Chapter 8
Risk Factors for Insulin-Dependent Diabetes

Janice S. Dorman, PhD; Bridget J. McCarthy, MS; Leslie A. O’Leary, PhD; and Anita N. Koehler, MPH, RD

SUMMARY

Insulin-dependent diabetes mellitus (IDDM) is one of the most common chronic diseases in childhood; its incidence is increasing in the Americas and around the world. However, the etiology of this disorder remains unclear. Epidemiologic patterns, including the higher IDDM incidence rates in Caucasians compared with African Americans or Hispanics, the increase in risk at puberty, and the more frequent occurrence of the disease during the winter months, suggest that viruses, nutrition, and socioeconomic factors may be involved. These environmental risk factors have been investigated in numerous populations but have yielded conflicting results. This has been due, in part, to a failure to account for host susceptibility in most studies. The genes that confer susceptibility to IDDM are located in the HLA region of chromosome 6. Individuals who carry alleles containing DNA sequences coding for arginine in position 52 of the DQα chain (DQA1*Arg-52) and an amino acid other than aspartic acid in position 57 of the DQβ chain (DQB1*non-Asp-57) are known to be at high risk for IDDM. Genetically susceptible individuals who also have autoantibodies to islet cell antigens or to glutamic acid decarboxylase are at greatest risk for developing IDDM. Despite our ability to identify several important risk factors, we are currently unable to prevent the occurrence of IDDM, even in those who are genetically susceptible and immunologically compromised. Future epidemiological studies of potential etiologic determinants, focusing on host and environmental risk factors and their interactions, are likely to provide important information regarding the causes of IDDM and lead to approaches for disease prevention.

POPULATION STUDIES OF IDDM

RACE AND ETHNICITY

IDDM is one of the most common chronic disorders of childhood (see Chapter 3). Standardized descriptive studies of the epidemiology of IDDM are being conducted around the world, providing much needed information regarding the frequency and potential risk factors for IDDM in developed and developing countries. In many areas, these investigations are being facilitated through the World Health Organization Multinational Project for Childhood Diabetes, known as Diabete Mondiale or the DiaMond Project, and the EURODIAB ACE Study in Europe. They have provided clear evidence that racial and ethnic background represents one of the most important risk factors for IDDM. As illustrated in Figure 8.1, IDDM incidence is highest (>20 per 100,000 per year) in children in the Scandinavian countries and Sardinia, Italy, and is intermediate (3-19 per 100,000 per year) in the United States, Spain, and Israel. Asian and Native American populations, as well as people in...
Latin American countries, such as Chile and Mexico, have some of the lowest incidence in the world, with rates of <3 per 100,000 per year.

Differences in IDDM incidence within countries have also been observed. More than a sixfold variation in risk exists in Italy, where rates range from ~6-7 per 100,000 per year in the northern and central parts of the country to 30 per 100,000 per year on the island of Sardinia. Studies in the United States have focused on Caucasians, African Americans, and Hispanics (Figure 8.2). In Allegheny County, PA, the incidence of IDDM in children is higher in Caucasians (18.0 per 100,000 per year) than African Americans (15.3 per 100,000 per year). An even larger racial difference has been found in Jefferson County, AL (15.6 per 100,000 per year in Caucasians versus 7.0 per 100,000 per year in African Americans). Among Hispanics in Colorado, the incidence of IDDM is lower than for non-Hispanics (9.5 per 100,000 per year versus 15.3 per 100,000 per year, respectively).

**GENDER AND AGE**

Gender does not appear to be a significant determinant of IDDM, since incidence rates are generally similar for males and females. The distribution of age at onset for IDDM is also relatively consistent across populations, with a small peak occurring at ~5 years of age in males (Figure 8.3) and a larger peak observed for both sexes occurring near puberty. This age pattern may reflect exposure to infectious agents during childhood, growth spurts, or hormonal changes that occur during adolescence. Interestingly, diabetic children diagnosed before puberty have been reported to be taller at IDDM onset than nondiabetic siblings or control children of the same age. Although a decreased growth velocity during the prediabetic period was reported by a recent twin study, most published data suggest that immunologic or metabolic factors related to accelerated growth, which is most significant during puberty, contribute to the etiology of IDDM. Thus, the risk of IDDM increases with age during childhood and adolescence. However, there is a decline in incidence of IDDM during adult years.

**SEASONAL VARIATION**

Seasonal variation in the onset of IDDM has been observed worldwide, suggesting that infectious agents are potential risk factors. Data from the Allegheny...
Most studies from both the northern and southern hemispheres have found a reduction in the number of cases occurring during the warm summer months. These epidemiologic patterns indicate that environmental factors such as viruses, which vary dramatically across populations, contribute to the etiology of IDDM. However, genetic differences also exist across racial groups and countries and appear to be a major determinant of the worldwide patterns of IDDM.

### Table 8.1

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Prevalence in parents</th>
<th>Risk to siblings before age 30 years</th>
<th>Risk to offspring of IDDM fathers and mothers before age 30 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>Montreal, Canada</td>
<td>3.2%</td>
<td>4.1% prevalence</td>
<td>3.3% prevalence</td>
</tr>
<tr>
<td>34</td>
<td>Boston, MA</td>
<td>5.7%</td>
<td>4.6% prevalence</td>
<td>3.3% prevalence</td>
</tr>
<tr>
<td>35</td>
<td>Pittsburgh, PA</td>
<td>2.6%</td>
<td>1.4% mothers</td>
<td>3.7% fathers</td>
</tr>
<tr>
<td>36</td>
<td>Minnesota</td>
<td>3.0%</td>
<td>5.5% prevalence</td>
<td>3.3% prevalence</td>
</tr>
<tr>
<td>37</td>
<td>Boston, MA</td>
<td>1.3%</td>
<td>3.1% (either parent)</td>
<td>1.1% (mother)</td>
</tr>
<tr>
<td>38</td>
<td>Boston, MA</td>
<td>2.0%</td>
<td>1.1% (mother)</td>
<td>1.1% (mother)</td>
</tr>
<tr>
<td>39</td>
<td>Pittsburgh, PA</td>
<td>1.0%</td>
<td>1.0% mothers</td>
<td>1.1% (mother)</td>
</tr>
<tr>
<td>40</td>
<td>Pittsburgh, PA</td>
<td>3.0%</td>
<td>1.4% (either parent)</td>
<td>1.0% (either parent)</td>
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<tr>
<td>41</td>
<td>Wisconsin</td>
<td>6.4%</td>
<td>15.4% prevalence</td>
<td>4.3% (father)</td>
</tr>
<tr>
<td>42</td>
<td>Pittsburgh, PA</td>
<td>6.3% incidence</td>
<td>6.3% whites</td>
<td>2.8% blacks</td>
</tr>
<tr>
<td>43</td>
<td>Boston, MA</td>
<td>4.8% (either parent)</td>
<td>3.4% (mother)</td>
<td>3.5% (mother)</td>
</tr>
</tbody>
</table>

Source: Reference 32

### GENETIC SUSCEPTIBILITY

**RISK OF IDDM IN RELATIVES**

More than 80% of cases of IDDM occur in individuals with no family history of the disease. However, in the remaining 20%, IDDM aggregates in families. The overall risk before age 30 years for North American Caucasian siblings, parents, and offspring of individuals with IDDM ranges from 1% to 15% (Table 8.1), compared with rates of <1% for individuals without IDDM relatives. Most data on risk of IDDM in family members are from Caucasian populations that have similar incidence rates. There is a paucity of information for other racial groups in the Americas, including African Americans and Hispanics. In Allegheny County, PA, there was a lower risk for developing IDDM in siblings of African-American IDDM patients, compared with Caucasians (2.8% versus 6.5% through age 30 years). Although the sample size was small for the African-American population, these findings parallel the racial difference in IDDM risk for the general population. There also appears to be an
increased risk of IDDM in relatives of subjects with non-insulin-dependent diabetes mellitus (NIDDM) \(^{44}\). This may be related to specific HLA haplotypes that confer susceptibility to both IDDM and NIDDM \(^{45}\).

For children with IDDM who have an IDDM parent, the father is more likely to have the disease than the mother\(^{39,39,41}\). The prevalence of paternal compared with maternal IDDM was 6.2% versus 2.3% in Sweden\(^{39}\) and 5.7% versus 2.6% in Finland \(^{4}\). Prospective studies that ascertained IDDM in the offspring of parents with IDDM have also revealed a higher risk of IDDM in children of affected fathers than mothers (6.6% and 2%, respectively; Table 8.1)\(^{37,40,43,47}\). Several studies that ascertained IDDM in the offspring of parents with IDDM also observed. DR7 in African Americans \(^{54}\), DR5 in Hispanics \(^{55}\), and DR9 in Chinese \(^{56}\) and Japanese \(^{53}\) also appeared. DR7 in African Americans \(^{53}\), DR5 in Chinese \(^{56}\), and DR3 in Japanese \(^{53}\) also appeared to contribute to IDDM susceptibility.

With advances in molecular biology, HLA studies of IDDM are being conducted at the DNA level in populations across the world. Molecular techniques have simplified procedures required for specimen collection from large population-based cohorts. They have also provided researchers with more precise markers of IDDM susceptibility than those afforded by conventional serological techniques. Analyses in a variety of racial and ethnic groups have revealed that DNA sequences in the DQB1 gene coding for the presence of an amino acid other than aspartic acid in the 57th position (non-Asp-57) is highly associated with developing IDDM, whereas sequences coding for aspartic acid appear to confer resistance to IDDM \(^{57,58}\). This association is much stronger than the association between IDDM and HLA-DR3 and DR4\(^{47}\) and reflects the results of older HLA-DQ serological studies, which revealed an increase in DR2 in African Americans with IDDM \(^{45}\). The consistency of the results of molecular studies of the DQB1 gene in most populations confirms its importance as a locus determining IDDM susceptibility.

An exception was found for the Japanese and the DR4-DQ4 susceptibility haplotype, which contains DQA1*0301 and DQB1*0401. The latter codes for aspartic acid in position 57 (Asp-57), but the DQA1 gene contains DNA sequences that code for arginine in position 52\(^{59,60,61}\). DQA1*0301 is also found in African American but not Caucasian DR7 haplotypes, both of which contain DQB1*0201 (non-Asp-57). Caucasian DR7 haplotypes carry the DQA1*0201 allele (non-Arg-52) and appear to be less diabetogenic. DQA1*Arg-52 genes are associated with IDDM in a variety of racial and ethnic groups and represent consistent independent markers of IDDM susceptibility \(^{45,49,51,52,54}\). For example, in Hispanics and non-Hispanics in Colorado, there was an increase in DQ1*0303 (Arg-52), as well as DQB1*0201 and DQB1*0302 (non-Asp-57) in individuals with IDDM compared with nondiabetic individuals \(^{55}\).

The combination of DQA1*Arg-52 and DQB1*non-Asp-57 alleles seem to be particularly diabetogenic. The associations between these molecular polymorphisms and IDDM may have a biological basis. The presence of aspartic acid in position 57 of the DQ \(\beta\) chain and arginine in position 52 of the DQ \(\alpha\) chain affects the peptide binding ability of the HLA molecule, which influences the recognition of the HLA-peptide complex by particular T cell clones\(^{49}\). Structural modifications such as these may explain the importance of specific amino acid sequences in determining susceptibility or resistance to IDDM, suggesting that the molecules are directly involved in IDDM etiology.

Immunogenetic studies have been conducted in populations in which the incidence of IDDM has been established from a registry\(^{51}\), including China\(^{51}\), Nor-
way49; Sardinia, Italy; and African Americans and Caucasians in Allegheny County, PA. The prevalence of the DQB1*non-Asp-57 genotypes varies significantly in people with IDDM from these five populations (from 6% in China to 100% in Sardinia), as well as in nondiabetic individuals (from 0% in China to 38% in Sardinia), with an increase in non-Asp-57 homozygosity in areas with a high incidence of IDDM59. In each of the five populations, the risk of IDDM in non-Asp-57 homozygotes compared with Asp-57 homozygotes was significantly increased, ranging from 14 to 11. For Allegheny County Caucasians, the incidence rate for IDDM was highest for non-Asp-57 homozygotes (47.6 per 100,000 per year), intermediate for heterozygous individuals (13.0 per 100,000 per year), and lowest for Asp-57 homozygotes (0.45 per 100,000 per year), suggesting a dose-response relationship between susceptibility and IDDM risk.

If the geographic differences in risk of IDDM are due to variation in genetic susceptibility to the disease, then incidence rates for IDDM should be similar in persons with the same genotype across populations59. Because the statistical properties of these estimates are currently under investigation, this issue was addressed indirectly by applying the genotype-specific incidence rates for Allegheny County Caucasians to the other four populations to predict the overall IDDM incidence rate for each area. Each of the predicted rates fell within the 95% confidence intervals for the rates established through IDDM registries (Figure 8.5).

Both the DQA1 and DQB1 genes are important in determining susceptibility to IDDM64. The risk of developing the disease appears to be markedly increased for individuals who are homozygous for both DQB1*non-Asp-57 and DQA1*Arg-52 alleles. Moreover, at least two-thirds of the incidence of IDDM (attributable risk of ≥62%) can be explained by the contribution of these high-risk genes in most populations. In contrast, individuals who are heterozygous at one of the two genetic loci have a risk for IDDM that is similar to that for the general population. These studies emphasize the importance of the complete DQ molecule (composed of an \( \alpha \) and a \( \beta \) chain) in the etiology of IDDM.

In the future, it will be important to directly evaluate the geographic variation in IDDM incidence in genetically homogeneous subgroups, and to accurately quantify the contribution of host susceptibility to the global patterns of IDDM. Knowledge of the proportion of susceptible individuals in a population and the magnitude of their risk will provide extremely important information for implementation of prevention strategies and health planning initiatives. The development of the field of molecular IDDM epidemiology will, therefore, test unique hypotheses and achieve a great deal in terms of scientific advancement and public health31.

ISLET CELL ANTIBODIES, INSULIN AUTOANTIBODIES, AND GAD

Islet cell cytoplasmic antibodies (ICA)69, as well as antibodies to insulin69, the 64kD islet cell antigen71, and the enzyme glutamic acid decarboxylase (GAD)72, are highly prevalent in persons with IDDM. However, it is unclear whether they play a direct role in the disease process or serve as markers of tissue damage initiated by other etiologic agents. Despite differences in the types of ICAs and variation in laboratory methodology used to detect these molecules, most studies have reported a very high prevalence of ICA (65%-100%) in patients with newly diagnosed IDDM73. This high prevalence contrasts with rates of 2%-5% in first-degree relatives (parents, offspring, and siblings) of patients with IDDM, and rates of 0.5% or less in nondiabetic persons64. In the United States, prevalence rates for ICA of 0.4%-0.8% have been reported13,16; ICA are potent risk factors for IDDM, and first-degree relatives of patients with IDDM have a risk of developing IDDM that is 50-500 times that of people without ICA12. However, most individuals with ICA will never develop the disease. Thus, the predictive value for ICA in identifying which individuals will eventually go on to develop IDDM is low, and has been estimated at ~20%13.
Several studies have examined the relationship between HLA and IDDM. An investigation of German schoolchildren revealed that non-Asp-57 homozygosity was increased in children who were ICA positive, compared with children who were ICA negative. A study of French schoolchildren found a similar distribution of DQB1*non-Asp-57 alleles in ICA positive and negative individuals. These findings are consistent with molecular studies of ICA positive and negative Caucasian family members from Allegheny County, PA. Although the proportions of first-degree relatives who were homozygous for both DQB1*non-Asp-57 and DQA1*Arg-52 were similar in those with (19%) and without (15%) ICA, the subsequent development of IDDM was restricted to individuals who were both ICA positive and genetically susceptible.

Insulin autoantibodies (IAA) are another immune marker for IDDM. However, methodologic variabilities and the ability to detect IAA in only ~50% of those who later develop IDDM limits their utility in identifying individuals at high risk for IDDM.

The most promising of the immune markers for IDDM are antibodies to GAD, originally identified as a 64,000-M protein islet cell antigen. Several studies have examined the prevalence of GAD in IDDM and nondiabetic subjects. In U.S. Caucasians, 84% of newly diagnosed IDDM patients and 82% of ICA-positive diabetic subjects were both ICA positive and genetically susceptible. GAD may also help discriminate between NIDDM and IDDM. In one study, 69% of patients with a short duration of IDDM were positive for GAD antibodies, while only 5% of individuals with NIDDM and none of the nondiabetic subjects were GAD positive. Accordingly, GAD potentially has the best ability to predict the development of IDDM. However, prospective investigations and studies of the general population are required to determine the accuracy of this marker in identifying individuals who will subsequently develop IDDM. By evaluating the presence or absence of high-risk IDDM susceptibility genes and organ-specific autoantibodies, future population-based family and case-control studies will assess both the relative and absolute risks associated with these potential determinants of the disease.

**ENVIRONMENTAL RISK FACTORS**

Twin studies have shown that genetic susceptibility to IDDM appears to be necessary, but is not sufficient to cause the development of the disease, because concordance for IDDM occurs in only ~36% of monozygous twin pairs. Thus, there must be a role for environmental factors in the etiology of IDDM. Nutrition and viruses have been suggested as potential determinants of the disease.

**NUTRITION**

Various nutrients and nutritional practices have been associated with the development of IDDM. Animal studies have consistently shown that diets containing intact protein, in contrast to diets with protein hydrolysates or an amino acid mixture, contribute to high rates of diabetes in susceptible animals. Studies in humans have revealed less dramatic effects. However, a positive association between ingestion of smoked/cured mutton by Icelandic women at conception and subsequent development of IDDM in their offspring was reported. In addition, the intake of foods containing high amounts of nitrosamines appears to be related to the etiology of the disease. Moreover, an ecologic relationship between nitrogen level in potable water supplies and IDDM incidence has been reported.

Studies have also examined the effect of nicotinamide, a water-soluble vitamin, on maintaining insulin secretion in newly diagnosed IDDM cases, but results have been inconsistent. Individuals with high ICA titres and low first-phase insulin response were significantly less likely to develop IDDM if they received daily doses of nicotinamide. However, longer follow-up of individuals in well-controlled clinical trials is needed before the efficacy of nicotinamide for preventing IDDM can be advocated.

The most widely studied nutritional risk factor for IDDM is breast-feeding and exposure to cow's milk protein. In the early 1980s, an inverse relationship between breast-feeding and IDDM incidence was observed, suggesting that breast-feeding was a protective factor. The incidence of IDDM is highly correlated with the amount of cow's milk consumed in various countries. Also, a positive correlation has been found between IDDM incidence and intake of unfermented cow's milk, and a negative correlation with the prevalence of breast-feeding through at least age 3 months. Studies in Canada, the United States, and other countries have corroborated these findings, showing a decreased IDDM risk in individuals who had a longer duration of breast-feeding, particularly those who were exclusively breast-fed.

A study of African Americans and Caucasians in Allegheny County, PA revealed that Caucasian children...
with IDDM were 50% less likely to have been breast-fed than those without IDDM. Although duration of breast-feeding did not differ by diabetes status for Caucasians or African Americans, African Americans with IDDM were more likely to have received breast milk substitutes at an earlier age than those without IDDM (5.1 weeks versus 11.9 weeks, p=0.02). This association, however, was not significant for Caucasians (5.5 weeks versus 7.1 weeks, p=0.18), which may indicate a larger genetic influence in Caucasians or the contribution of other environmental factors to the etiology of IDDM.

Meta-analysis of selected studies on breast-feeding or early exposure to cow’s milk and the development of IDDM revealed that patients with IDDM were 43% more likely to have been breast-fed <3 months and 63% more likely to have been exposed to cow’s milk before age 3-4 months. Thus, early exposure to cow’s milk may be an important risk factor for IDDM and appears to increase the risk ~50%.

The relationship between exposure to cow’s milk and IDDM has been investigated in genetically high- and low-risk Caucasian IDDM cases in Colorado. Exposure to cow’s milk at age <3 months was 11-fold higher in persons with IDDM, compared with non-diabetic persons among high-risk cases, defined as DQB1*non-Asp-57 homozygotes. This association was not found in low-risk individuals. These data suggest that there is an interaction between the genetics of the individual (DQB1*non-Asp-57) and an environmental factor (cow’s milk) in the development of IDDM. However, additional studies are needed to confirm these findings in other ethnic groups in the Americas.

Lactoglobulin (casein), the major portion of protein in cow’s milk, was significantly associated with an increased risk of IDDM in Sweden. A Finnish study also found significantly higher levels of antibodies to both cow’s milk and to lactoglobulin in IDDM children, compared with non-diabetic siblings and unrelated non-diabetic individuals. Antibody levels were especially high in IDDM children age <3 years, suggesting that cow’s milk proteins may have a particularly significant effect on the development of IDDM in young children.

The whey protein, bovine serum albumin (BSA), is the suspected milk protein trigger of an autoimmune response in genetically susceptible individuals. Antibodies to a 17-amino acid section of the BSA molecule (ABBS), which react with a β-cell surface protein, have been found in children with IDDM. Since infants have an immature digestive system, exposure to large proteins such as BSA may allow these molecules to pass directly into the bloodstream. It has been proposed that genetically susceptible children who have been exposed to cow’s milk at age 3-12 months (prior to gut closure) may develop antibodies to ABBS. On exposure to viral infections at a later time, the sensitized immune system may mistake the β-cell protein for ABBS and contribute to the β-cell destruction that occurs in IDDM. Similar studies in Caucasians, African Americans, and Hispanics living in the Americas are needed to fully evaluate the nutritional etiology of IDDM.

Table 8.2

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Exposure</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>IDDM patients from New York diabetic clinic; non-diabetic individuals were friends.</td>
<td>No breast-feeding vs. some breast-feeding</td>
<td>1.00 (0.45-2.24)</td>
</tr>
<tr>
<td>97</td>
<td>IDDM patients from Colorado registry; non-diabetic individuals from office practices and an unrelated study.</td>
<td>Breast-feeding &lt;3 months vs. ≥3 months</td>
<td>1.47 (0.85-2.56)</td>
</tr>
<tr>
<td>98</td>
<td>IDDM patients from Montreal, Canada, registry; non-diabetic individuals were friends and relatives.</td>
<td>No breast-feeding vs. some breast-feeding</td>
<td>1.30 (0.70-2.50)</td>
</tr>
<tr>
<td>99</td>
<td>IDDM patients from Allegheny County, PA and Children’s Hospital registries; non-diabetic individuals were siblings.</td>
<td>No breast-feeding vs. some breast-feeding</td>
<td>2.00 (1.11-3.33)</td>
</tr>
<tr>
<td>100</td>
<td>IDDM patients from Colorado registry; non-diabetic individuals from licensed drivers.</td>
<td>No breast-feeding vs. some breast-feeding</td>
<td>1.09 (0.68-1.76)</td>
</tr>
<tr>
<td>100</td>
<td>IDDM patients from Colorado registry; non-diabetic individuals from licensed drivers.</td>
<td>Cow’s milk before age 3 months vs. after age 3 months</td>
<td>4.50 (0.90-21.40)</td>
</tr>
<tr>
<td>101</td>
<td>Meta-analysis</td>
<td>Breast-fed &lt;3 months vs. ≥3 months</td>
<td>1.43 (1.15-1.77)</td>
</tr>
</tbody>
</table>

CI: confidence interval
Source: References are listed within the table
VIRUSES

Strong arguments have been made for the role of recent exposure to the Coxsackie B virus in IDDM etiology. Coxsackie viruses B2, B3, B4, and B5 have all been isolated from the sera of persons with newly diagnosed IDDM. The Coxsackie B4 virus has most often been associated with the disease, but the findings are not consistent. Although it is unknown whether the virus may initiate or accelerate β-cell destruction, it is hypothesized that variants of the Coxsackie B virus have different potential in causing diabetes. However, the majority of IDDM cases show no evidence of recent viral infection at diagnosis of IDDM. Interestingly, Coxsackie B virus infections were more prevalent in IDDM patients in Wisconsin who were DR3 positive, compared with those who were DR3 negative, thus suggesting a potential host-environment interaction contributing to the development of IDDM.

Attention has recently focused on persistent viral infections as possible triggers of autoimmune disease. The incorporation of human cytomegalovirus (CMV) gene segments into genomic DNA has been significantly associated with IDDM in newly diagnosed patients, and a relationship between CMV genome positivity and islet cell antibodies has also been reported. Persistent CMV infection may lead to the expression of viral or host antigens on the β-cells of the pancreas, resulting in the production of ICA. Alternatively, molecular mimicry may contribute to the production of antibodies that recognize both viral and host antigens. Aberrant β-cell expression of HLA class II molecules may also contribute to the beginning of an autoimmune response, particularly in the presence of DQB1*non-Asp57 and DQA1*Arg52. These issues need to be further explored in etiologic research.

Congenital rubella syndrome (CRS), which results from maternal exposure to the virus causing measles during pregnancy, has been associated with the development of IDDM. Approximately 20% of CRS patients in the United States also have IDDM. The highest frequency of IDDM occurred in CRS cases with HLA-DR3 and DR4. In addition, islet cell surface antibodies occurred in 20% of individuals with CRS, which is consistent with the frequency of these antibodies in patients with IDDM. It has therefore been hypothesized that exposure to rubella infection in utero triggers an autoimmune mechanism in genetically susceptible individuals, subsequently resulting in IDDM.

Several case reports have described a temporal relationship between mumps virus infection and the development of IDDM. Epidemiological studies validating this observation have met with limited success. The incidence of IDDM parallels that of mumps, after allowing for a 4-year lag period in Erie County, NY, and ~50% of children with IDDM in this population had mumps or exposure to mumps ~4 years prior to IDDM onset. However, no evidence of antecedent mumps infection and subsequent onset of IDDM was found in residents of Montreal, Canada. As with Coxsackie B virus, it has been suggested that a particular variant of the mumps virus in combination with genetic susceptibility is necessary for development of IDDM. If mumps is a cause of IDDM, it is likely to be so in only a small proportion of cases.

OTHER POTENTIAL RISK FACTORS

In addition to nutrition and viruses, other potential IDDM risk factors include stress, maternal age, birth order, and socioeconomic status. Several investigators noted that life events such as accidents, pregnancy, and personal problems frequently occurred during the year prior to IDDM onset. These observations were supported by a family study that revealed an increase in the reporting of at least one serious life event during the 6 months prior to disease onset in IDDM compared with nondiabetic siblings. Although investigations of stress and IDDM have, in general, reported positive associations, most studies have been retrospective and suffered from methodological difficulties in assessing stress and measuring its frequency, intensity, and duration. Thus, prospective evaluations of the interaction among stress, the immune system, and the occurrence of autoimmune diseases are warranted.

Characteristics such as older maternal age at birth and higher birth order have also been associated with increased IDDM risk. Several Caucasian studies have reported a higher prevalence of IDDM in children born to older mothers and in children with a higher birth order. These investigations concluded that of the two related potential determinants of IDDM risk, advanced maternal age (i.e., age >35 years at the child’s birth) was the more significant risk factor. Reasons for this association are unclear, but it has been suggested that it may be related to the intrauterine environment. Interestingly, a study from southern India failed to corroborate these findings and, in fact, reported opposite results, with an increased IDDM risk for children with lower birth order and children born to younger mothers. Additional investigations in other ethnic groups, such as African Americans, Asians, and Hispanics, are needed to determine the etiologic significance of these potential risk factors.

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risk factors.

Studies of deprivational differences in IDDM risk emphasize the importance of socioeconomic factors in the etiology of IDDM. In northern England, IDDM incidence rates were highest in the most deprived areas and lowest in the least deprived areas. The deprivation index employed for this study assessed levels of unemployment, car ownership, home ownership, and overcrowding. However, a study from Scotland reported conflicting results, with higher IDDM incidence rates in affluent areas. The authors, therefore, concluded that deprivation appeared to confer significant protection from developing IDDM. These studies reflect earlier conflicting reports indicating that either high or low socioeconomic status was related to IDDM incidence. Such discrepancies may be related to methodologic differences, including different assessments of socioeconomic status or deprivation, which may reflect the influence of different environmental agents in different populations.

Dr. Kelly West, the founder of diabetes epidemiology, said in his landmark book, Epidemiology of Diabetes and Its Vascular Lesions, "It has become evident that many factors contribute in an important way in increasing or decreasing susceptibility to diabetes, and that systematic epidemiologic study has great potential for elucidating mechanisms by which both diabetes and its specific manifestations are caused or prevented." Since that time, much has been learned about the epidemiologic patterns of IDDM in racial and ethnic groups around the world. In the Americas and other continents, new data are emerging for Caucasians, African Americans, and Hispanics regarding potential risk factors for IDDM. These studies are also employing molecular technology to study both genetic and environmental determinants of the disease and will provide critically important information regarding IDDM etiology during the next decade. It is hoped this will lead to the prevention of the disease through risk factor modification in individuals who are genetically susceptible. With the continued efforts of scientists and clinicians in the United States, and the rapid progression of the field of diabetes epidemiology, Dr. Kelly West's vision will be achieved.

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