The epidemiology of diabetes mellitus

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Abstract. Insulin-dependent diabetes mellitus (IDDM) develops predominantly in children and young adults, but may appear in all age groups. The incidence of IDDM differs greatly among populations, with Finland and Sardinia showing the greatest incidence rates (~30–35% of cases annually per 100 000 children up to age 14 years) and oriental populations showing the lowest rates. IDDM is diagnosed more frequently in the winter months. The major genetic susceptibility to IDDM is linked to the HLA complex on chromosome 6. These genetic backgrounds interact with environmental factors (possibly certain viruses, foods and climate) to initiate the immune-mediated process that leads to β-cell destruction.

Non-insulin dependent diabetes (NIDDM) is the most common form of diabetes. The prevalence of NIDDM varies enormously from population to population. The greatest rates have been found in Pima Indians. The major environmental factors identified as contributing to this form of diabetes are obesity and reduced physical activity. NIDDM shows strong familial aggregation in all populations and is clearly the result of an interaction between genetic susceptibility and environmental factors. Before NIDDM develops, insulin concentrations are high for the degree of glycaemia and of obesity, reflecting the presence of insulin resistance. As insulin resistance worsens, glucose levels increase, with the appearance of glucose intolerance and, finally, of NIDDM, when insulin response cannot compensate for insulin resistance.

Key words: epidemiology; genetics; type I diabetes mellitus (IDDM); type II diabetes mellitus (NIDDM)

Type I diabetes mellitus (IDDM)

Type I diabetes mellitus (IDDM) develops predominantly in children and young adults, but may be present in all age groups. IDDM is a world-wide disease but occurs with considerable geographical and ethnic variations. The greatest incidence is identified in Nordic countries, particularly in Finland, as compared with the rest of Europe. Overall, Europe encompasses a >10-fold difference in incidence annually, ranging from ~35 new cases in Finland [1] to two to three new cases in Macedonia [2] per 100 000 children aged 0–14 years. The geographical pattern is not a simple north to south incidence gradient but in fact there are sharp differences between neighbouring regions. For example, Sardinia shows an incidence of diabetes approaching that of Finland and which is several times greater than the rest of Italy [3]. Another area of contrast is Estonia; despite its ethnic and cultural similarities with Finland, it has an incidence of only one-third that in Finland. On the other hand, the Russian population residing in Estonia presents a disease risk less than that of the native Estonians. So far, the reasons for this wide variation in the risk of IDDM in Europe are unknown, and the power of genetic variation and of environmental factors has yet to be established. From the comprehensive coverage of the European populations, it can be estimated that among 100 million children aged 0–14 years, some 10 000 will develop IDDM each year.

The epidemiology of IDDM according to time

Temporal trends in the incidence of IDDM comprise both secular changes and seasonal variations. The incidence of IDDM shows a steady increase in its frequency during the last few decades [4], corresponding in some instances to an estimated doubling in incidence per generation. Some authors have tried to explain the changing incidence of environmental factors, such as changing breast-feeding habits, but no obvious explanations have yet been identified. On the other hand, the increasing frequency cannot be attributed to improved survival and reproducitiveness among IDDM patients. Recent studies found a correlation between apparent levelling off in the increase in incidence with a decline in the occurrence of mumps antibodies in newly diagnosed IDDM children due to the
introduction of the mumps–measles–rubella vaccine. These data suggest that the temporal variations in the incidence of IDDM can be modified, and that the geographical distribution of the disease may change in the future as a result of implementation of health promotion programmes.

Furthermore, there is seasonality of IDDM onset, and in fact it is diagnosed more frequently during the winter and autumn months, particularly during puberty [5]. As IDDM is an autoimmune disease and the destruction of the β-cells begin several years before its clinical onset, this seasonality probably reflects the importance of certain environmental precipitating factors, such as viral infections. However, there is no evident explanation for why this pattern exists. The identification of non-genetic determinants of IDDM is of particular importance as these are potentially modifiable with the aim of disease prevention. Some studies have demonstrated that a short duration of breastfeeding during infancy seems to be associated with an increased risk of developing IDDM. This possible association may point to an aetiological role of cow’s milk protein. Antibodies for cow’s milk are much more prevalent and at higher titres in children with recent-onset IDDM than in control subjects. In fact, the neonatal gut is relatively permeable to a large quantity of proteins, and it is postulated that bovine albumin increases the antibodies which cross-react with a protein in the β-cell membrane. At present this hypothesis remains controversial.

Genetic factors

Islet cell autoantibodies, insulin and glutamic acid decarboxylase antibodies, markers of autoimmune disease, may be detected in the circulation some years before the clinical onset of IDDM, providing a powerful tool for individual assessment of subsequent risk of overt disease. IDDM clusters within families: it is estimated that the risk of developing the disease in siblings and children of IDDM patients is ~5–10%, compared with ~0.5% in the general population [6]. The risk is smaller for the offspring of diabetic women than in offspring of diabetic men, and the risk of IDDM in children seems to be increased with advancing maternal age [7]. Such differential risk patterns probably reflect selection due to particular features in the reproductive capacity of IDDM women rather than genetic mechanisms.

In Caucasian populations, strong IDDM associations are found in the serologically determined HLA markers DR3 and DR4, the heterozygous state DR3/DR4 and the genes which encode them at the HLA-DQ loci on chromosome 6 [8]. On the other hand, HLA-DR2 and DR5 seem to confer protection against IDDM. Recent studies have provided evidence of genetic susceptibility to IDDM linked to several other loci, including the insulin gene on chromosome 11 [9]. The disease susceptibility genes occur frequently but have low penetrance; therefore, even for those marker combinations most strongly associated with IDDM, the absolute risk of IDDM is ~5–10% at the most.

Type II diabetes mellitus (NIDDM)

Type II diabetes mellitus (NIDDM) is the most common form of diabetes. Population studies based on standardized methods and diagnosis have shown great variation in the frequency of the disease, and prospective studies have provided new insights into its associated risk factors and its pattern of development.

Prevalence

The prevalence of NIDDM varies enormously from population to population and throughout the world [10]. The highest rates are recorded in Pima Indians, but also in the Micronesian population living on Nauru Island in the Central Pacific. Proportions in different ethnic groups living in the same country may vary considerably. Rates differ in migrants as compared with natives remaining in their own country. Moreover, the ratio in migrants is greater than in the indigenous population, and these increases appear to be related to rapidly changing lifestyles. The prevalence is parallel with rapidly developing countries and among underprivileged individuals in developed nations. It has been estimated that the number of people with diabetes will be ~100 million by the year 2000. In Italy, NIDDM accounts for up to 85% of the total cases of diabetes and affects 5–7% of the population; it is likely that many cases (perhaps up to 50%) currently are undiagnosed [11,12].

NIDDM describes various types of diabetes, and only in a few of these is the aetiopathology known. NIDDM is rarely associated with insulin receptor (leprechaunism) or the glucokinase gene (MODY) mutations. It may be caused by or associated with other endocrinological disorders (Cushing’s syndrome, pheochromocytoma or acromegaly).

Genetic factors

NIDDM results from the interaction of genetic and environmental factors. The disease shows familial aggregation, but there is no information on the mode of inheritance or on whether it is caused by one or several genes [13]. Other evidence for the importance of genetic determinants comes from studies of mixed populations and from populations of different genetic backgrounds living in similar environments. Other data come from studies on populations residing in the same environment but within which there is a genetic admixture. For example, among the populations of the Gila River Indian Community, the prevalence of NIDDM is twice as great in full-blooded Pima Indians as in non-Indians, and the prevalence among those of half-
Pima, half-non-Indian ancestry is intermediate [14]. Genetic susceptibility does appear to be a basic step for the development of NIDDM, but the expression of the disease is determined largely by environmental factors.

Environmental factors

The development of NIDDM is influenced by exposure to different environments. Some of the environmental effects can be assessed by comparing the frequency of the disease in migrants with that amongst individuals who remain in the original environment, assuming that both groups share similar gene pools. Therefore, Asian Indian, Japanese and Chinese populations present a lower prevalence of NIDDM in urban rather than in rural areas, and in countries of origin rather than in a different part of the world, where the prevalence increases from ~2-fold to 5- to 6-fold [15]. Another example comes from the Polynesians of Wallis Island who migrated to New Caledonia and changed their way of life (from traditional to industrial); the prevalence of diabetes increased over 10 years from 3 to 12%. These differences in the prevalence in migrant populations provide evidence for the importance of environmental factors as determinants of NIDDM.

Rapid changes have occurred in the prevalence of diabetes within certain populations. For example, among the Pima Indians, age-adjusted prevalence rates for diabetes increased >40% during 1967–1977 [16]. In 1967, the prevalence of NIDDM among the Pima Indians was 10 times higher than in the US population as a whole, yet 30 years earlier the prevalence of diagnosed diabetes was no greater among the Pima Indians than among the general population. Changes such as this over the course of few generations can only be attributed to changes in lifestyle; hence, they reflect the major influence of environmental factors on the expression of the disease.

Obesity

Obesity is a major determinant in the incidence of NIDDM, but only a small proportion of obese individuals develop the disease. Longitudinal studies among the Pima Indians have demonstrated that the likelihood of developing NIDDM results from an interaction between the effect of obesity in the offspring and a parental history of diabetes, which presumably reflects inherited susceptibility [17]. Thus, even when genetic susceptibility is present, the expression of the disease is largely dependent on other factors.

Not only the presence but also the distribution of obesity influences the risk of developing NIDDM. Central obesity is associated with an increased possibility of developing NIDDM, as has been shown in many different ethnic and racial groups. Central obesity in many populations is also associated with an increased incidence of coronary heart disease, hyperinsulinaemia, high serum triglyceride, low high-density lipoprotein (HDL) cholesterol levels, hypertension and disturbances in the patterns of sex hormones. Hyperinsulinaemia, or insulin resistance, appears to be a central feature of this cluster of abnormalities related to abdominal obesity. Insulin resistance is a characteristic of patients with NIDDM, but also precedes and predicts the development of the disease [18]. Differences in the extent of distribution of obesity, however, do not entirely account for differences in the prevalence of diabetes among or within populations, nor does obesity entirely account for differences in the prevalence of diabetes among migrants. Thus, it has been necessary to search for other factors.

Physical activity

Physical activity influences the incidence of NIDDM, the prevalence of the disease among physically inactive individuals typically being two to three times greater than among active subgroups of the same population [19]. Increased obesity and reduced physical activity favour the development of insulin resistance, which appears to be a critical component in the pathogenesis of NIDDM [18]. Another factor that may contribute to the development of insulin resistance is a high calorie diet containing a high percentage of calories from saturated fat, a low fibre content, and a decreased unrefined carbohydrate content (i.e. a shift from a traditional to a westernized environment).

Insulin resistance

Insulin resistance is a characteristic that precedes the development of impaired glucose tolerance (IGT) and NIDDM. Hyperinsulinaemia, especially in the fasting state, represents an index of insulin resistance. Insulin resistance shows familial aggregation and is associated with obesity and physical inactivity. The development of IGT is predicted by the presence of hyperinsulinaemia, and IGT is a strong risk factor for NIDDM and can be considered as a stage in the development of the disease.

Longitudinal epidemiological studies have shown that hyperinsulinaemia, even at a stage when glucose tolerance is within the normal range, is an important predictor of NIDDM [20]. The increase in insulin concentration appears to be a compensatory response to increased intracellular insulin resistance, which leads to small increases in circulating glucose, and as a result an increment in insulin secretion, as well as subsequent increases in both fasting and stimulated insulin levels. As insulin resistance degenerates, the glucose tolerance deteriorates and IGT eventually occurs. After IGT develops, when insulin responsiveness to secretagogues (particularly to glucose itself) diminishes, hyperglycaemia worsens and diabetes appears.
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References


