CRS patients is 5-20 years (86). "Molecular mimicry" has been reported between a rubella virus protein and a 52 kD ß-cell auto antigen (87).

Enteroviruses have been most strongly linked to human type 1 diabetes, but convincing proof of causality remains elusive (88). Enteroviruses include the group of polioviruses, coxsackie viruses and echoviruses. Investigators have associated antibodies to Coxsackie viruses and coxsackie viral RNA with T1DM. Several case-control studies have compared the prevalence of enteroviral antibodies in children with T1DM and non-diabetic controls (89). A study from Finland has shown that enterovirus infection may be associated with the activation of anti-islet autoimmunity as measured by anti-islet antibodies (90-92). Coxsackie virus B could initiate ß-cell autoimmunity through "molecular mimicry" between CBV (Coxsackie virus B) P2-C protein and GAD (93).

Studies from Finland (90)and Sweden(94;95) have suggested in-utero enteroviral infections can lead to type 1 diabetes in a significant proportion of cases. Other viruses studied to date include mumps virus, cytomegalovirus and rotavirus.

Antenatal/Perinatal Factors

The pathogenic process leading to T1DM may begin early in life, even in utero. A Swedish nationwide study looking at perinatal variables of 2,757 infants who developed T1DM between 1978-1988 indicated that several odds ratios were increased especially in the 0-4 age group. Those included maternal age over 35, and maternal-child ABO blood group incompatibility. It was concluded by the authors that an early immunological event due to maternal-child blood group incompatibility, known to be associated with neonatal beta-cell dysfunction, represents an increased risk for T1DM in young children.(96;97).

Increased Growth Rate

An increased growth rate in childhood is an associated risk factor for the development of T1DM. A case-control study using prospectively recorded length-weight charts from birth on, showed that children who later developed T1DM had an increased growth rate several years before onset and that a high growth rate was a significant risk factor. The authors concluded that rapid linear growth is a risk factor for T1DM in childhood, and may either be a promoter of T1DM or be a marker of a physiological mechanism that affects both growth and the pathogenesis of T1DM (98).

Insufficiency or Deficiency of Vitamin D

It has been observed that there may be a correlation between vitamin D metabolism and autoimmune disease, including type 1 diabetes(99). In vitro, vitamin D acts as an immunosuppressive agent, reducing lymphocyte proliferation

and cytokine production (100). In animals, the administration of vitamin D (1,25 (OH)2 D3) seems to prevent development of type 1 diabetes (101;102). Correlations between genetic markers of vitamin D (vitamin D receptor and vitamin D binding protein alleles) and the risk of type 1 diabetes have been described in different populations (99;103-106).

A study by Dalquist et al. found that infants who received vitamin D supplementation in their first months of life had a lower incidence of T1DM (106). A similar protective association was seen in a population-based case control study when cod liver oil was given during pregnancy and subsequently there was a lower risk of T1DM in the offspring (107). A large prospective birth-cohort study published in 2001 by Hypponen et al. in Northern Finland showed that the relative risk of developing type 1 diabetes by age 30 among children who were given daily vitamin D supplements during infancy was much less than those infants who had not received vitamin D supplements (108).

1.7 Summary

Immunologic, genetic and epidemiologic research during the past 2 decades has tremendously increased the knowledge with respect to the pathogenesis of T1DM. A pattern of interactions between genetic prerequisites and environmental triggers is emerging where multiple different exposures at different times may be operating to initiate an autoimmune destruction of pancreatic beta cells.

The incidence of childhood T1DM is known to vary widely between and within countries (18). In most populations the incidence has been increasing in a linear pattern since the mid-1950's (19).

2 Chapter 2: Purpose, Significance and Research Questions

2.1 Purpose

The aim of the present study was to determine the incidence of T1DM in children aged 0-14 years living on the Avalon Peninsula, Newfoundland from 1987-2002.

2.2 Significance

It was suspected that there were a high number of cases of T1DM patients being treated at the study center hospital as compared to the number of cases being treated in other tertiary care centres. It is important to verify the incidence in our population. Continued research to determine the reasons for such a high incidence is warranted and further study into our unique population may contribute to a better understanding of the etiology and pathogenesis of T1DM.

2.3 Research Questions

1. What is the incidence of T1DM in children less than 15 years of age on the Avalon Peninsula, Newfoundland, between 1987 and 2002?

2. Is the incidence of T1DM in children less than 15 years of age on the Avalon Peninsula changing over time?

3. What are the demographic characteristics of children (0-14 years) with T1DM (male: female ratio, age of onset, month of onset, birth month)?

4. What is the prevalence of T1DM in first-degree family members of probands with T1DM?

3 Chapter 3: Methods

3.1 Research Design

This prospective study was performed at the Janeway Children's Hospital, which is the only tertiary care children's hospital servicing the Province of Newfoundland and Labrador. All children with T1DM who live on the Avalon Peninsula are followed from the time of diagnosis at the Janeway Pediatric Diabetes Clinic where comprehensive clinical records are retained. This area was chosen for a study of the incidence of diabetes because it is well defined geographically and there is only one pediatric diabetes clinic for the area. This enabled confidence about the degree of ascertainment achieved. Also, forty-six percent of the childhood population of Newfoundland lives on the Avalon Peninsula(109;110). Other epidemiologic information collected on the population included sex ratios, month of onset of diabetes, month of birth, and age of onset.

Classification and Case Definition

The diagnosis of T1DM was confirmed based on current guidelines from The Canadian Diabetes Association classification of diabetes and diagnostic criteria. The diagnostic criteria for diabetes includes a fasting (no caloric intake for at least 8 hours) glucose >7.0 mmol/L or a casual plasma glucose ≥ 11.1 mmol/L with the classic symptoms of diabetes which are polyuria, polydipsia and unexplained weight loss. Also an elevated 2-hour plasma glucose ≥ 11.1 mmol/L in a 75-gram oral glucose tolerance test is diagnostic(3).

Inclusion Criteria

Patients included were those <15 years at the time of diagnosis of Type 1 Diabetes Mellitus and were living on the Avalon Peninsula, NL.

Exclusion Criteria

Patients excluded were those with Type 2 diabetes, Maturity Onset Diabetes of Youth (MODY), transient hyperglycemia, and diabetes caused by chemotherapy or cystic fibrosis. A small percentage of patients with diabetes diagnosed <15 years have type 2 diabetes mellitus. The pediatric endocrinologist or diabetologist normally identifies those patients. Patients with suspected and confirmed type 2 diabetes mellitus (patients with obesity, acanthosis nigricans, polycystic ovarian syndrome, metabolic syndrome with hypertension, obesity, and hyperlipidemia, and those from a high-risk ethnic group i.e. First Nations Children) were excluded. Although there are some First Nations patients with diabetes followed at the JCHCC Diabetes clinic, there were none included in this study because they were not living on the Avalon Peninsula (occasionally patients travel to the clinic from Labrador for medical care).

Case ascertainment

From 1987 to 2002, all newly diagnosed children with T1DM were admitted to the Janeway Hospital and were subsequently followed at the Hospital Clinic. Subjects included in this study were ascertained from three independent sources. First, subjects were ascertained from the diabetic register for T1DM, which was kept at the Janeway Hospital by the diabetic nurse educator from 1987 onwards. This list was collected prospectively. Next, research nurses carried out a search of the Hospital Medical Records Department using the diagnostic index code for insulin dependent diabetes from

1987 – 2002. Subjects were also ascertained from the office records of pediatricians who cared for patients with diabetes. The latter two lists were collected retrospectively. Using the previous three sources a master list of all patients with T1DM was established. The Research Nurse reviewed all charts obtained from the various sources described. Using a data abstraction form, basic demographic details were reported including the child's name and sex, date of birth, date of diagnosis and address at diagnosis. The geographical address of the child at the time of diagnosis was recorded and confirmed to be located on the Avalon Peninsula.

Finally, a registry for the Provincial Diabetes Camp was obtained from years 1987-2002 from the provincial diabetes camp director. All camp participants with addresses on the Avalon Peninsula were identified and matched to those from the master list compiled by the JCHCC research nurse. One hundred percent ascertainment was confirmed using the capture-recapture method (see section 1.2.1.7) (111). (All cases that were on the diabetes camp list were also on the list compiled by the research nurse as explained in the previous paragraph.)

Incidence study population

The denominator for the analysis was a child less than 15 years of age with residency in the study area, which is defined geographically to correspond with census boundaries. The data described is incidence per 100,000 of the age-specific population. The overall size of the population was obtained from census data (109). These are published by Statistics Canada, a department within the Government of Canada. A national census is performed every five years and was undertaken in 1991, 1996, and 2001. This is performed by a Census of Population Questionnaire, which is sent to all Canadian households. Population figures between census years are extrapolated according to population trends.

Family History Information

A complete first-degree family history was collected on all available families, which included history of type 1 diabetes mellitus, date of diagnoses and age of diagnosis. This information was obtained using a family history

questionnaire (Appendix A & C), telephone or personal interview. Parents were asked to fill out the questionnaire. The information was reviewed via a telephone interview with a research nurse. The investigator, using the family history questionnaire developed by the World Health Organization for the DiaMOND Study as a template, developed the questionnaire.

3.2 Statistical Analysis

The incidence was calculated as the number of newly diagnosed subjects per 100,000 persons per year in the age group 0 – 14 years and in 5-year age groups (0-4, 5-9, and 10-14 years), and 95% confidence intervals calculated. Comparisons were made between males and females. Descriptive analysis and chi square analysis was performed on other demographic data.

3.3 Ethical Considerations

The Memorial University of Newfoundland and Health Care Corporation of St. John's Ethics Committees approved the study.

All patient information entered into our database was kept strictly confidential. Probands and family members were assigned pedigree numbers to avoid using family names and to keep this information strictly confidential. Identifying information is kept separately and securely, accessible only to the investigator and research nurse coordinator. Consent was obtained from parents for the family questionnaires.

4 Chapter 4: Results

4.1 Results

Incidence

A total of 294 new cases of T1DM were identified among children ages 0 – 14 years during the study period. The overall incidence per 100,000 persons per year over the period 1987–2002 was 35.93 with a 95% confidence interval of (32,40), for the Avalon Peninsula, Newfoundland. See table 4 for the mean incidences for the various age groups, males and females. See table 5 for raw data used to calculate incidence.

The incidence per year for the age group 0-14 years from 1998 to 2002 has remained above 40/100,000. (Table 4) The linear regression model fits well for the data of the incidence of males and females on years, with p-value less than 0.01. The value of the correlation coefficient between the total incidence and years is 0.7. The estimated rate at which the incidence is increasing per year in this population over the period 1987-2002 using the linear additive regression model is 1.25 per 100,000 per year.

The incidence in the 0-14 year age group was 31.30/100,000 per year (1987-1991); 32.68/100,000 per year (1992-1996); 43.45/100,000 per year (1997-2001). There is a statistically significant increase in the third time period as compared to the first two time periods.

The incidence for the 0-4 year age group was 24.95, 5-9 year age group was 37.01, and 10-14 year age group was 43.62 per 100,000 respectively (figure 2). The yearly incidence for the 0-14 age group is depicted in Figure 3.

Male: Female Ratio

There was no significant difference between the incidence of 36.15 for males and 35.69 for females during this 16-year period with a p-value of 0.752. The corresponding Z-score was –0.316 (figure 4).

Age of onset

Figure 5 shows the age of onset of T1DM. There was only one case of T1DM onset < 1 year of age. The age of onset depicts a bimodal distribution with the first peak at 4 years of age and the second peak at ages 9-12 years.

Month of Onset

Figures 6 and 7 refer to the month of onset of T1DM. July had the fewest cases. When the month of onset was categorized into season of onset there were fewest cases in the summer season (June, July, August) however this was not statistically different than the other seasons (chi square analysis, P=0.11).

Birth Month

Figures 8 and 9 refer to the birth month of patients and the fewest probands were born in April, the most in June. When the birth month of patients was categorized into seasons, fewer probands were born in winter (December, January, February) and spring (March, April, May) as compared to summer and fall, however they were not statistically significant (chi square analysis p=0.12).

Prevalence in 1st Degree Family Members

Table 6 lists the number of cases of T1DM in 1st degree family members and the prevalence of the disease in siblings and parents. Sufficient information to assess the prevalence if T1DM in family members was available for 200 of the 294 probands. Those with inadequate information included families with incomplete family history information and those who chose not to participate with family history information.

Table 4. Incidence of Type 1 diabetes (0-14 years) per 100,000 persons, Avalon Peninsula, NL, Canada, 1987-2002.

Year	M/F	0-14 years	0-4 years	5-9 years	10-14 years
87-02	M&F	35.93	24.95	37.01	43.62
87-02	Male	36.15	28.65	35.23	42.83
87-02	Female	35.69	21.13	38.85	44.46
87-91	M&F	31.30	22.96	23.83	45.23
92-96	M&F	32.68	23.29	40.74	32.80
97-01	M&F	43.45	31.21	48.40	48.21
1987	M&F	38.86	33.23	35.39	46.83
1988	M&F	27.44	28.15	05.14	47.39
1989	M&F	20.84	17.32	20.65	23.95
1990	M&F	28.22	17.55	15.68	48.82
1991	M&F	41.26	17.79	42.60	59.73
1992	M&F	27.20	36.14	16.17	30.01
1993	M&F	33.15	24.65	49.30	25.22
1994	M&F	35.97	19.23	34.09	50.96
1995	M&F	41.02	27.13	81.40	15.58
1996	M&F	26.15	07.09	23.89	42.42
1997	M&F	37.49	14.75	31.12	59.83
1998	M&F	45.16	60.87	25.91	50.21
1999	M&F	44.42	15.69	67.11	46.05
2000	M&F	43.22	39.69	55.91	35.18
2001	M&F	47.56	24.92	65.86	48.93
2002	M&F	47.56	16.61	43.91	73.39

Table 5. Number of new cases of Type 1 diabetes with mid-year population for age groups (0-4, 5-9, 10-14 years), Avalon Peninsula, NL

			1987-1991	1992-1996	1997-2001	Total
Males	0-4	New cases	13	10	12	35
		Mid year population	44,266	39,212	32,508	115,986
	5-9	New cases	8	21	18	47
		Mid year population	48,214	45,003	37,895	132,112
	10-14	New cases	16	21	21	58
		Mid year population	53,901	49,776	44,443	148,120
	0-14	New cases	37	52	51	140
		Mid year population	147,381	133,991	114,846	396,218
Female	0-4	New cases	7	8	8	23
		Mid year population	42,834	38,070	31,579	112,483
	5-9	New cases	15	15	18	48
		Mid year population	47,297	43,356	36,530	127,183
	10-14	New cases	31	11	21	63
		Mid year population	50,002	47,778	42,676	140,456
	0-14	New cases	53	34	47	134
		Mid year population	140,133	129,204	110,785	380,122
Total	0-4	New cases	20	18	20	58
		Mid year population	87,100	77,282	64,087	228,469
	5-9	New cases	23	36	36	95
		Mid year population	86,511	88,359	74,425	259,295
	10-14	New cases	47	32	42	121
		Mid year population	103,903	97,554	87,119	288,576
	0-14	New cases	90	86	98	274
		Mid year population	287,514	263,195	225,631	776,340

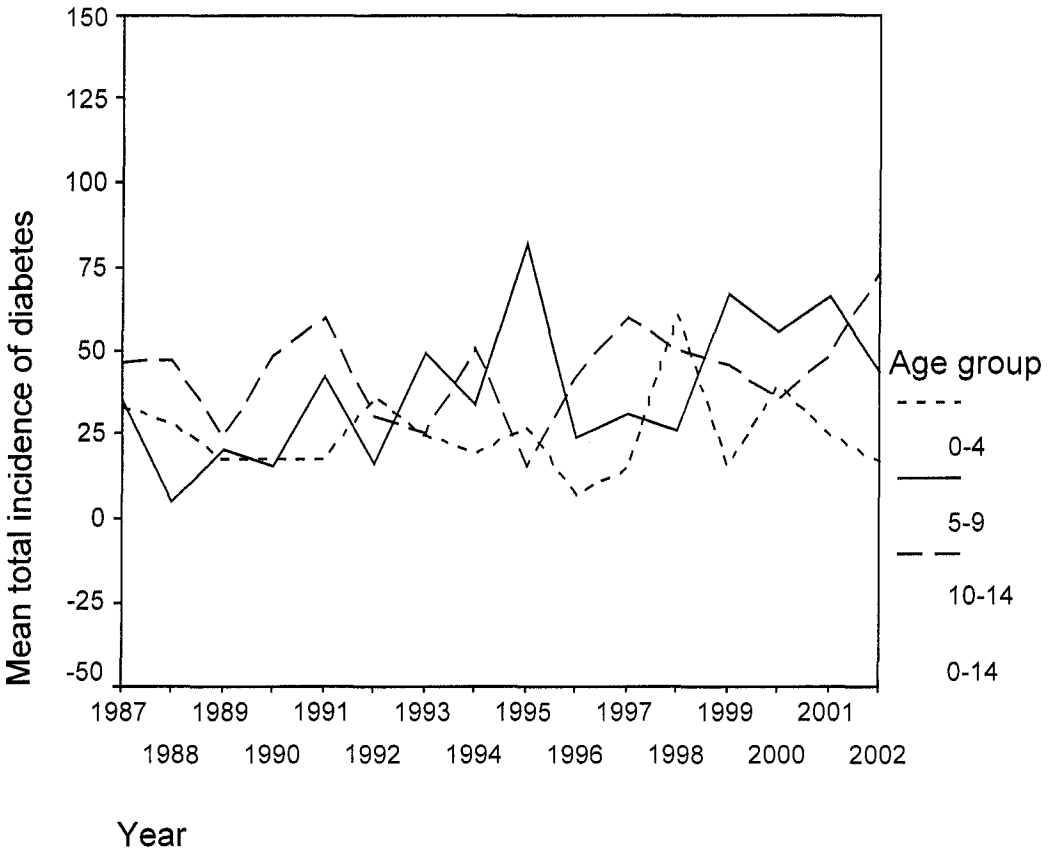

Figure 2. Incidence of T1DM per age group (0-4 years, 5-9 years, 10-14 years)

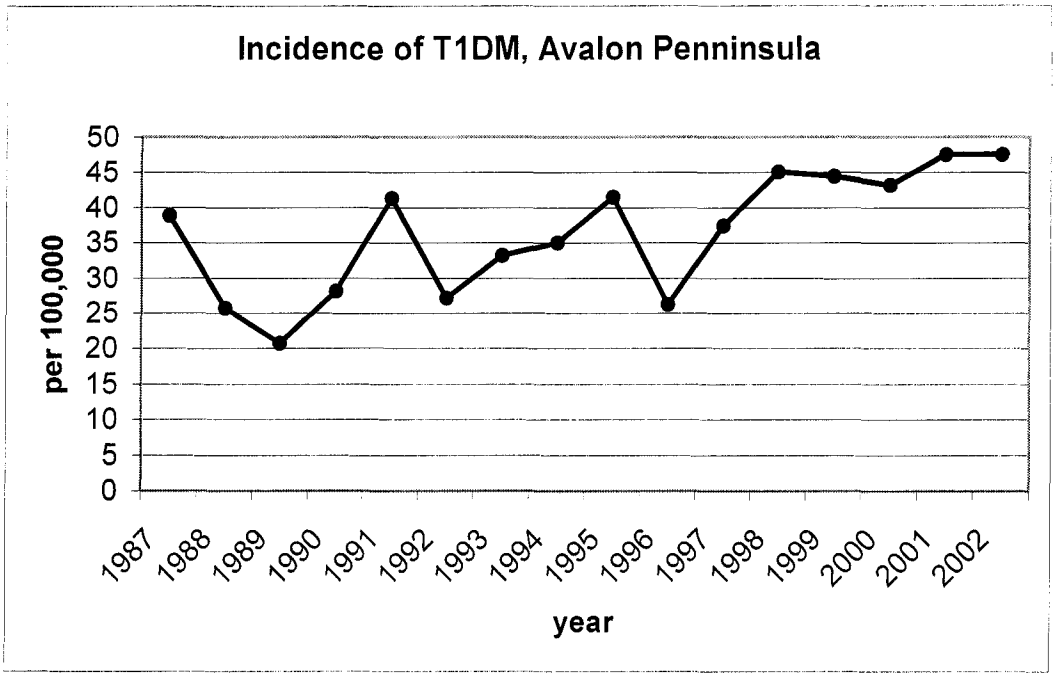

Figure 3. Annual incidence of T1DM 0-14 years 1987-2002 per 100,000 population, Avalon Peninsula, NL

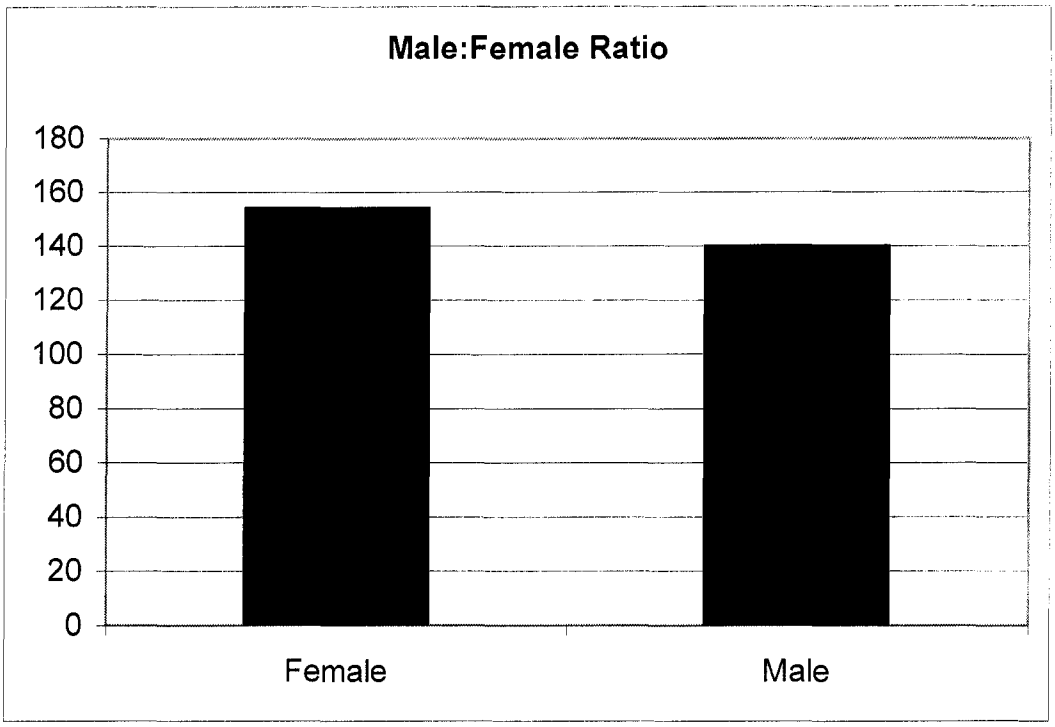

Figure 4. Male: Female Ratio

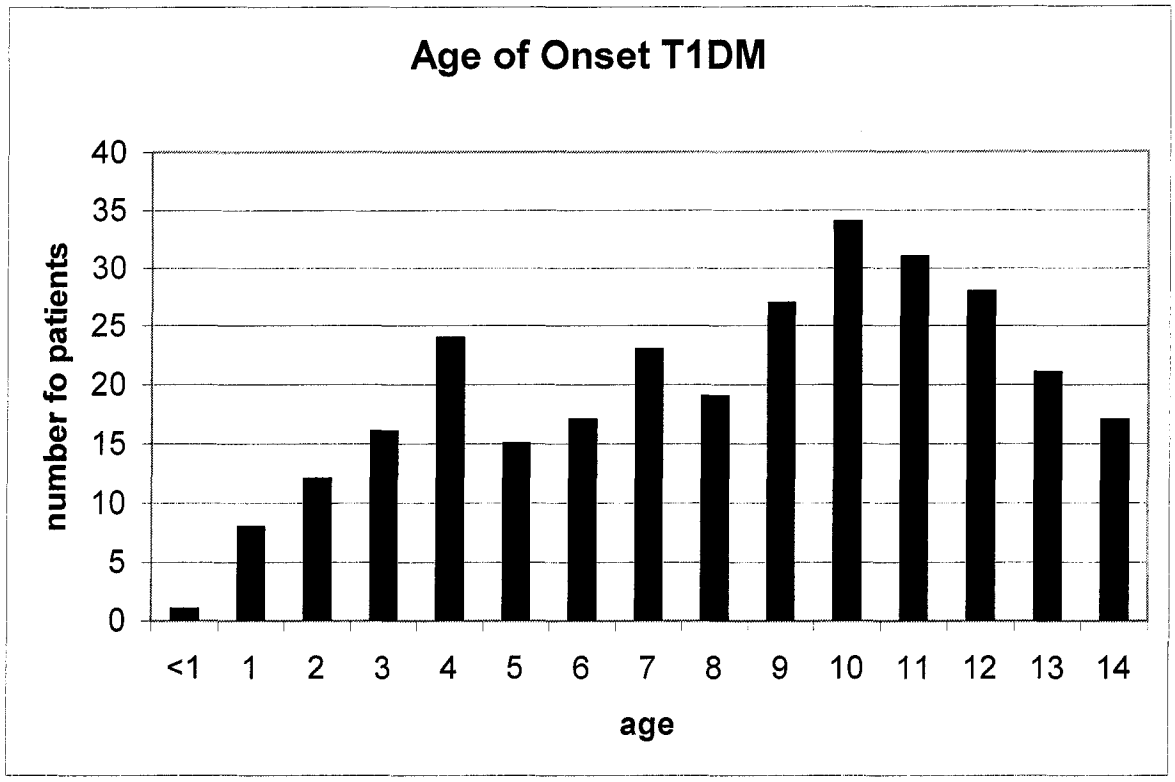

Figure 5. Age of Onset T1DM

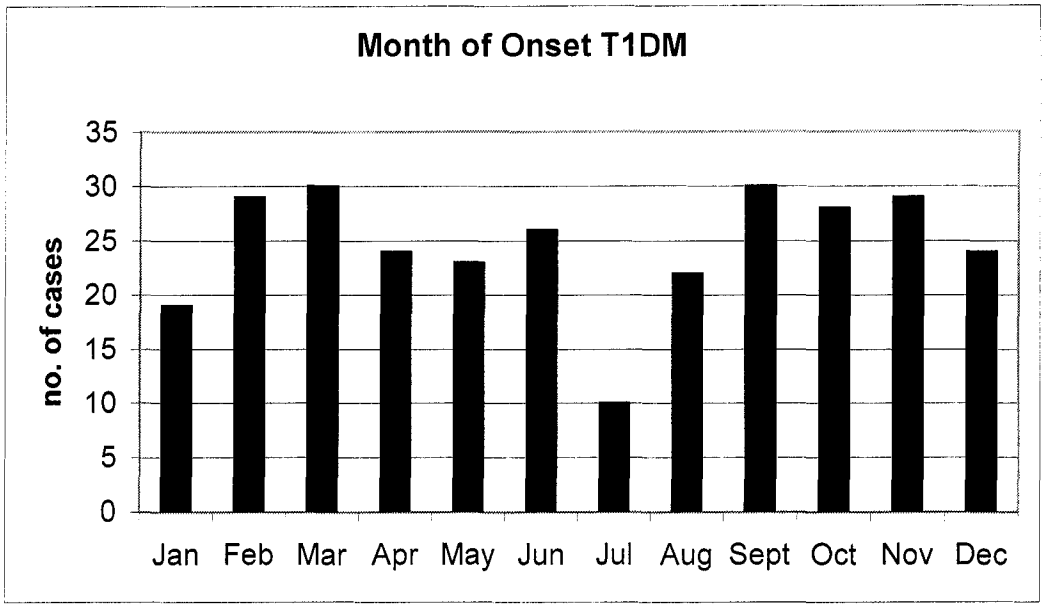

Figure 6. Month of Onset T1DM

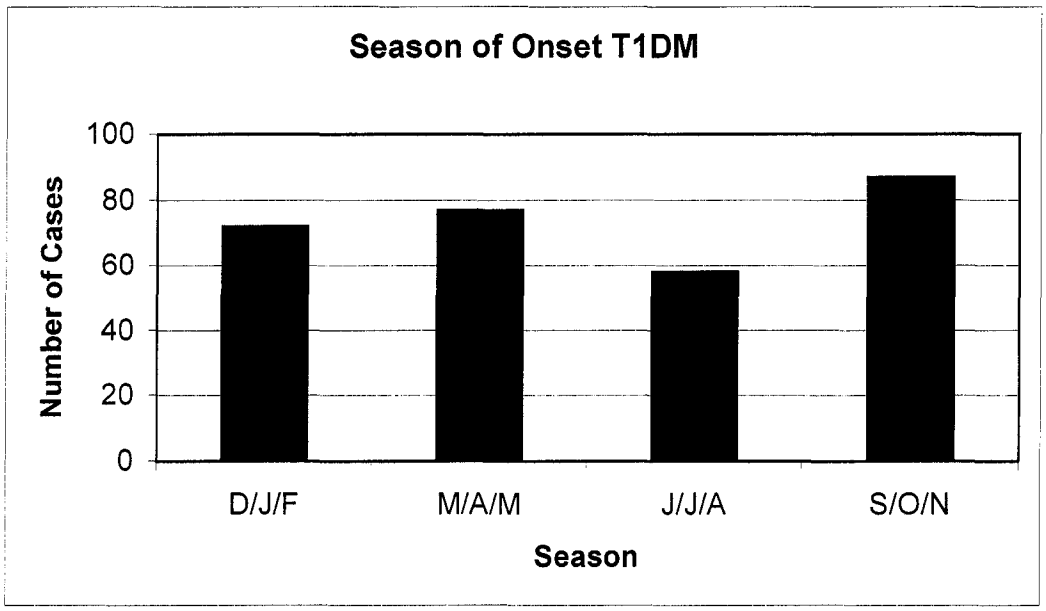

Figure 7. Season of Onset T1DM

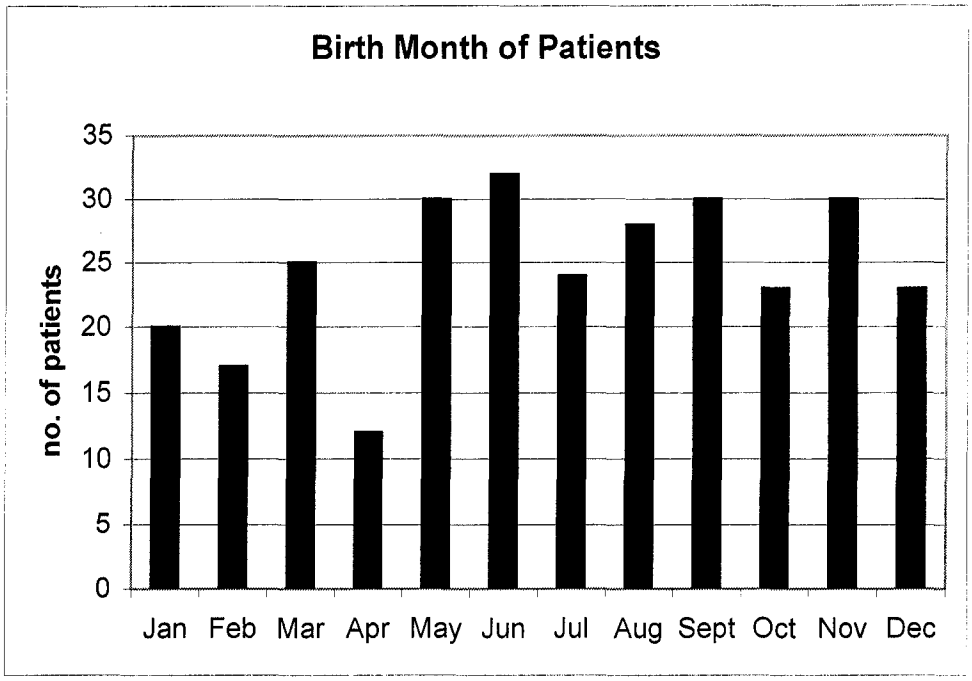

Figure 8. Birth Month of Probands with T1DM

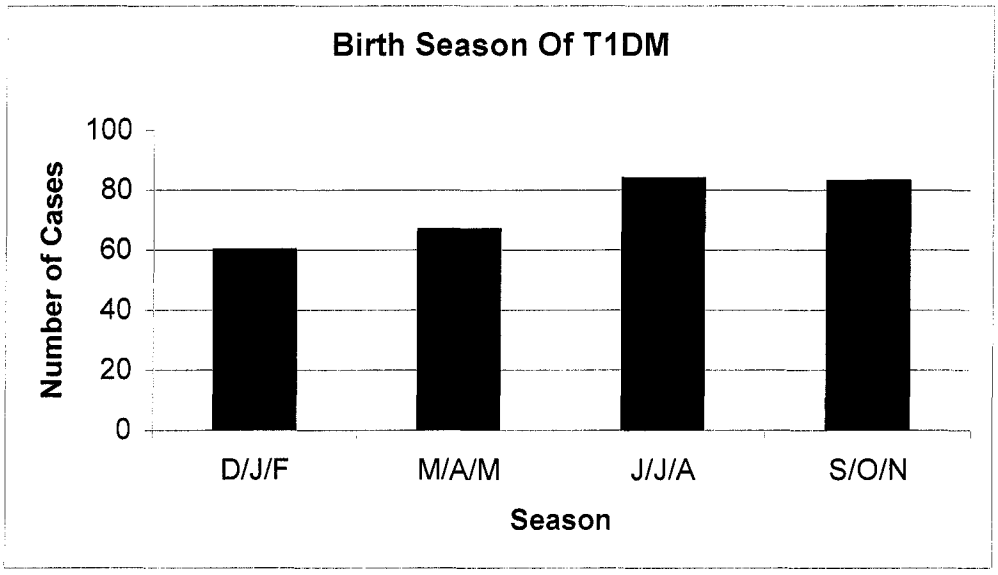

Figure 9. Season of Birth of Probands with T1DM

Table 6: Prevalence of T1DM in 1st degree family members

	Total (N)	Number Affected with T1DM (n)	Prevalence of T1DM in 1st degree family members (%)
Probands	N=200	N=200	
1st degree family members	N=711	N=25	3.6
Mothers (including 5 stepmothers)	N=205	N=3	1.5
Fathers (including 18 stepfathers)	N=218	N=8	3.7
Sisters (including 14 stepsisters)	N=155	N=9	5.8
Brothers (including 12 stepbrothers)	N=133	N=6	4.5
Total Siblings	N=288	N=15	5.2

5 Chapter 5: Discussion, Summary, Limitations, Implications

5.1 Discussion

This current study represents an analysis on the population of children 0-14 years with T1DM from the Avalon Peninsula of Newfoundland, confirming the high and increasing incidence over the 16-year study period. The incidence from 1987 to 2002 was 35.93/100,000, one of the highest reported worldwide. Over the study time frame the incidence was variable with peaks every 3 to 4 years, except for the last 5 years when it has remained more than 40/100,000.

The incidence is increasing. Comparing 3 different 5-years time intervals the incidence has increased from 31.30/100,000 (1987-1991), to 32.68/100,000 (1992-1996), to 43.45/100,000 (1997-2001). This represents a 39% increase from the 1st and 3rd time intervals.

The incidence differs between the three age groups: 24.95/100,000 (0-4 years); 37.01/100,000 (5-9 years); and 43.62/100,000 (0-14 years). This pattern of increasing incidence with age concurs with the worldwide literature. The incidence is increasing over the study period, with the highest increase in the 5-9 year age group (Table 4). Incidence studies elsewhere has suggested the highest increase in the 0 to 4 year age group(39).

With respect to the age of onset, there is a peak at age 4, then at ages 9-12 years. The worldwide literature also reports a bimodal distribution with peaks at ages 4-5 years and 10-14 years(18). This is similar to our findings although the peaks appear to be occurring at slightly younger ages. This difference may be due to the small sample size. It is hypothesized that the bimodal distribution of disease onset in T1DM may be due to different etiologic factors occurring at different ages. The disease in younger children may be due to genetic factors and/or related to environmental factors occurring in-utero or during the first few years of life. The later peak in onset may be due to pubertal hormones, changes in diet or exercise, or may be related to school attendance.

Most populations worldwide have shown that males and females have a similar risk for developing the disease, concurring with our results. The incidence has an increasing trend in all age groups for both males and females.

Worldwide, there is a wide variation in the incidence among various populations. In addition there is a general increase in the incidence of T1DM in many European(112) and Middle Eastern countries(19), which is confirmed in our population.

5.2 Hypotheses: Why is the Incidence Very High in NL population?

5.3 Increased Genetic Susceptibility

5.3.1.1 The Newfoundland Population

The current Newfoundland population is composed mainly of descendants from around 20,000 English and Irish immigrants who settled there in the mid 1700's (113). The cod fishery spurred the settlement of Newfoundland, which occurred particularly in the late 18th and early 19th centuries. Immigrants came from primarily two main areas, Southwest England and Southeast Ireland. By the mid-1830's the major migrations had concluded and the population of Newfoundland was about 75,000. Following this, natural increase became the mechanism for population growth. Other factors, including geographic isolation, lack of roads, segregation by religion and limited immigration and emigration kept related families together. In 1982 fifty percent of the population lived in communities less than 2500, and forty-one percent in communities of less than 1000. The Newfoundland population can be considered to have relatively homogeneous origins as a result of how the population was settled and expanded (114). Founder effects have been identified in several other diseases in this population (115;116) and it is hypothesized that this may also be the case for T1DM, perhaps accounting for high incidence in the Avalon Peninsula. It does not explain the rising incidence over a relatively short period, therefore implicating environmental factors causing a rise in a genetically at risk population.

5.4 Early Infant Diet

The early infant diet may be related to the risk of developing T1DM. . Breastfeeding for > 3 months may be protective against type 1 diabetes mellitus (76). Breastfeeding has protective effects, reducing enteric infections early in life. Early introduction of cow's milk protein into an infants diet may possibly be harmful (117). Breastfeeding rates in Newfoundland and Labrador for initiation and duration are the lowest in Canada. In 2001, initiation rates were 58%. After 3 months only 48% of mothers were still breastfeeding and after 6 months this drops to 27% (118), however the rate of breastfeeding initiation has increased gradually over the same study period from 39% (1992) to 58% (2001) (119).

5.5 Insufficiency or deficiency of Vitamin D

It has been observed that there may be a correlation between vitamin D metabolism and autoimmune disease, including type 1 diabetes (99). Correlations between genetic markers of vitamin D (vitamin D receptor and vitamin D binding protein alleles) and T1DM have been described in different populations. (26;99;103-105;107;108)

Most of our vitamin D is produced endogenously when the skin is exposed to sunlight. Latitude is an important factor, which affects the angle at which sunlight penetrates the atmosphere. Less vitamin D is produced in the skin during winter months, especially in northern areas (120). St. John's is the capital city of NL, and lies within the Avalon Peninsula. St. John's has a northern latitude (47°37' N) with less hours of sunlight than most areas of Canada. Of all the major Canadian cities, St. John's is the foggiest, snowiest, and cloudiest(121). Less sunlight may potentially mean less effective vitamin D synthesis. Other lifestyle changes, such as fewer hours outdoors, advice to keep babies and children out of the sun, and use of sunscreen on infants and toddlers, may also be affecting vitamin D synthesis.

Vitamin D insufficiency may be an added risk factor for Newfoundland children who are genetically at risk. Other possible environmental factors may include short duration of breast-feeding and early introduction of cow's milk protein. Risk factors such as infections are not specific to Newfoundland children. Due to the genetically homogenous population

of Newfoundland, genetic predisposition likely plays a significant role contributing to the high incidence. However the increasing incidence over the last 14 years is likely due to unknown environmental factors.

5.6 Study Strengths

There are several strengths in this study. This study is straightforward and has accurately determined the incidence of T1DM in the Avalon Peninsula, Newfoundland. Incident cases were recorded prospectively since 1987, giving added strength to the study design. Although this study did not include information on the entire province (this is being done prospectively since 2000) almost one-half of Newfoundland children live on the Avalon Peninsula. Early data from our province-wide study suggests the incidence is very similar across the province.

We are very confident that we have excellent ascertainment. This is in part due to the study centre being the only Pediatric Diabetes Centre in the district. Also, there are no private pediatric services available in our province and all pediatricians that work in census district 1 are affiliated with the Janeway Hospital and all pediatric patients with T1DM are referred there. Capture-recapture analysis has confirmed one hundred percent ascertainment. Our research coordinator has traveled to the closest pediatric diabetes treatment centre (G.B. Cross Memorial Hospital, Clarenville, NL) and has reviewed the hospital charts as part of a province-wide genetic study. There were no pediatric patients (<15 years) with T1DM from census district 1 being followed at this hospital.

5.7 Limitations

The study of incidence on the Avalon Peninsula includes a relatively small sample size, making it impossible to draw firm conclusions with respect to some of the epidemiologic information that is usually examined on similar populations (i.e. Month of birth, month of onset, prevalence in family members). Once the province-wide data are available on approximately 1000 probands and their families we will re-analyze the data.

It is possible that there may be over-ascertainment of cases if a small minority of patients were classified as T1DM but are actually T2DM. There is occasionally some difficulty in distinguishing between T1DM and T2DM in young adolescents and the diagnosis becomes clearer in 2-3 years after initial diagnosis. We did exclude patients with suspected T2DM from our analysis. If over-ascertainment occurred, it would account for a tiny proportion of the probands and would not have significantly affected the overall high incidence. Under-ascertainment due to visibility bias is unlikely but possible for a few patients. There is one main treatment centre for pediatric diabetes in census district 1, which is at the study centre. There is another diabetes centre at the G.B Cross Memorial Hospital in Clarenville Newfoundland. As part of a province-wide genetic study our research coordinator has reviewed the charts from the Clarenville hospital and there were no cases of pediatric T1DM from district 1 being followed at this small centre.

The family history information was completed for 200 out of 294 families. Some families were lost to follow-up because of emigration from the area. Some families refused to participate or returned incomplete information. There may be self-selection bias for families with more than one family member with T1DM, increasing the overall prevalence of T1DM in family members. Once our province wide data is available we plan to calculate the recurrence risk for family members.

5.8 Implications and Directions for Future Research

Continued research to determine the reasons for such a high incidence is warranted. This research has provided the impetus for other studies that are currently underway or are in the planning stages. Examples of research studies that are currently in progress include a province-wide prospective epidemiologic study, which will document the incidence and collect further demographic data. Also, a large genetics study is underway which is in the process of recruiting 1000 probands and their families to study the genetics of T1DM in Newfoundland and Labrador. Blood samples are being collected and tested for several common and suspected T1DM loci and autoantibody analysis. More extensive pedigrees are being collected to include second-degree family members and multiplex families. We also hope to study some of the possible environmental factors that may be at play

including the possible role of Vitamin D insufficiency or deficiency. Our diabetes centre is also a study site for the TRIGER study looking at the role of early infant diet and its association with T1DM (78). It is our hope that further study into this unique population may contribute to a better understanding of the etiology and pathogenesis of T1DM.

Confirming the high incidence in our population has implications for our health care system, identifying a need for increased health care services for our patients and their families. Identifying this unique population as an area of high incidence will be important for initiating future research

5.9 Summary

Although the etiology of T1DM is unknown, it is proposed that environmental factors may be at play in genetically susceptible individuals, triggering an immune response that leads to the destruction of the pancreatic beta cell. The Avalon Peninsula in Newfoundland appears to have the highest incidence of childhood T1DM in North America, with recent incidence data approaching those of Finland and Sardinia. The incidence of T1DM has increased, especially over the last 5-year period. The high incidence is likely due to a combination of genetic and environmental factors.

APPENDIX A: Data Abstraction Form: Family History

PATIENT'S NAME: _____

D.O.B. _____

Genetics Study of Type 1 Diabetes
Family Medical History Form
Instructions

When completing the form, please indicate the following:
Any person who has died, and the reason, if known (include miscarriages and stillbirths)
Medical problems

Examples of medical problems are:

Type 1 Diabetes Mellitus
Type II Diabetes
Thyroid Disease
Asthma
Celiac Disease
Psoriasis
Crohn's Disease
Ulcerative Colitis
Heart Disease
High Blood Pressure
High Cholesterol
Peripheral Vascular Disease
Rheumatoid Arthritis
Congenital Rubella
Autism
Cystic Fibrosis
Parkinson's Disease
Down's Syndrome
Organ Transplant
Lupus
Myasthenia Gravis
Addison's Disease
Grave's Disease

Family Member	**Full Name (Including maiden name where applicable)**	**Spouses Name (Including maiden name where applicable)**	Sex	Date of Birth/Death	Medical Problems
Father					
Mother					
Patient's Name					
Sibling					
Sibling					
Sibling					
Sibling					

Grandparent Data

Patient's *Father's* Family

***Father's* mother's full name, including maiden name (paternal grandmother)**

_____

What community was she from? _____

Date of Birth/Death: _____

Illnesses: _____

***Father's* full name (paternal grandfather)**

_____

What community was he from? _____

Date of Birth/Death: _____

Illnesses: _____

Patient's *Mother's* Family

***Mother's* full name, including maiden name (maternal grandmother)**

_____

What community was she from? _____

Date of Birth/Death: _____

Illnesses: _____

***Mother's* father's full name (maternal grandfather)**

_____

What community was he from? _____

Date of Birth/Death: _____

Illnesses: _____

Paternal Aunt/Uncle Data

Father's Brothers and Sisters

Name	Date of Birth D/M/Y	Medical Problems	Spouse's Full Name (Including Maiden Name)	Children – Full name, including married/maiden name, DOB, spouses/children's name(s)

***Continue on back of sheet if necessary

Mother's Brothers and Sisters

Name	**Date of Birth D/M/Y**	**Medical Problems**	Spouse's Full Name (Including Maiden Name)	**Children – Full name, including married/maiden name, DOB, spouses/children's name(s)**

***Continue on back of sheet if necessary

Please note: We will not contact any family members listed except through their own diabetes clinic.

Other Family Members With Type 1 Diabetes Not Listed

Name_____DOB_____Hometown_____

_

Relationship_____

Name_____DOB_____Hometown_____

_

Relationship_____

Name_____DOB_____Hometown_____

_

Relationship_____

Name_____DOB_____Hometown_____

_

Relationship_____

Name_____DOB_____Hometown_____

_

Relationship_____

Name_____DOB_____Hometown_____

_

Relationship_____

Name_____DOB_____Hometown_____

_

Relationship_____

APPENDIX B: Data Abstraction Form: Patient Information

Newfoundland & Labrador Diabetes Data Abstraction Form Patient Medical Information
Patient Name:
Address: Street: City/Town: Province: Postal Code:
Chart # (MCP)
Pedigree # Family ID # Individual ID #
Sex: ☐ M ☐ F
DOB:
Age:
Location of Diagnosis: Hospital Name:
Attending Physician:
Family Doctor: Address:
Diagnosis: ☐ Type 1 Diabetes: ☐ Type 2 Diabetes: Other:
Date of Diagnosis:
Date insulin started:

Blood work at diagnosis: Glucose HbA1C ☐ PH ☐ Ketonuria ☐ Glucosuria
☐ DKA at diagnosis?
Symptoms at diagnosis? ☐ Hyperglycemia ☐ Weight loss ☐ Polyuria ☐ Polydipsia ☐ Bedwetting
☐ Allergies ☐ Medications List:
Admissions to hospital Admission date Discharge date Diagnosis DKA

APPENDIX C: Data Abstraction Form: Family Information

Newfoundland & Labrador Diabetes Data Abstraction Form Family Information
Fathers Name:
Mothers Name:
Marital Status: Mother: S □ M □ W □ D □ Sep □ CL □ Comments _____ Father: S □ M □ W □ D □ Sep □ CL □ Comments _____
Number of Siblings:_____
Sibling # 1
Sibling # 2
Sibling # 3
Sibling # 4
Sibling # 5
Sibling # 6
Sibling # 7
Sibling # 8
Twins
Adopted children
First degree relatives with T1DM Mother □ Sister □ Father □ Brother □
Relatives With Diabetes
Name: Relationship: Diagnosis: Age at diagnosis: Age insulin started: Complications:
Name: Relationship:

Diagnosis: Age at diagnosis: Age insulin started: Complications
Name: Relationship: Diagnosis: Age at diagnosis: Age insulin started: Complications:
Name: Relationship: Diagnosis: Age at diagnosis: Age insulin started: Complications:

APPENDIX D: Consent Form

FACULTY OF MEDICINE- MEMORIAL UNIVERSITY OF NEWFOUNDLAND

AND
HEALTH CARE CORPORATION OF ST.JOHN'S
Consent to Participate in Bio-Medical Research

TITLE: Genetic Study of Type I Diabetes in Newfoundland

INVESTIGATOR (S): Drs. Leigh Anne Newhook, Joseph Curtis, Andrew Paterson, Jane Danska and Carol Joyce

You (or your child or ward) have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time without affecting your normal treatment.

Information obtained from you or about you during this study, which could identify you, will be kept confidential by the investigator(s). The investigator will be available during the study at all times should you have any problems or questions about the study.

PURPOSE OF STUDY:
The purpose of the study is to:
Determine how many children in Newfoundland have been diagnosed with type 1 diabetes mellitus.
Determine the risk of family members developing type 1 diabetes mellitus.
Develop a provincial database (a collection of children with diabetes) to help find out the number of children who have been diagnosed with the disease, the complications of the disease and aid in the development of future projects. This database will be used for research only and will only be accessible to those involved in the research.

DESCRIPTION OF PROCEDURES AND TESTS
You will be asked to:
Complete a family questionnaire, and take part in an interview by phone or in person with the research nurse
Let us review your medical records (or your child's medical records) to confirm the diagnosis and identify other associated illnesses
Give blood for: genetic studies
Measuring certain markers for Type I Diabetes

DURATION OF INVOLVEMENT
Completion of the questionnaire may take an hour or so. You may need to phone affected members to get further information from them.
You will be asked to go to your local hospital or clinic to have a blood sample taken. If your child has diabetes, the blood sample can be taken when your child has routine blood work done at the diabetes clinic.

Possible risks, discomforts, or inconveniences
Inconvenience of filling out the questionnaire and discussing it with the research nurse. There is a risk of bruising at the insertion site of the needle; some individuals may feel faint at the time of the blood collection.

Benefits
There is no guarantee that you will benefit from participating in this study, however researchers may learn more information about the development of diabetes
Alternative Procedures or treatment for those not entering the study

You or your child's care will not be changed or affected if you choose not to participate

Liability Statement
Your signature indicates your consent and that you have understood the information regarding the research study. In no way does this waive your legal rights nor release the investigators or involved agencies from their legal and professional responsibilities.

STATEMENT ON GENETIC STUDIES
In order to interpret the results of the research properly, it is essential to have accurate information Concerning parentage. Sometimes the research results may point out discrepancies in parentage (Which might occur in case of adoption or a mistake in the identity of a father). If this happens, the Information will be kept in the strictest confidence and will not be released to anyone, including Family members or yourself.

The immediate goal of this study is to identify where the genes for diabetes are located. This study will be a foundation for future studies that will be directed at determining the precise gene(s) for diabetes.

FUTURE USE OF DNA SAMPLES
In order to preserve a valuable resource, your DNA samples may be stored at the end of this research project. It is possible that these samples may be useful in a future research project that may or may not be related to the current research project. Any future research would have to be approved by a Research Ethics Board (REB).

Please tick one of the following four options:
1. ☐ I agree that my DNA samples can be used for any REB-approved research project, including those in which my name is given to the researchers, without obtaining further consent from me.

2. ☐ I agree that my DNA samples can be used for any REB-approved research project, as long as my name is not given to the researchers

3. ☐ Specific consent must be obtained from me before using my DNA samples in any future research project in which my name is associated with the sample. *

4. ☐ Under no circumstances may my DNA samples be used for any future research project. The samples must be destroyed at the end of the present project.

Signature: _____ Date: _____

Witness: _____ Date: _____

* It is possible that a Research Ethics Board could approve the use of your stored samples in an anonymous research project without obtaining further permission, as long as your name could not be connected to the results.

SIGNATURE PAGE

Title of Project: Genetic Studies of Type I Diabetes in Newfoundland

Name of Principal Investigator: Dr. Leigh Anne Newhook

To be signed by participant

I, _____, the undersigned, agree to the participation of myself (my child or ward)_____in the research study described above.

Any questions have been answered and I understand what is involved in the study. I realize that participation is voluntary and that there is no guarantee that I will benefit from my involvement.

I acknowledge that a copy of this form has been given to me.

(Signature of Participant)_____ (Date) _____

(Signature of Witness) _____ (Date) _____

To be signed by investigator

To the best of my ability I have fully explained the nature of this research study. I have invited questions and provided answers. I believe that the participant fully understands the implications and voluntary nature of the study.

(Signature of Investigator) _____ (Date)
_____

Phone Number (709) - 777 - 4537

Assent of Minor participant (if appropriate)

(Signature of Minor Participant) _____ (Age____)
Relationship to Participant Named Above_____

APPENDIX E: Publication Abstract

Diabetes Care 27:885-888, 2004
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Epidemiology/Health Services/Psychosocial Research
Original Article

High Incidence of Childhood Type 1 Diabetes in the Avalon Peninsula, Newfoundland, Canada

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OBJECTIVE—The aim of this study was to determine the incidence of type 1 diabetes among children aged 0–14 years in the Avalon Peninsula in the Canadian Province of Newfoundland.
RESEARCH DESIGN AND METHODS—This was a prospective cohort study of the incidence of childhood type 1 diabetes in children aged 0–14 years who were diagnosed with type 1 diabetes from 1987 to 2002 on the Avalon Peninsula. Identified case subjects during this time period were ascertained from several sources and verified using the capture-recapture technique. Data were obtained from the only pediatric diabetes treatment center for children living on the Avalon Peninsula.
RESULTS—Over the study period, 294 children aged 0–14 years from the Avalon Peninsula were diagnosed with type 1 diabetes. The incidence of type 1 diabetes in this population over the period 1987–2002 inclusive was 35.93 with a 95% CI of 31.82–40.03. The incidence over this period increased linearly at the rate of 1.25 per 100,000 individuals per year.
CONCLUSIONS—The Avalon Peninsula of Newfoundland has one of the highest incidences of type 1 diabetes reported worldwide. The incidence increased over the 16-year study period.
Abbreviations: JCHCC, Janeway Child Health Care Centre

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