Commentary

New directions for research into type 1 diabetes in India-
An immunological perspective

Dysfunction of the pancreatic beta cell is an essential prerequisite for the development of chronic hyperglycaemia characteristic of diabetes mellitus. The extent, nature and aetiology of the beta cell defect, however, vary in different forms of diabetes. In type 2 diabetes, the defect is postulated to arise from beta cell "fatigue" when an individual is exposed to high levels of insulin resistance over a prolonged period of time. In certain rare monogenic forms of diabetes such as maturity onset diabetes of the young (MODY), the defect arises from a mutation in one or other genes responsible for normal pancreatic development and differentiation, or those concerned with insulin synthesis and function. However, the most severe form of beta cell defect is, that associated with autoimmune type1 diabetes mellitus (T1DM). In this situation, in genetically predisposed individuals, the body's immune system, under the influence of certain triggers, turns against its own beta cells and progressively destroys them, leading to a stage of complete beta cell failure and dependence on exogenous insulin for survival.

While the broad picture of the pathogenesis of T1DM has become clear in the recent years, the exact aetiology remains tantalizingly elusive. In this issue, Dhanwal *et al*[1] attempt to elucidate some of the aspects of the aetiopathogenesis of T1DM in Indian youth, with particular reference to the immunological profile. This assumes importance in light of the fact that there have been only a few studies from India on the autoantibody profile of youth onset diabetes, and none on the viral triggers of the disease.

The destruction of beta cells in T1DM is predominantly mediated by the cellular immune system, with T cells playing a major role (Figure). However, studies since the 1970s have shown high levels of beta cell specific autoantibodies in the serum of patients with T1DM, suggesting a probable role for the humoral immune system as well. These autoantibodies are directed against various antigenic determinants of the beta cell, such as glutamic acid decarboxylase (GAD-65), islet antigen-2 (IA2) and insulin itself (insulin autoantibodies- IAA). Up to 95 per cent of newly diagnosed patients with T1DM have been shown to be positive for one or other of these antibodies, and these may be present even months to years before diagnosis[2]. A good proportion also shows positivity for more than one autoantibody, with a higher number of autoantibodies predicting progression to clinical disease in asymptomatic relatives of children with T1DM[3]. However, similar data are scarce from India, with some studies suggesting a lower prevalence of autoantibody positivity in Indian patients with T1DM[4], while some have suggested comparable rates[5].

Dhanwal *et al*[1] have shown that nearly 50 per cent of patients clinically diagnosed with T1DM are positive for at least one autoantibody, a figure similar to that shown in many western populations. Also, more than 10 per cent were positive for two antibodies and 4 per cent tested positive for all three antibodies. The GAD-65 antibody was found in all patients who tested antibody positive, reiterating its role as a screening test for autoimmune T1DM. However, it is also possible that those testing antibody negative in the present study might have had elevated titres of other well-characterised as well as unknown beta cell autoantibodies in their serum. For instance, antibodies to zinc transporter 8 (ZnT8) are the most recently characterized autoantibodies in T1DM. Testing for this and other antibodies might conceivably lead to more patients in the antibody-negative group being reclassified as antibody-positive; however, the clinical and therapeutic implications as well as cost-effectiveness in clinical practice of such an approach are as yet unclear.
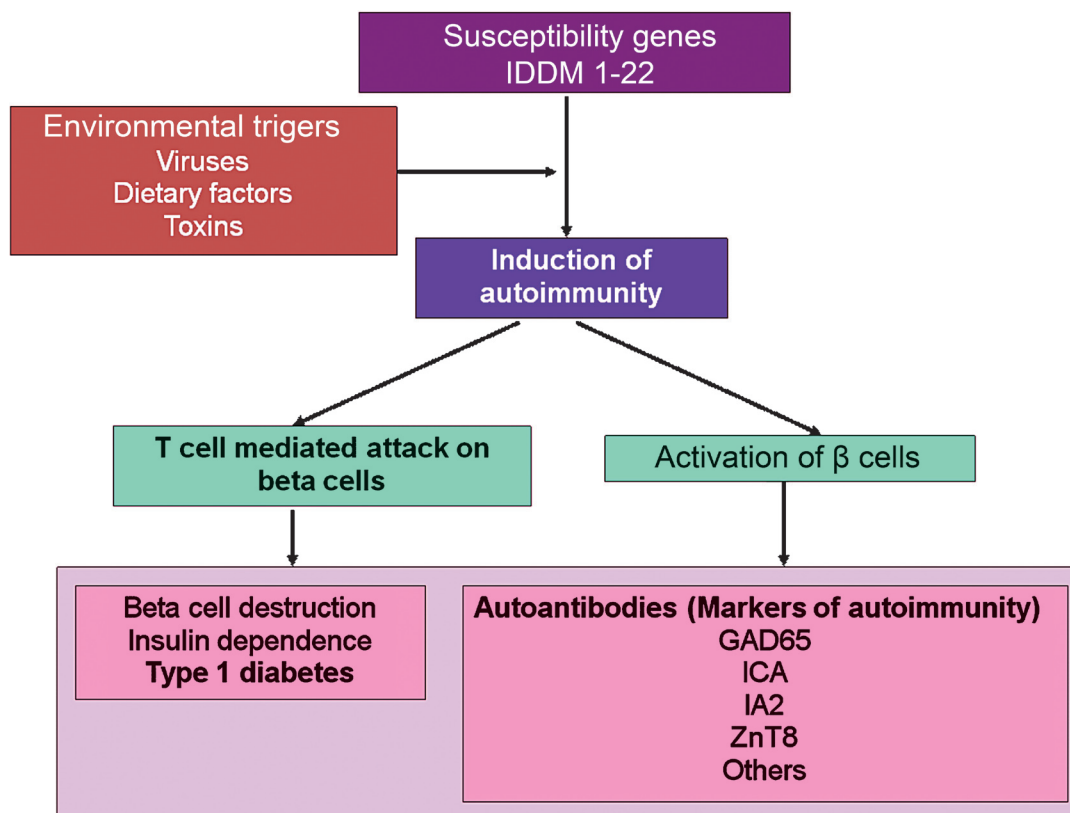
Fig. Simplified model of mechanism of autoimmunity and beta cell destruction in type 1 diabetes. IDDM, insulin dependent diabetes mellitus; GAD, glutamic acid decarboxylase; ICA, islet cell antibody; IA2, islet antigen-2; ZnT8, zinc transporter-8.

Also, it has been shown that many patients who fit the phenotype of type 2 diabetes (T2DM) have autoantibodies to one or other of the beta cell antigens in their serum[6], particularly if they are lean or (less commonly) even if they are overweight or obese. Many of these patients may ultimately develop a clinical picture similar to T1DM, a condition called latent autoimmune diabetes of adults (LADA); the significance of these autoantibodies in those who do not develop insulin dependence is unclear. In their study, Dhanwal *et al*[1] have excluded individuals with clinical features suggestive of T2DM (Body mass index more than 30 kg/m^2 and/or signs of insulin resistance). It would be interesting to see how many of those young individuals classified as T2DM test positive for autoantibodies. This information would also help to assess the usefulness of autoantibody screening as a diagnostic tool to differentiate between T1DM and T2DM. It has also been shown that autoantibodies may be present in a small proportion of individuals with fibrocalculous pancreatic diabetes (FCPD)[7] and malnutrition-modulated diabetes mellitus (MMDM)[8];

it is not known how many, if any, of the subjects in the present study had either of these two types of diabetes. In fact, it has been reported form a large Asian cohort[9] that only 60 per cent of autoantibody-positive young patients with diabetes showed clinical features suggestive of T1DM. Extending the search for autoantibodies to those without classical features of T1DM might, therefore, help to uncover more antibody positive cases.

The environmental triggers of the autoimmune process in T1DM have received wide attention. Much of the interest has centred on infectious agents (viruses) and dietary factors such as early introduction of cow's milk and gluten in the diet and presence of nitrates in food, as well as vitamin D deficiency[10].

Viral infection as a trigger for pancreatic autoimmunity is of particular importance on account of the ubiquity of viruses as well as the potential for prevention. While direct evidence of a viral aetiology for diabetes is available only for congenital rubella infection, other viruses have been indirectly

implicated in the pathogenesis[11]. The main candidates are the enteroviruses (Coxsackie A and B viruses and echoviruses), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and mumps virus. Here again, much of the data come from Caucasian populations residing in industrialized western nations, and the background prevalence of these viral infections may vary widely between these countries and developing nations like India.

To date, there are little data from India on immunological markers of viral infection in patients with newly diagnosed T1DM, a situation which has been rectified to an extent by the present study. It is, however, surprising that none of the patients showed evidence of infection with those viruses that have been traditionally associated with T1DM (CMV and EBV). Further studies are warranted to see if this is on account of a true difference in susceptibility to the triggering mechanism of these viruses, or if it merely indicates geographical or seasonal variations in the incidence of these infections. It is also interesting to note that five patients had evidence of hepatitis E infection. The hepatitis E virus (HEV), a member of the hepeviridae family, has not been hitherto associated with the development of T1DM. Larger studies are needed to confirm this finding, which is of importance since HEV infection is widespread wherever sanitation is poor, particularly in developing countries. A role for HEV in the pathogenesis of T1DM, therefore, offers possibilities for prevention (by means of improving food and water sanitation since a vaccine is as yet unavailable).

In summary, the study by Dhanwal *et al*[1] opens up intriguing new possibilities for further research in this important aspect of diabetology. We still do not have robust epidemiological data on the burden of T1DM in our country. We need to know more about the genetic markers of susceptibility to T1DM in populations in different parts of the country and whether they differ significantly from those described for western populations. The environmental triggers for the autoimmune attack need further elucidation, irrespective of whether these are infectious or dietary in origin. Research along these lines will help us to better characterize our young patients with T1DM so that the most appropriate management strategies can be directed towards them.

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