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Nutrition and environmental factors in insulin-dependent diabetes mellitus: a genetic–epidemiological perspective

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Insulin-dependent diabetes mellitus (IDDM) develops, by immune-mediated destruction of the insulin-producing β-cells of the pancreas, as the result of interaction(s) between genetic susceptibility factors and exposure to non-genetic factors. The present paper reviews the aetiology of IDDM from a genetic-epidemiological perspective, with particular emphasis on the role of nutritional factors in the causation of IDDM.

EVIDENCE OF A GENETIC CONTRIBUTION TO INSULIN-DEPENDENT DIABETES MELLITUS

The importance of genetic susceptibility to IDDM is clearly demonstrated by twin studies. Even though representative twin data are scarce, it has been suggested that the concordance rate of IDDM in identical (monozygotic) twin pairs is 25–60 % *v.* 10–15 % in non-identical (dizygotic) twin pairs (Kaprio *et al.* 1992; Leslie *et al.* 1992; Kyvik *et al.* 1995). A genetic component to IDDM is further supported by the well-established tendency to clustering of IDDM within families. Several studies have on a purely empirical basis found rather consistent estimates of recurrence risks of IDDM in the range of 5-10 % among siblings and children of IDDM patients (Degnbol & Green, 1978; Tillil & Köbberling, 1987).

In Caucasian populations strong associations with IDDM are found for the human leucocyte antigen (HLA) markers DR3 and DR4 and their DNA analogues at the HLA-DQ locus (Thorsby & Rønningen, 1993), particularly when present in the heterozygous state DR3/DR4. HLA-DR2, and perhaps DR5, seem to confer protection against IDDM.

The degree of haplotype-sharing in siblings from IDDM families influences the recurrence risk considerably, with an estimated recurrence risk of about 15–20 % for HLA-identical siblings, a risk of about 6 % for haplo-identical siblings and close to 0 % for non-identical siblings (Kumar *et al.* 1993). It is important to note that the estimated risk for HLA-identical siblings seems to be considerably lower as compared with the concordance rate in monozygotic twins. On the other hand, the risk for HLA-identical siblings is considerably higher than the risk among unrelated individuals that carry high-risk HLA markers (i.e. the HLA-DR3/DR4 heterozygous category).

It is at present not certain whether the genetic susceptibility to IDDM is conferred by susceptibility gene(s) from a single locus (like HLA-DQ), or whether susceptibility genes from several loci on an extended haplotype are necessary (Tuomilehto-Wolf *et al.* 1989).

Evidence of possible influence from genetic markers outside the HLA-region has been suggested for some years (for a review, see Field, 1991). As part of the efforts to map the

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human genome, new data support the evidence of genetic susceptibility to IDDM linked to several loci, including the insulin gene on chromosome 11 (Davies *et al.* 1994; Hashimoto *et al.* 1994) and other loci (Davies *et al.* 1994). The concept of additional, non-HLA-linked susceptibility to IDDM is supported by the higher concordance rate among monozygous twins as compared with HLA-identical siblings, although higher degree of sharing of environment in twins also may contribute to this difference.

Attempts have been made to establish models of the genetic susceptibility to IDDM. Although no definite models have been obtained, it seems that simple dominance is unlikely, and that the frequency of the disease-susceptibility gene(s) is rather high with a low penetrance (Green *et al.* 1985; Rich *et al.* 1987; Pascoe *et al.* 1989). If this reflects the reality, the largest contribution to the pool of susceptibility genes originates from non-affected individuals.

It should be stressed that only a limited part of the genetic susceptibility to IDDM is explained at present. Even for those marker combinations most strongly associated with IDDM (e.g. the HLA DR3/DR4 heterozygous class), calculations show that the absolute risk of IDDM is only 5–10 % at most. For example, it can be shown by simple algebra that if the general population risk is 0·5 % and the relative risk (ratio between two absolute risks) of a given marker is as high as 50, the corresponding absolute risk for individuals carrying this marker is about 8–9 %. Accordingly, only very few individuals belonging to a high-risk-marker category will eventually develop IDDM.

It should also be kept in mind that in spite of the apparent strong genetic determination of IDDM susceptibility, about 80–90 % of newly-diagnosed children will represent single-case families, i.e. without previously known cases of IDDM among close relatives (Dahlquist *et al.* 1989).

EVIDENCE OF A NON-GENETIC CONTRIBUTION TO INSULIN-DEPENDENT DIABETES MELLITUS

The most striking evidence of a non-genetic contribution to IDDM relates to the fact that the concordance rate in monozygotic twins is far below unity (Kaprio *et al.* 1992; Leslie *et al.* 1992; Kyvik *et al.* 1995). Since monozygotic twin partners have identical genes, this difference can only be attributed to the influence of non-genetic exposures.

Two additional lines of evidence provide support for the non-genetic contribution. First, the huge variation in the incidence of IDDM between Caucasian populations (Green *et al.* 1992) cannot be explained by the geographical distribution of susceptibility genes. For example, the risk of developing IDDM is several times higher in Finland as compared with genetically-similar populations like Estonia and Hungary. Similarly Iceland shows a risk of IDDM that is two-fold less than that in Norway from where the founders of Iceland emigrated centuries ago. Second, the rising incidence of IDDM, as observed in many European populations (Bingley & Gale, 1989), cannot possibly be explained by increased size of the pool of susceptibility genes (Green, 1990). As mentioned previously most new cases of IDDM develop in families without a previously known history of the disease and this indicates that the large majority of all susceptibility genes are carried by unaffected individuals, thereby supporting the genetic models described previously.

The identification of non-genetic determinants of IDDM is of particular importance because they are potentially modifiable for the purpose of disease prevention. In spite of intensified efforts, the results have not so far led to a unified hypothesis for the non-genetic contribution to IDDM diabetes (for reviews, see Leslie & Elliott, 1994). The research has

focused on viral infections, stressful life events, and socio-economic status, as well as nutritional factors.

Virus infections, as reviewed by Yoon *et al.* (1992), have been implicated for a long time in the causation of IDDM. It has been demonstrated that congenital rubella infection is associated with a high risk of subsequent development of IDDM (Menser *et al.* 1978). The development of IDDM has been associated also with cytomegalovirus infection, mumps and Coxsackie B infections (Banatvala *et al.* 1985). The mechanisms by which infectious agents cause β-cell destruction by immune-mediated mechanisms are largely unknown. It may also be possible that viral infections are associated with clinical precipitation of IDDM in subjects suffering from ongoing β-cell destruction.

A few studies have addressed the possible aetiological role of psychological factors and stressful life events in the period preceding clinical onset of disease. Although with rather weak associations, several reports have provided consistent evidence of such possible influences (Robinson & Fuller, 1985; Siemiatycki *et al.* 1989; Hägglöf *et al.* 1991). It is most likely that stressful life events and psychological dysfunction may, through elevated stress hormone levels, increase the demand for endogenous insulin production and thereby accelerate clinical precipitation of IDDM in individuals with ongoing β-cell destruction.

Conflicting results have been reported regarding the influence of socio-economic status on the risk of developing IDDM. After attempts to stratify their study populations according to income level and other indicators of socio-economic status, Christau *et al.* (1977), in the Copenhagen area, Denmark, found higher incidence of IDDM in regions with relatively low average income level, whereas Siemiatycki *et al.* (1988) found an opposite trend. In both studies, however, the incidence differences between social classes were rather modest only, and neither study applied a case–control technique to evaluate the extent to which the individual cases from the various sub-areas in fact were representative of those particular status levels. In a Swedish case–control study (Blom *et al.* 1989) a positive, but rather weak association between IDDM and low educational and income level was found.

The results from studies of associations between indicators of socio-economic status and IDDM are difficult to interpret. First, comparisons between studies are hampered by differences in definitions, study design and methods of data analysis. Second, as proposed by Blom *et al.* (1989), such associations are probably explained by unknown events and factors in life style that influence the risk of developing IDDM as well as the socio-economic status.

NUTRITIONAL FACTORS IN THE CAUSATION OF INSULIN-DEPENDENT DIABETES MELLITUS

Following results from animal studies indicating that dietary changes influence the incidence of diabetes (Elliott & Martin, 1984), several studies in human subjects have focused on the possible role of dietary factors in IDDM. A study from Iceland suggested that exposure to nitrosamines in women at the time of conception may increase the risk of IDDM in the male offspring (Helgason & Jonasson, 1981). Some support for this concept has come from the case–control studies in Sweden (Dahlquist *et al.* 1990, 1991) and Finland (Virtanen *et al.* 1994*a*), but the finding needs confirmation and does not explain the high IDDM incidence level in populations where exposure to nitrosamines is less common than in Iceland.

The association between IDDM and breast-feeding has been extensively studied since Borch-Johnsen *et al.* (1984) concluded that reduced length of breast-feeding during infancy seems to be associated with increased risk of developing IDDM. Some studies have confirmed this finding (Mayer *et al.* 1988; Blom *et al.* 1989; Virtanen *et al.* 1992; Verge *et al.* 1994), whereas another Danish study (Kyvik *et al.* 1992) and a recent Swedish study (Samuelsson *et al.* 1993) have been unable to do so. The literature on cows'-milk exposure and IDDM has been reviewed extensively (Gerstein, 1994; Scott *et al.* 1996). In general, the associations described have been weak and, if causal, can explain the development of diabetes in only a limited number of cases. Also, changes in breast-feeding habits over time as well as recall biases are potential confounders that are difficult to control.

The possible association between reduced breast-feeding and IDDM risk may reflect an aetiological role of cows'-milk protein, as indicated by a much higher occurrence of antibodies to cows'-milk protein in newly-onset diabetic children as compared with control subjects (Karjalainen *et al.* 1992; Verge *et al.* 1994). This possible association is in accordance with migrant studies from New Zealand, demonstrating that Samoan children in New Zealand, following introduction to milk formula, increased their risk of IDDM as compared with children in Samoa (Elliott, 1992). Also, in an ecological analysis Dahl-Jørgensen *et al.* (1991) found an almost perfect correlation between population incidence of IDDM and consumption of milk products. Accordingly, the increased IDDM risk among children with lack of or with reduced duration of breast-feeding might be explained by early introduction to a protein that acts as a trigger for the immunological destruction of the β-cells, possibly by cross-reaction with a membrane protein(s) of the β-cell (Robinson *et al.* 1993). At present, however, this hypothesis remains controversial. First, the epidemiological evidence concerning the association between breast-feeding and IDDM is rather weak and inconsistent (as mentioned previously). Second, a recent large-scale study from the USA (Atkinson *et al.* 1993) could not confirm the initial findings of Karjalainen *et al.* (1992). The present evidence suggests that cows'-milk protein may be only one of several possible factors initiating the destruction of the β-cells.

As a curiosity, Tuomilehto *et al.* (1990) reported, from an ecological study, that the population incidence of childhood IDDM correlates very well with coffee consumption. Additional support for this possible association, which remains unexplained, was provided in a Finnish case–control study (Virtanen *et al.* 1994*b*).

EVIDENCE OF INTERACTIONS BETWEEN GENES AND ENVIRONMENT

It is unknown how genetic susceptibility factors and non-genetic determinants of IDDM exert their effects. Some recent findings suggest that the causation of IDDM involves an interaction between genetic and non-genetic factors. It appears that the populations, like Finland and the other Nordic countries, UK, The Netherlands and Sardinia, in which the incidence of IDDM has been increasing (Bingley & Gale, 1989), all have a rather high prevalence of genetic susceptibility factors (K. S. Rønningen, T. S. Halstensen, D. E. Undlien, R. Ploski, K. Welsh, J. A. Todd, I. Kockum, N. de Vries, A. Kimura, E. Thorsby and A. Green, unpublished results). Analyses showing a strong current correlation between population incidence of IDDM and prevalence of HLA-DQ markers would have revealed no firm correlation if performed a few generations ago. This implies that something has happened in the environment and/or life style in populations that also are characterized by high prevalence of susceptibility genes, making individuals at high genetic risk more susceptible. This concept is further supported by the recent observation that the risk of IDDM in parents and siblings of newly-onset cases with IDDM is positively correlated

with the general population risk of IDDM (Green and EURODIAB ACE Study Group, unpublished results). It remains to be established whether new risk factors have been introduced in these populations or whether susceptibility has been increased in individuals carrying susceptibility genes. The nature of the increasing incidence of IDDM, described in most populations as a gradual rise, supports the latter possibility.

CONCLUSIONS AND IMPLICATIONS FOR PREVENTION OF INSULIN-DEPENDENT DIABETES MELLITUS

Several lines of evidence from different types of investigations suggest that nutritional factors play a role in the aetiology of IDDM. The exact causative mechanisms need to be determined, particularly in relation to whether nutritional factors exert their effect in the initiation of the β-cell destruction or whether they act as precipitators of overt IDDM.

Various combinations of genetic factors confer various levels of individual risk of IDDM. Furthermore, several different non-genetic factors have, in addition to nutrition factors, been associated with the disease. Possibly, IDDM may develop as a consequence of the interaction between many different combinations of individual genotypes and environmental exposures. Accordingly, IDDM may represent a case of aetiological heterogeneity, even though the different possible aetiologies may lead to a common pathogenetic pathway of immune-mediated β-cell destruction. If so, prevention of IDDM requires individual risk assessment before possible intervention, and measures implemented at the population level will most probably prove less efficient.

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