

How, When, and Why to Predict IDDM

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Insulin-dependent diabetes remains a serious disease replete with life-threatening complications. The onset of the disease is becoming increasingly predictable through the detection of its associated autoantibodies. The natural history of pathogenic events is attenuated in those with adult onset over that seen in infants and children. Immunosuppression therapies in newly diagnosed patients have been shown to induce remissions, whereas various intervention strategies in rodent models (BB rats and nonobese diabetic mice) can delay and even prevent the onset of diabetes. The stage is set for serious consideration of intervention trials to delay the clinical disease in humans. *Diabetes* 37:1591-94, 1988

If the ravages of insulin-dependent diabetes mellitus (IDDM) cannot be prevented, then IDDM itself must be. Among unaffected high-risk relatives of people with IDDM, IDDM is becoming increasingly predictable through the identification of disease-specific autoantibody markers, and the same appears to be true for the general population. Immunotherapy given on diagnosis has been demonstrated to induce remissions in the disease and, if given before this time, should delay clinical onset. Whereas studies to prove this contention are probably imminent, there is need to perfect better markers for disease activity and improved prognostic metabolic measures, so that the short-term effects of therapy on the prediabetic state can be monitored. Even when the ability to delay the clinical onset of IDDM becomes fact, it will take many more years of study before it can be conclusively demonstrated that the benefits from delaying IDDM will outweigh the problems caused by the drugs needed to maintain the prediabetic state.

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HOW TO PREDICT IDDM

Over a decade ago, islet cell autoantibodies were first identified in IDDM, providing evidence of its autoimmune nature (1,2). Only recently, however, have the questions arisen of how long before diagnosis had such autoantibodies been there and whether they could be used to predict the disease (3). The discovery that islet cell autoantibodies (ICAs) of the cytoplasmic type long preceded clinical onset changed the notion of pathogenesis from that of a dramatically acute and probably viral disease that was caught in the fall and early winter to one of an indolent, smoldering autoimmune disease process that often took years to develop.

Several centers have involved themselves in ICA studies of high-risk relatives of probands affected by IDDM. ICAs are polyclonal autoantibodies of the IgG type (4), which are demonstrable by indirect immunofluorescence of islet cell cytoplasm on unfixed cryocut sections of human pancreas. The antigen is thought to be a complex ganglioside present in all islet cell types (5). ICAs are present in a low percentage of first-degree relatives at frequencies that depend on the methods used to detect them. Weakly positive reactions are usually artifacts of limited predictive value, whereas higher titers of ICA that coincide with the properties of complement fixation or reaction with lightly acetone-fixed rat pancreas have excellent predictive value. After three international workshops, it has been possible for most laboratories to standardize the ICA assay. Titer is expressed in terms of Juvenile Diabetes Foundation units, with reference to standard-strength patient sera (6). In follow-up studies of 5-8 yr duration, the cumulative risk of IDDM in relatives without ICA is only ~1%, whereas from 40 to 70% of those with ICA (depending on titer) are observed to progress to IDDM (7,8). In such studies, the relative risk of IDDM dependent on the presence of ICA exceeds 150; however, ~20% of individuals developing IDDM will not have ICA beforehand (9), albeit many of them presumably have had ICA earlier, before they were able to be tested.

More recently, the possible value of insulin autoantibodies (IAAs) to predict IDDM has also been tested (10). IAAs among unaffected relatives are associated with ICA. Rela-

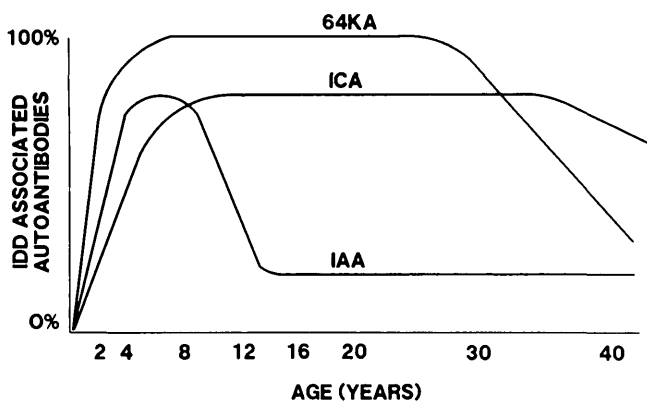


FIG. 1. Time courses of IDDM-associated autoantibodies to 64,000-M, β -cell protein (64KA), islet cell cytoplasm (ICA), and insulin (IAA) in impending IDDM are depicted. Extrapolation of data from human relatives of IDDM probands and nonobese diabetic mouse, which may require modification as more human data become available, is represented.

tives with both ICA and IAA have more impaired insulin responses and are more likely to progress to IDDM than are those with only one of them (9). Finally, autoantibodies to a putative β -cell membrane protein of 64,000 M, (64KA) have been shown to hold the greatest promise as predictive markers of IDDM (11, 12). Essentially, 100% of children and young adults will have 64 KA before onset of IDDM, and some of those developing IDDM in mid to late life will have lost the autoantibody by the time of clinical onset (Fig. 1).

Much has been made of the orderly loss of insulin release after administered glucose before onset of IDDM (13). However, my prejudice is that less than critical use of this metabolic marker will cause confusion. There are extraordinary variabilities in insulin responses at diagnosis ranging from near normal to absent. Moreover, whereas in general patients with impending IDDM showing falling insulin responses over time, many show constant degrees of insulin impairment for long periods preceding their diagnoses. Insulin resistance consequent to hyperglycemia is often present but is reversible with insulin therapy. Hyperglycemia downregulates insulin secretion from impaired β -cells, an effect that is also reversible with insulin replacement leading to the well-known honeymoon period after diagnosis. Normal puberty is associated with marked changes in insulin resistance resulting in increased plasma insulin levels to various stimuli. Undoubtedly, these pubertal changes prove to be too much for many prediabetic adolescents, accounting for the predominance in incidence of IDDM during this time of life. Alternatively, adult relatives with ICA can be identified in whom persistent insulinopenia is relatively stable and only slowly progressive over time (Figs. 1 and 2).

Whereas the study of relatives has greatly enhanced understanding of the natural history of IDDM, only ~15% of patients with IDDM know of affected relatives. Thus, studies of the general population are needed to prove the universal value of the markers. In the few studies undertaken to date, ICAs have been reported to occur at a frequency of ~0.3%, whereas their occurrences are restricted to those predisposed to IDDM, as evidenced by a positive family history of diabetes and/or thyroid autoimmunity and IDDM risk-associated HLA-DR3/4. Indeed, ICA in the general population

has also been associated with subsequent development of IDDM (14).

HLA markers as predictors of IDDM are of limited to no value in the general population. Whereas 95% of patients with IDDM have DR3/4, ~50% of all U.S. Caucasians also have these alleles. For the 3% who are DR3/4 heterozygotes and thus at the highest risk for IDDM, their lifetime risk of the disease only approximates 1 in 40. Even with the new molecular genetics of DQ loci and the ability to split DR4 (and DR2) chromosomes into IDDM-prone and -resistant types, the predictability of IDDM based on HLA typing can only be improved by about twofold. Thus, screening for IDDM based on immunological markers and supported by subsequent HLA typing provides the most cost-effective and logical approach.

WHEN TO SCREEN FOR IDDM

The ability to predict IDDM has some practical benefits. First, many patients with incipient IDDM, especially during mid-to late life, pass through a phase of non-insulin-dependent diabetes (NIDDM) en route to true insulin dependence, whereas others can recover to NIDDM for a time after their stabilization with insulin (Fig. 2). The identification of ICA, especially among nonobese patients with NIDDM, helps to identify those who are developing IDDM and who should not delay their insulin-replacement therapy. Pregnancy, like puberty, is a time of markedly increased insulin resistance. A fraction of patients with gestational diabetes have underlying incipient IDDM. Because pregnancy is also a time of natural immunosuppression, the pathogenic process may remit; however, the expression of diabetes would depend on the degree of β -cell damage already present. Identification of impending IDDM from among those with gestational diabetes would best be achieved by detection of ICA 3–6 wk after delivery.

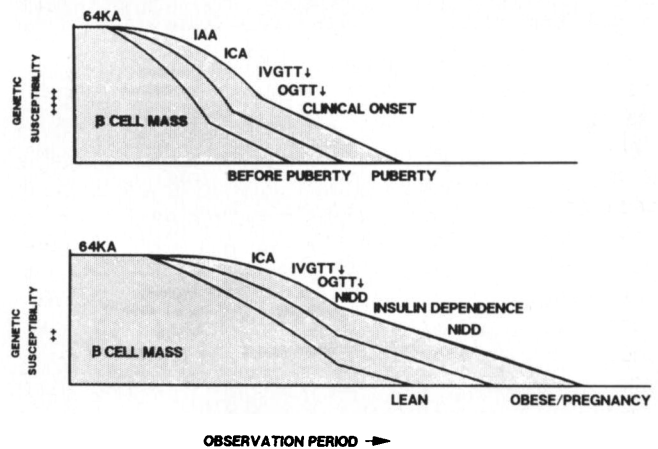


FIG. 2. Sequences of events in natural history of IDDM in infants and children (top) versus adults (bottom). Younger age at onset is associated with greater genetic loading, e.g., higher frequencies of HLA-DR3/4 heterozygotes. Rapidity of β -cell loss is inversely related to age. Diabetogenic stresses from puberty, pregnancy, and obesity may induce clinical diabetes with relatively greater retentions of pancreatic β -cells. These and other factors lead to a spectrum of individual time courses represented by 3 curves for children and for adults. NIDDM may precede or temporarily follow period of insulin dependence in adults. 64KA, 64,000-M, β -cell protein; IAA, insulin autoantibody; ICA, islet cell antibody; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

In most other respects, ICA remains an investigational tool to study the natural history of IDDM. As already mentioned, ICA is much more predictive of IDDM among children than adults (Fig. 2). Thus, of the 2–3% of ICA⁺ nondiabetic parents of offspring with IDDM, only ~15% will become overtly diabetic over a 5-yr observation period. IAAs predict IDDM but usually only before puberty. Younger children who are developing IDDM are more often IAA⁺ and have the highest titers and greatest serum insulin-binding capacities by radioimmunoassay. The 64KA predicts IDDM at all ages. However, the absence of the autoantibody from many patients with late onset of IDDM during mid- and late life suggests that the pathogenic process, once active long before, had become relatively quiescent before diagnosis. The important issues of what ages are best to screen for IDDM and with which autoantibody is unresolved. Pending this information, the screening of relatives for ICA and IAA should occur anytime ≥ 6 mo of age and should be repeated every 1–2 yr.

Recently, our group showed that nonobese diabetic (NOD) mice often develop 64KA as early as 2 wk of age, before weaning (15). After ≥ 2 mo of age, antibodies to insulin develop, coincident with peak β -cell injury. Thus, IAAs appear to arise secondarily, perhaps as a consequence of released β -cell retroviral type A particles, at least in NOD mice (16).

WHY SCREEN FOR IDDM?

Apart from the few practical reasons already cited, screening for IDDM is justified to resolve its natural history in regard to its eventual prevention. Encouragement toward this goal comes from two sources: 1) the successes with immunotherapy in newly diagnosed patients with IDDM (17) and 2) the documented abilities to prevent diabetes in the spontaneously diabetic rodent models. Various nonspecific immune interventions, including antilymphocyte sera, cyclosporin A, silica (to eliminate macrophages), neonatal thymectomy, repeated whole-blood transfusions, and the creation of stable radiation chimeras, can effectively reduce the rate of diabetes in BB rats and NOD mice. Other modifiable factors may also contribute to the diabetic outcome. Diets stripped of complex proteins have been shown to delay onset and to reduce the frequency of diabetes, whereas pretreatment with the antioxidant nicotinamide may dramatically prevent diabetes in the NOD mouse (however, 1 trial in prediabetic humans has failed to do so). The greatest hopes for a specific prevention of IDDM are 1) the avoidance of unidentified triggering agents and 2) that specific immunotherapy can be contrived in which T- and B-lymphocytes autoreactive with a primary β -cell-specific autoantigen can be identified and eliminated. The first possibility implies that molecular mimicry between an environmental dietary or infectious agent and a β -cell autoantigen exists such that a cross-reactive immune response initiates β -cell damage. The second possibility depends on the probability that a single β -cell autoantigen (e.g., 64KA) is primary to the autoimmune process underlying IDDM and all of the others (e.g., those reacting with IAA, islet cell surface antibody, and ICA) are secondary to islet cell damage.

In summary, prevention of IDDM appears to be an attainable goal. The ability exists to predict impending clinical IDDM in high-risk relatives and even in the low-risk general population. The optimal choice of markers for different age groups has become clearer. Metabolic remissions after clinical onset of IDDM have been well demonstrated, and prevention of spontaneous IDDM in the rodent models has been achieved by multiple means.

Before a person could be put onto the moon, enough committed people had to want it to be done and to believe it was possible. Indeed, if this article could help to recruit sufficient numbers of contributing investigators to its cause, then IDDM would soon become a preventable disease. Like other great scientific truths, however, it would need to pass through three classic stages.

First, people would say it conflicts with the Bible (or other established doctrines or scientific dogmas). Next, they would say that it had been discovered before. Lastly, (as it became established fact) they would say they had always believed it.

Louis Agassiz
American naturalist

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