Trends In the Incidence of Type I Diabetes Mellitus Worldwide

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ABSTRACT

The incidence of Type I diabetes mellitus in children has increased worldwide over the past 50 years. This increase has occurred in rich and poor countries in Europe, Asia, the Americas and Oceania. Rapid increases in incidence in genetically stable populations eg Finland and Sardinia imply that environmental factors are of paramount importance as driving forces in this changing trend. The significance of these trends and putative aetiological factors are reviewed.

Tendencias en la Incidencia de la Diabetes Mellitus de Tipo I a Nivel Mundial

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RESUMEN

La incidencia de la diabetes mellitus de tipo I en los niños ha aumentado a nivel mundial en los últimos 50 años. Este aumento ha tenido lugar tanto en los países ricos como en los países pobres de Europa, Asia, las Américas y Oceanía. Los rápidos aumentos de incidencia en las poblaciones genéticamente estables, tales como Finlandia y Sardinia, implican que los factores ambientales desempeñan un papel primordial como fuerzas impulsoras de esta tendencia cambiante. Se examinan la significación de estas tendencias y los factores etiológicos putativos.

INTRODUCTION

Type I diabetes mellitus, which accounts for 5–10% of all cases of diabetes, is a T-cell mediated autoimmune disease (1). Insulin producing B-cells of the pancreas are surrounded by T-lymphocytes, macrophages and dendritic cells which eventually destroy the B-cells. Markers of this immune destruction of the B-cells are Islet Cell Autoantibodies (ICA), autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65) and autoantibodies to the tyrosine phosphatases I A – 2 and I A – 2B.

At time of diagnosis one or more of these autoantibodies were present in patients of Caucasian origin. This phenomenon occurs in only < 10% of genetically susceptible individuals. The most important genes involved in disease susceptibility are located in the HLA class II locus on the short arm of chromosome 6 (2). The two main class II alleles that predispose to diabetes are DR3 and DR4. DR2 allele confers resistance to the development of diabetes (3). Genomewide scans have shown two gene regions that confer genetic susceptibility to Type I diabetes mellitus *ie* IDDMI in the HLA region and IDDM2 on the short arm of chromosome 11 (4–6).

Since less than 10% of genetically predisposed individuals progress to clinical diabetes, additional factors are necessary to trigger and drive B-cell destruction. Environmental factors have been implicated as positive triggers and potentiators of B-cell destruction (7–9). Monozygotic twins show only a 13–33% concordance for Type I diabetes mellitus, suggesting that there is either acquired postconception genetic discordance or differential exposure to environmental factors (10–11). The clinical manifestation of Type I diabetes mellitus is preceded by an asymptomatic period of variable duration (12). Rapid B-cell destruction mainly in children and adolescents make ketoacidosis the first manifestation of Type I diabetes mellitus. Some subjects, in particular adults may retain residual B-cell function to prevent ketoacidosis for many years, presenting with overt diabetes even in the eighth and ninth decades of life.

The incidence of Type I diabetes mellitus has increased significantly from the latter half of the 20th century especially in the 0–14 years age group. This rising incidence in various populations worldwide provides a significant database to determine putative aetiological factors and as a consequence, development of plausible preventative strategies (13).

Geographic Variation in Incidence

Type I diabetes mellitus was uncommon and rapidly fatal at the beginning of the 20th century. The discovery of insulin changed the natural course of Type I diabetes from an in-

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evitably fatal disease to a condition in which prolonged survival was possible. The first report on the frequency of this disease and the trends worldwide was published in the 1970s by West (14). He summarized the available clinical and population based studies at that time and delineated the flaws in the epidemiology of this disease.

The limited number of studies available were restricted to Europe and North America but comparison was impossible because of lack of standardization. Different age groups and case definitions were used and there was not a method to determine ascertainment of completeness of the data (15). The necessity for rigorous epidemiological methods, to monitor and compare geographical variations in the incidence and temporal trends in Type I diabetes mellitus, was recognized in the 1980s. The World Health Organization sponsored diabetes mondiale (Diamond) project and eurodiab study were created as a consequence (16, 17).

World Health Organization (WHO) Diamond Incidence Study
The data centre for this study is located at the diabetes and genetic epidemiology unit of the National Public Health Institute in Helsinki, Finland. This centre along with the centre in Pittsburgh, Pennsylvania, developed the standards for the incidence studies, assisted in processing the data and in the coordination of the data analysis. To be eligible for participation in the WHO Diamond study, each centre had to have a well defined population based registry. There were 100 participating centres that recruited persons from 14 years of age and under with residency in the study area. The centres were defined geographically to correspond with administrative and census boundaries.

The total number of children 14 years and under in the populations participating in the study was 75.1 million. The numerator comprised 19 164 children in this age group diagnosed with Type I diabetes mellitus from 1990 to 1994 in the Diamond study areas. The definition of Type I diabetes mellitus was based on the 1985 WHO classification and diagnostic criteria for diabetes mellitus (18).

Eligible individuals were placed on daily insulin injections before their 15th birthday and were resident in the area of registration at the time of the first insulin administration. Twenty-five of the 50 countries participating in the WHO Diamond study were part of the eurodiab aetiology or childhood diabetes on an epidemiological basis (ACE) study. The registries were prospective or retrospective or a combination of both. Data on gender, ethnic group, date of birth, date of first insulin administration and family history of diabetes are included in the data base.

Completeness of registration was confirmed by estimating the degree of ascertainment using the capture-recapture method (19).

The primary data source consists of the cases of Type I diabetes who meet the criteria for registration and have been identified from the hospital records or from the records of paediatricians or family physicians. Records of the local Diabetes Associations school health records and social insurance schemes were used as a secondary independent source of cases. Incidence rates were calculated as the incidence per calendar year and 100 000 individuals at risk age adjustment for the rates was done in five year intervals (0–4, 5–9, 10–14 years) using the direct method with standard population consisting of equal numbers of children in each of the three subgroups.

The 95% confidence intervals were estimated assuming the poisson distribution of the cases. The distribution of incidence rates was arbititrarily divided into five groups:
1) very low, < 1/100 000 per year, 2) low, 1–4.99/100 000 per year, 3) intermediate, 5–9.99/100 000 per year, 4) high, 10–9.99/100 000 per year, and 5) very high, 20 or greater /100 000 per year.

Results of this study reported in 2000 showed that the incidence rates of Type I diabetes mellitus varied from a low of 0.1/100 000 per year in Zunyl China and Caracas, Venezuela to a high of 36.8/100 000 in Sardinia and 36.5/100 000 in Finland. This represents a more than 350 fold variation in the incidence among the 100 populations worldwide. Sub-Saharan Africa was not represented in the study. Populations in nor-thern Africa had intermediate incidence rates of Type I diabetes mellitus. Most of the populations in the Asian continent had very low or low incidences. Kuwait and Israel were exceptions with high and intermediate incidences respectively. Both countries represent Caucasoid populations. Incidence rates were high in North America. Alberta and Prince Edward Island in Canada had very high incidence rates: 24 and 24.5/100 000 respectively. South American populations had very low to intermediate incidence rates. In Central America and the West Indies, the populations in Puerto Rico and The Virgin Islands had high incidence rates and the rest had intermediate or low incidence rates. In Oceania, the incidence rates were high in Australia and New Zealand. In Europe, half of the populations had intermediate rates and the other half had high or very high incidence rates. Sardinia and Finland had the highest incidence rates of Type I diabetes mellitus followed by Sweden and Norway. Significant variations within country was found in Italy where the incidence rate in Sardinia was 3–5 times that of continental Italy. In Sardinia and Oxford, United Kingdom, a statistically significant male excess was found. None of the populations showed a female excess.

Hot Spots in the Incidence of Type I Diabetes Mellitus
Finland and Sardinia have the highest incidence rates of Type I diabetes mellitus worldwide. Both areas have shown significant annual increases in incidence rates over the second half of the 20th century and the beginning of the new millennium. Both populations are genetically stable implying a significant role for environmental factors. Analysis of data from

Sardinia provides valuable insights into the epidemiology and positive aetiological factors of Type I diabetes mellitus.

Sardinia, an island off the coast of Italy has an incidence rate for Type I diabetes mellitus 305 times that of continental Italy (Table). A recent report observed a rising trend of incidence from 37.7/100 000 in 1989 to 49.3/100 000 at the end of 1999 (20). This showed an estimated average annual increase of 2.8%. There was also a significant male to female preponderance. The geographical distribution of Type I diabetes risk was unchanged and remained homogeneously distributed during the study period 1989 to 1999. The authors speculated on the possible putative factors for the Sardinian experience. The association of the indicators of national prosperity in Europe with increasing incidence of Type I diabetes is not a significant factor since Sardinia falls far from the regression line in that report (21).

They postulated that an environmental agent operating in the genetically susceptible Sardinian population was a more likely cause of the increasing incidence of Type I diabetes mellitus. In the 1950s, a campaign aimed at the eradication of malaria occurred. Large amounts of DDT were sprayed all over the island and its metabolites continue to be detected in the food chain. The areas with past high malaria morbidity seem to be at a lower risk for Type I diabetes mellitus. They hypothesized that the *Plasmodium falciparum* may have had a protective role against the development of Type I diabetes. The parasite either selected high risk genes or that its presence was an indicator of other parasitic infestation that could be protective against Type I diabetes. Thus the disappearance of malaria might be an epiphenomenon of some radical changes occurring in the Sardinian environment during and after the 1950s. This is in accordance with the hygiene hypothesis (22–24).

Environmental Factors
Hygiene Hypothesis
Gale noted the parallels between the epidemiology of the atopic disorders and that of Type I diabetes mellitus. A similar increase in prevalence that occurred with Type I diabetes, has been seen with childhood onset asthma, hay fever and eczema in the latter part of the 20th century. All of these disorders showed the highest incidence rates in the developed western world. Some protective agent may have been lost from the childhood environment over recent decades, a concept known as the hygiene hypothesis. This hypothesis evolved from epidemiological data which suggested that atopic disorders were more common in affluent societies as compared to traditional societies and that this might be related to reduced exposure to infections and other immune challenges (22, 23, 25). Gale (2002) suggested that this protective agent that has been lost is the helminth *Enterobius vermicularis,* the pin worm or some other helminth species. He noted that in the Nod mouse, the animal model of Type I diabetes mellitus, rodent pinworms inhibit the development of diabetes. He postulated that human pinworms may have the potential to modulate immune responses and thus protect against progression of immune mediated diseases such as Type I diabetes and asthma.

NUTRITION
1.   *Cow's Milk*
Elliot and Martin showed that manipulation of the protein component in the diet of BB rats influenced the natural history of autoimmune diabetes mellitus (26). The use of a semisynthetic amino acid diet from the onset of weaning instead of milk protein supplementation resulted in a significant decline in the incidence of Type I diabetes.

In comparison to human milk, cow's milk has a higher protein concentration due to the larger casein content. B-lactoglobulin, the main whey protein in cow's milk, is not present in human milk and the serum albumin amino acid sequences differ in the two types of milk. There is also a 3 amino acid difference between bovine insulin present in cow's milk and human insulin. Several studies by Virtanen in Finland have shown that the duration of exclusive breast feeding and the time of introduction of supplementary feeding with cow's milk influenced the risk for Type I diabetes mellitus (27–30).

Young children with Type I diabetes were predominantly breast fed for less than six months and exclusively breast fed for less than three months. The majority of the affected children had received supplementary cow's milk based formula over the first three months of life. This group also observed that a high consumption of cow's milk in childhood was associated with a more frequent appearance of diabetes-associated autoantibodies in initially unaffected siblings of children with Type I diabetes mellitus.

Harrison and Honeyman postulated that early exposure to cow's milk, in genetically susceptible individuals, resulted in impaired intestinal mucosal immune function and predisposition to Type I diabetes mellitus (31). An International multicentre study (trial to reduce IDDM in genetically at risk, TRIGR) was initiated in 2003 to determine the significance of early exposure to cow's milk in the pathogenesis of Type I diabetes mellitus (32).

2.   *Other Dietary Factors*
Norris *et al* in a prospective study reported that early (before the age of 4 months) and late exposure (at the age of 7 months or later) to gluten and Gluten free cereal were associated with an increased risk of B-cell autoimmunity (33). Also early exposure to cereal by infants in Germany resulted in an increased risk of B-cell autoimmunity (34).

Vitamin D Supplementation has been shown to prevent Type I diabetes mellitus in NOD mice (35). A multi-centre European study showed that vitamin D supplementation in early childhood was associated with decreased risk of Type I diabetes mellitus. The Eurodiab sub-study showed that even irregular vitamin D supplementation in infancy resulted in a decreased risk of Type I diabetes mellitus (36).

Viruses

Several viruses, coxsackie B, rubella, mumps and cyto-megalovirus have been implicated in the pathogenesis of Type I diabetes mellitus (37). Possible mechanisms are molecular mimicry, in which the immune response to the infection cross reacts with islet antigens, and secondly a direct cytotoxic effect of the virus on the pancreatic B-cells. Enteroviruses belong to the Picornavirus family. There are 4 sub-groups: polioviruses, coxsakie B viruses, coxsackie A viruses and echoviruses. Polymerase chain reaction (PCR) methodology has enabled the direct measurement of viruses in serum, whole blood and mononuclear cells.

A prevalence of 33% of patients with newly diagnosed Type I diabetes had detectable enterovirus MRNA compared to 3% of controls in studies done in four countries (32). Enterovirus MRNA has been detected in the pancreatic islets of patients with Type I diabetes mellitus (38, 39). Molecular Homology between the VP7 Protein of Rotavirus and certain islet cell antigens has been reported (40). The same group in a prospective study of infants genetically predisposed to Type I diabetes, observed that the appearance of autoantibodies was associated with a significant rise in rotavirus antibodies (41). However, a Finnish prospective study did not show a significant role for rotavirus infection in the development of diabetes associated autoantibodies (42).

Other Environment Factors

A Finnish Study showed that children with Type I diabetes mellitus were heavier and taller during infancy (43). However this maybe a result of early exposure to cow's milk which is known to be a putative factor in the pathogenesis of Type I diabetes mellitus.

On the basis of such data, the accelerator hypothesis was proposed (44). This states that insulin resistance is an important factor in the rising incidence of both Type 2 and Type I diabetes and the only difference between the two types is the rate of progression to overt disease. However, this is too simplistic to account for the fulminant presentation with ketoacidosis of a significant number of patients with Type I diabetes.

Maternal stress and early childhood stress are now implicated as potential triggers in the aetiology of Type I diabetes mellitus (45).

Lessons From the Bahamas

Peter *et al* reported an incidence of 10.1/100 000 of Type I diabetes mellitus age 0-14 years in the Bahamas (46). The commonwealth of the Bahamas is an archipelago consisting of over 700 islands and Cays off the eastern coast of Florida, USA. Thirteen of these islands are inhabited. The population as of the 2000 census is 310 000. People of African ancestry comprise 85% of the population and have been in the Bahamas for over two centuries. This incidence of Type I diabetes mellitus is the highest worldwide in people of African origin. It is 2–3 times that of the US Virgin Islands and Barbados. Current data from this cohort show that there is an equal male to female ratio but a preponderance of positivity to islet autoantibodies, GAD65 and insulin autoantibodies (IAA) in males as compared to females 60% to 23% positivity to GAD65 and 70% to 46% to IAA.

Bahamians tend to be xenophobic and as such there is not much genetic admixture, resulting in a "limited gene pool". Thus, genetic susceptibility maybe contributing significantly to this high incidence. Environmental factors are also of significance.

The Bahamas has the highest per capita income in the Caribbean region. The infant mortality rate has declined significantly in the past 10 years and breastfeeding is now much less common than 50 years ago. Currently genetic studies are underway in this cohort.

Future Directions

Casu *et al* have projected that in Sardinia, one of the hot spots of Type I diabetes, incidence will be 52.7/100 000 in 2010 and 69.5/100 000 in 2020 (20). This will represent one of the heaviest burdens for the Sardinian Health Care system. This trend is reflected worldwide.

Preventative measures *eg* vaccines, identification of protectors in the environment, stem cell research and immune modulating therapies are necessary to abort this overwhelming trend. One of the most promising therapies has recently been reported by Bisikirsk and Herald, 2004 (47). Treatment with anti-CD3 monoclonal antibody prevented the loss of insulin production over the first two years of the disease. Similar studies would portend a better future in the struggle against Type I diabetes mellitus.

Area	Incidence/100 000
Algeria	5.7
Zunyl	0.1
China	1.4
Denmark	15.5
Finland	36.5
France	8.5
Sardinia	36.8
Alberta	24.0
Prince Edward Island	24.5
Allegheny, PA	17.8
Chicago IL	11.7
Caracas	0.1
Barbados	2.0
Bahamas	10.1
New South Wales	14.5

Table: Incidence of Type I diabetes mellitus by area.

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