REVIEW

Rising Incidence of IDDM in Europe

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A rising incidence of insulin-dependent diabetes mellitus (IDDM) has been reported in many northern European countries, with a rate equivalent to a doubling time of 20–30 yr in some. North American and Japanese studies report a similar trend, although they are less uniform in their findings. Although the number of genetically susceptible individuals within these populations has increased, the rapidity of the change suggests that environmental factors are responsible. If these could be identified, primary prevention might become possible. ***Diabetes Care*** **12:289–95, 1989**

Insulin-dependent diabetes mellitus (IDDM) is a chronic, currently irreversible disease with a range of crippling complications; current therapy is palliative at best. There are, however, grounds for hope that primary or secondary prevention may eventually be possible.

Current interest is directed mainly toward secondary prevention. Detailed knowledge has accumulated concerning the molecular basis of genetic susceptibility, of the autoimmune processes associated with β-cell destruction, and of the long prodrome that precedes clinical onset. Interruption of the disease process during this prodromal period may therefore be possible (1–3). At the same time, it is unclear how the process is initiated in genetically susceptible individuals; therefore, the prospect of primary prevention appears remote. Environmental factors are often assumed to play an important role, but direct evidence is lacking. There are, however, indirect indications that this is the case. For example, most people with the genetic potential to develop diabetes never do so. Only one in three monozygotic cotwins initially discordant for IDDM and one in six HLA-identical siblings develop the disease (1,4). There are major geographic differences in the frequency of IDDM, but it is difficult to determine the relative contributions of environmental and genetic differences between populations (5). On the other hand, a well-documented change in incidence within a population would argue strongly for the intervention of environmental factors.

Several recent studies have reported a rapid rise in incidence of IDDM, equivalent to a doubling period of 20–30 yr in some countries. Is this really the case? Some large prospective studies are in progress, but most of the evidence rests on retrospective analysis of epidemiological information gathered over 20–30 yr. This is technically difficult; there are obvious pitfalls in drawing conclusions from studies performed under varying conditions, in different countries, at differing times, and over different age ranges. If such a rise can be documented and ascribed to environmental factors, primary prevention would become possible because the environment can be manipulated. With these points in mind, we offer a critical assessment of the evidence.

NORTHERN EUROPE

The Scandinavian countries offer many advantages for epidemiological studies. They have ethnically homogeneous, relatively stable populations together with centralized well-organized health-care systems. They also have the highest documented incidence of IDDM

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in the world. They are, therefore, especially suitable for longitudinal studies of IDDM.

Finland and Sweden. The national drug register in Finland provides accurate data for the incidence of diabetes in individuals <20 yr of age, with an estimated ascertainment well over 95%. Over a 12-yr study period, during which the method of ascertainment was unchanged, the incidence rose from 27.3 cases/100,000 per year in 1970–1976 to 38 cases/100,000 in 1983 (6). Prospective registration of all newly diagnosed cases provides the most accurate way to follow the incidence of a disease, and a central registry was set up in Sweden in 1977 for this purpose. The study is supplemented by annual checks in local hospital registers for missed cases, and ascertainment is estimated to be 100%. The results for two 3-yr study periods, 1977–1980 and 1980–1983, show an overall increase from 22.7 to 25.1 cases/100,000 per year (7). This increase is consistently found even when the data are subdivided by sex, age, or geographic region.

Norway. Norwegian studies dating back to 1925 have shown a small but sustained increase in the incidence of IDDM. Westlund (8) analyzed hospital records and death certificates from Oslo for the period 1925–1955 and retrospectively derived an incidence of 6.2/100,000 per year up to 15 yr of age. Ustvedt and Olsen (9) extended the study to 1965, finding an incidence of 10.8/100,000 per year but gave no estimate of the completeness of case ascertainment. In the later period, new cases were no longer routinely admitted to hospital, and this might have created a bias, although the effect would be to underestimate the incidence and does not detract from the conclusion that there had been a genuine rise in the incidence of IDDM in the city. A third study confirmed the trend with an incidence of 11.6/100,000 per year in 1966–1974 (9). More recently, Joner and Sovik (10) found a considerably higher rate (20.6/100,000 per year in the city in 1973–1977), but this figure was derived as part of a study looking at the whole country, which used case-ascertainment methods and checks that probably ensured the inclusion of children whom earlier studies would have missed. The result is therefore of limited comparability, although the authors estimated that they had only improved case ascertainment by 5%. The uncertain ascertainment levels in these studies make the conclusion of a rise in incidence less firm than in other studies.

Denmark. Christau et al. (11) reported that incidence rates in Denmark had not changed between a study in 1924 and their own survey in 1970–1976, but it has been suggested that this was based on a misinterpretation of prevalent cases as incident cases in the older data. Green and Andersen (12) studied a series of male birth cohorts and identified diabetes from the records of those rejected for conscription on health grounds at 20 yr. Ascertainment was estimated at 95%, and corrections were made to allow for members of the original cohort who had emigrated or died. This analysis, with a regression model described as "the most parsimonious," showed a significant increase in incidence from the early 1950s to the mid 1970s.

The Netherlands. As in Denmark, compulsory registration for conscription offers a powerful source of epidemiological information because it provides almost total ascertainment for the entire male population at a given age. The results demonstrate a steady increase in the prevalence of IDDM from 0.99/1000 in 1960–1964 to 1.98/1000 in 1985–1986. Even with the proviso that small alterations in incidence will be magnified when prevalence figures are considered, there seems to have been a major increase (13; G.J. Vaandrager, M. Van Ormondt, and G.J. Bruining, unpublished observations).

England and Scotland. Study of three separate British national birth cohorts by essentially comparable methods has shown that the prevalence of IDDM (estimated at age 10–11 yr) rose from 0.1/1000 in 1957 to 1.3/1000 in 1980 (14). A potential problem is that only a third of the first cohort were followed, and this sample was nonrandomly selected; results have, however, been weighted to account for the sampling procedures. The first two cohorts were studied at 11 yr of age and the last at 10 yr of age, but this should have decreased rather than increased prevalence estimates. The numbers involved were small, with only one case in the first cohort of 5362 children and 18 in the third cohort of 13,823, and consequently the 95% confidence intervals were wide. Nonetheless, the first and third cohorts differed significantly, and the rise was confirmed on linear-trend analysis. Follow-up of the earlier cohorts to age 23 yr showed that the difference in prevalence diminished as they grew older (15). However, most of the cases diagnosed in the first cohort probably would not have fulfilled the usual entry criteria because only 7 of the 15 patients diagnosed after age 17 yr had been treated with insulin, and most presented as the result of some screening procedure (16). All cases in the second cohort presented with an acute onset of symptoms characteristic of IDDM. Comparisons between these groups may therefore be invalid.

The incidence of IDDM up to age 10 yr within the county of Oxfordshire between 1969 and 1983 was studied by means of clinic records (17). The mean annual age-specific incidence rate rose most markedly in the 0- to 5-yr-old group, but neither the confidence intervals nor the number of incident cases were stated.

A study in Scotland showed a rise from 10.0 in 1968 to 18.3 in 1976 (18). A central record of Scottish hospital admissions for the period 1968–1976 was used to identify 2505 individuals <19 yr old with a diagnosis of diabetes. The record did not distinguish between first and subsequent admissions with this diagnosis, and no information was available on admissions before 1968, so that it was impossible to differentiate newly diagnosed cases from those already diabetic at the start of the study. To overcome these problems, the authors calculated correction factors for each of the years 1968–1976 based on readmission rates in the later years of

the study. The annual incidence rate derived after exclusion of known readmissions, but without employing the correction factor, was remarkably constant throughout the study period, varying from 14.9 to 21.8, with the highest figure in the 1st yr of the study. The estimated rise in incidence thus depends entirely on the derived correction factor, the accuracy of which does not appear to have been tested. The authors do state, however, that a conservative estimate based on extrapolation from known readmission figures suggests that the real increase in incidence cannot be <30% during the period 1968–1979. The study has been continued up to 1983; the incidence has remained high, but the rising linear trend was no longer significant (19). Because there was no independent check of the completeness of ascertainment, interpretation depends on the accuracy of the centralized hospital-admission register that they used. A validation of the study methodology was later carried out in the Tayside region (population 394,415, 8% of Scotland's population), and several of the basic assumptions were found to be wrong (20). Approximately 3% of true incident cases known to have been admitted had no recorded admissions under the code for diabetes; addresses were misrecorded, and some children had admissions at greater time intervals than allowed for in the original study. The correction factor for readmissions was not constant as had been assumed. These imperfections could result in a cumulative 12–16% overestimate after only 7 yr of the 9-yr study. The Scottish figures therefore need to be interpreted with caution.

Poland. Rewers et al. (21) recently reported an apparent epidemic of IDDM in midwestern Poland. The incidence is much lower than in the other northern European countries but appears to have risen from 3.5/100,000 children <17 yr of age in 1970–1981 to 6.6/100,000 in 1982–1984. If the earlier period is broken down into 3-yr intervals, however, the data might equally be interpreted as showing a gradual rise through the 1970s with a small dip immediately before the apparent epidemic. Continued observation will be needed to show if the incidence continues to rise or falls, which would mark the end of the "epidemic." A change in data-collection methods, from retrospective examination of hospital records to ongoing registration of cases, may also have contributed to this apparent increase.

MEDITERRANEAN COUNTRIES

Israel. A low incidence of IDDM has been observed in Israel in studies performed in 1962, 1968, and 1975–1980 (22). The last study did show a small increase, from 3.3/100,000 in 1975–1976 to 3.8/100,000 in 1979–1980, although the rise is not statistically significant.

Incidence studies are in progress in other Mediterranean countries but have not been running long enough to allow assessment of temporal changes.

NORTH AMERICA

It is unclear whether there has been a concurrent increase in the incidence of IDDM in other parts of the world during this time. Longitudinal studies in North America are in general less solidly based than some of the European surveys. Two of these studies found a significant rise in incidence, and three did not.

The main exception to the general upward trend is observed in the Rochester, Minnesota, study (23; Table 1). This formed part of the Rochester Epidemiologic Project, a central file of records from all sources of medical care in the area. Case ascertainment was probably complete, but the population studied was small, 26,500 at the beginning of the study in 1945 and 52,629 in 1970. Only 35 patients were diagnosed before age 30 yr in 25 yr of study, and the small size of the sample makes it inadequate for statistical analysis.

A shorter study in Montreal also failed to detect any increase (24). Ascertainment was by search of hospital records, on the assumption that all newly diagnosed patients would have been admitted to hospital over that period; there was no check on the degree of case ascertainment. The incidence rates reported are considerably lower than in contemporary studies from North America and Europe, which raises suspicion of under-ascertainment.

Other studies in the United States have reported an increase in incidence; Sultz et al. (25) investigated the incidence of diabetes in children in Erie County, New York, between 1946 and 1972. Figures were obtained from a survey of hospital records, specialist physician's office records, death records, and school health records in 1961. These were updated annually to the end of the reported period. The rate of rise appears lower than in Europe, with a 50% increase over 26 yr. The authors found a similar increase in the incidence of several other chronic childhood diseases during the study period, suggesting the observed rise may be partly artifactual due to missing cases in the early years.

A survey carried out on schoolchildren in Michigan in 1973 estimated a much greater rate of increase, a doubling within 10 yr (26). These figures were, however, obtained by means of a single questionnaire sent to the superintendents of each public school district, who were asked to list the date of birth and date of diagnosis of each child known to have diabetes—a method that would appear particularly prone to error. Recording and reporting would probably be incomplete, particularly in cases diagnosed long before the survey was carried out. Schools would be more likely to be aware of the diagnosis in those who had recently developed diabetes, and older children would also be less likely to be reported because the school would usually be less involved in management of the disease. No attempt was made to define the degree of ascertainment. All these factors would tend to exaggerate any increase in incidence.

TABLE 1
North America

Area	Period	Age range (yr)	Population (*n*)	Incidence		Methods	Ref.
				Period	Cases/100,000/yr		
Rochester, MN	1945–1969	0–30	26,500–52,629*	1945–1959	7.9	Case records	23
				1960–1969	6.5		
Erie County, NY	1947–1972	0–16	1.7 million	1947–1949	7.0	Health record survey	25
				1959–1961	11.5		
				1965–1967	15.0		
				1971–1972	12.5		
Michigan	1959–1972	0–10	191,000–338,000	1962–1964	6.2	School survey	26
				1971–1972	15.0		
Allegheny county, PA	1965–1976	0–19				Diabetes register	27
Whites			434,496–511,282	1965–1967	11.4		
				1968–1970	16.8		
				1971–1973	15.8		
				1974–1976	17.6		
Non-Whites			59,125–61,180	1965–1967	11.3		
				1968–1970	7.1		
				1971–1973	8.2		
				1974–1976	13.5		
Montreal	1971–1977	0–16	851,076	1971–1972	9.6	Hospital records	24
				1973–1974	7.9		
				1975–1976	9.1		

*All ages.

The most carefully controlled epidemiological reports from North America have come from a register of IDDM set up in Allegheny County, Pennsylvania, in 1965. Since then, new cases of IDDM diagnosed before age 20 yr have been recorded with an estimated maximal error rate of 9.4%. From 1965 to 1976, a gradual increase in the incidence of diabetes among Whites was observed but did not reach statistical significance in either sex. There was no increase in incidence among non-Whites over the same period (27).

ASIA

There is a marked paucity of information on the incidence of diabetes in Asia, although it appears that the incidence is much lower than in Europe. The only studies available come from Japan, where a central registry system for childhood diabetes, based on a provision for reimbursement of medical expenses on application to the Ministry of Health and Welfare, was set up in 1974. This was supplemented by a nationwide hospital questionnaire survey in 1980. Both studies found a steady increase in the annual incidence between 1974 and 1980, estimated in the latter to rise from 0.31/100,000 per year in 1974 to 0.54/100,000 in 1980 (28). However, validation against a detailed survey in Tokyo with essentially complete ascertainment revealed that only 60% of cases had been reported to either study. Both methods of study were probably least accurate in the earlier years; the central registration system had just been established, and its existence was not widely known; the nationwide questionnaire was retrospective, and cases diagnosed several years before the survey were probably underreported.

AUSTRALIA, NEW ZEALAND, AFRICA, AND SOUTH AMERICA

There have been several published studies of the incidence of IDDM in Australia and New Zealand, but each provides data for only a single period of up to 5 yr, and longitudinal data are not yet available.

No results are available from African or South American studies.

DISCUSSION

The information available on temporal changes in incidence rates is inadequate in many diseases, and IDDM is no exception. For most of the world's population, we lack even a single estimate of the incidence of the disease, and it will be many years before changes can be assessed. Of the studies available, many are flawed; particularly striking is the common omission of external validation of the degree of case ascertainment. Many centers are involved in prospective registration of new cases, and this approach will eventually clarify the situation.

It is technically much more difficult to demonstrate that the incidence of a condition is changing than to determine incidence at a single time. Accuracy and completeness of ascertainment remain of primary importance, but comparability becomes the major issue

because changes of method and varying ascertainment easily introduce bias. Data have been manipulated in some studies to improve estimates of incidence when they were felt to be incomplete or to allow comparison between results obtained at two time points. False estimates may thus arise at the level of data collection or at analysis. At the same time, alterations in the population studied, e.g., changes in age structure or sex distribution, must be taken into account.

Error may also arise in various ways specific to diabetes. A reported increase in incidence might reflect changes in diagnostic criteria, improved access to diagnostic facilities, fewer deaths of undiagnosed cases outside the hospital, or fewer deaths of newly presenting cases in diabetic ketoacidosis. The definition of diabetes has certainly changed; the WHO criteria were established as recently as 1980 (29). These are, however, mainly relevant to the characterization of borderline non-insulin-dependent diabetes, whereas IDDM is usually not a diagnostic problem because it presents with marked hyperglycemia and typical symptoms. For the same reason, it seems unlikely that improved diagnosis due to increased availability of reagent strips for measurement of urine or blood glucose would have a major effect on the figures. Undiagnosed children will ultimately require admission with ketoacidosis or infection, and it can be assumed that few will have died outside the hospital in Western countries over the past 30 yr. Death at first admission is another possible cause of bias, but there is no evidence that the childhood mortality from ketoacidosis has decreased over the 30-yr period of this review. A problem for contemporary incidence studies is that it is no longer routine for newly diagnosed children to be admitted to hospital to start on insulin, so that hospital admission statistics, at least in the United Kingdom, can no longer be relied on as a primary source of ascertainment.

Despite these cautions, the evidence is sufficient to justify the conclusion that there has been a genuine increase in the incidence of childhood diabetes, at least in parts of northern Europe. The rise has been steady and sustained over the past 20 yr or more, and the rate has doubled in several countries over this period. There are also indications that the incidence is rising in other parts of the world, but this awaits confirmation. We emphasize that reliable evidence is only available under age 20 yr and that ~35% of IDDM cases are estimated to occur after this age (30). It might therefore be argued that the disease is not becoming more common but that susceptible individuals are culled at a younger age. This is supported by the findings of the British national cohort studies (15).

What could explain such a rapid rise? Could changes in the genetic susceptibility of the population occur over such a short period? Children with diabetes have survived and raised families of their own for the past 60 yr, so that genetic susceptibility will inevitably become more common in the population. Preferential transmission of susceptible alleles has also been described in families with a diabetic child (31–33). The nature, extent, and importance of this phenomenon remain controversial, but it could accelerate changes in the population gene pool resulting from the increased fertility of diabetic women. Even so, only one in eight new cases has an affected first-degree relative, and the rise is so rapid that genetic factors can provide only a partial explanation. It does seem reasonable, overall, to conclude that environmental agents are mainly responsible for the rise in incidence, but clear delineation of the contribution of genetic and environmental factors may be impossible.

The argument for the involvement of environmental factors in the causation of IDDM rests on analogy and inference rather than direct evidence. The importance of environmental factors is well established in animal models that share the characteristics of genetic susceptibility, autoimmune pathology, and variable expression of the disease; e.g., diet influences alter expression of diabetes in the BB rat (34–36). A role in human disease has been inferred from epidemiological studies. A recent review by the Diabetes Epidemiology Research International study group compares the epidemiological features of some types of environmentally caused cancers with those of diabetes (5). For example, both show striking geographical variation; IDDM is 35 times more common in Finland than Japan (5). In itself this might simply reflect genetic differences between the populations, but there are indications that migrants from low-risk countries take on the risk of their adopted countries. For example, French children in Canada have an incidence of 7.4/100,000 compared with the 4.7/100,000 found in contemporary studies of children in France (37,38). Migrant studies would provide the best means of separating out genetic and environmental factors, but no adequate studies are available.

Although many possible external factors including rising living standards, more refined diet, food additives, vaccination programs, breast-feeding, and psychosocial factors have been considered, the environmental causes of IDDM remain unknown. Viruses remain the most popular and plausible environmental trigger for IDDM. They are, for example, compatible with the observed correlation between incidence and latitude and with the variations and clustering of cases that have been described within countries (39). Certain analogies can be drawn with other diseases of known or postulated viral etiology to support the role of a similar causative agent in IDDM. Multiple sclerosis shows a pattern of geographic variation similar to that described for IDDM (40). Alterations in the pattern of viral infection may result in changes in its clinical manifestations. For example, a recent increase in the proportion of paralytic polio among those infected with the virus has been described and attributed to improved living standards; fewer children are infected in early childhood when subclinical infection is usual and more at a later age when the paralytic form of the disease is more common (41). A similar model would be attractive for IDDM but

is hampered by the lack of a definitely identified infective agent. The congenital rubella syndrome provides the strongest link between a virus and the development of IDDM. Ginsberg-Fellner et al. (42) found that 30 of a cohort of 242 (12%) had developed apparently typical IDDM, and 17 more had impaired glucose tolerance. It is not clear whether these children have true IDDM. There have also been links with Coxsackie virus B4 and B5, with reports of high titers of antibodies against these viruses in up to 60% of new cases of IDDM (43). Because these are taken to represent recent infection and the disease is known to have a long latency, their role is probably to precipitate clinical diabetes in those with established β-cell damage.

In conclusion, the rising incidence of childhood diabetes in northern Europe probably has an environmental cause, although (and despite much speculation) the nature of the environmental agent or agents responsible is unknown. Because almost 50% of all cases occur by age 15 yr and the disease is known to have a long incubation period, exposure to an environmental agent would need to occur early in life or perhaps even in utero. Contact with the agent might trigger a series of autoimmune processes that eventually result in β-cell destruction. An alternative hypothesis would be that most or all genetically susceptible individuals undergo some form of subclinical damage to their β-cells and that the role of environmental agents is to sustain or enhance this to the point of clinical diabetes. Current research into the pathogenesis of IDDM is directed toward reliable detection before the onset of glucose intolerance in the hope that the disease can be aborted at this early stage. True prevention of diabetes is a much longer term objective and, despite uncertainty, is most likely to be achieved by the epidemiological approach.

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