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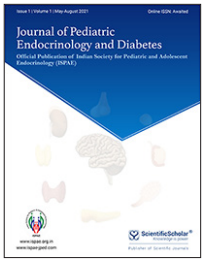

Editorial Commentary

Pancreatic autoantibody and other organ-specific autoantibodies and their relevance in diabetes mellitus

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Autoimmune diseases can affect most endocrine glands including pituitary, thyroid, parathyroid, pancreas, adrenal and gonads. Cell-mediated autoimmunity coupled with humoral over-activity against self-antigens mainly due to susceptibility from Class-I to II HLA and contribution from *AIRE, PTEN,* and *CTLA4* genes constitute the major mechanism of endocrine autoimmunity. Humoral over-activity manifesting as organ and non-organ-specific autoantibodies is considered a secondary response to autoantigenic exposure following CD8-mediated T-cell cytotoxic damage of the endocrine organs.

Pancreatic endocrine autoimmunity manifesting as type 1 diabetes (T1D) is the second most common organ-specific endocrine disorder after autoimmune thyroid disorders, that is, Hashimoto's thyroiditis and Graves' disease. T1D often manifests acutely when 90% of the pancreatic reserve as determined by C-peptide (<0.6 ng/mL) is lost. However, studies in twins of T1D have shown that there is often a subclinical/latent phase in T1D characterized by the presence of various pancreatic autoantibodies and loss of first-phase insulin response. Insulin autoantibodies are usually the first pancreatic autoantibodies occurring in 70% of T1D, followed by autoantibodies against GAD65, Zn-finger-8 transporter, and IA2 antigens. The term 'islet cell autoantibody' is an umbrella for the overall reactivity of autoantibodies against pancreatic islets usually detected by indirect immunofluorescence. About 60% of such reactivity is accounted for by GAD65.[1] Although the functional significance of various pancreatic autoantibodies invading GAD and IA2 is not exactly clear, these have a possible role in the release of insulin from the secretory granules of the beta cells. The general principle holds true that the more the number and titer of pancreatic autoantibodies, the more are the chances of these manifesting as T1D at an earlier age. The latent phase in T1D as detected by pancreatic autoantibodies and normal glucose tolerance but with impaired first-phase insulin response gives a window for immune-manipulation/vaccine use for prevention of T1D, that is, "oral insulin" exposure and sensitization and elimination of auto-reactive T-cells against pancreatic beta-cells. At present, such an intervention is not in clinical mode but is performed in the controlled environment of the research setting.

In the absence of a strategy for routine screening of pancreatic autoantibodies, clinically, T1D often manifests in various forms including severe hyperglycemia alone or with ketosis/ketoacidosis. Insulin requirement and occurrence of ketoacidosis is invariably the final consequence of severe autoimmunity. The absolute requirement of insulin for glycemic control is the hallmark of T1D and may occur rapidly within a few days of manifest hyperglycemia in children. In some adults, especially women in their thirties, hyperglycemia could be managed

with oral hypoglycemic agents/diet for 6 months, sometimes for a few years before they require insulin support. The entity is often named "latent autoimmune diabetes" (LADA). GAD65 autoantibodies rather than other autoantibodies are the hallmark of LADA.[2]

A major clinical significance of detecting pancreatic autoantibodies in T1D is in the spread of autoimmunity to various other organs.[3] Thus, patients with T1D are screened annually or biannually for common autoimmune thyroid disorders and gluten sensitivity/celiac disease by serum thyroid peroxidase and anti-tissue transglutaminase autoantibodies, respectively. Patients with T1D have 20–40% thyroid autoantibody positivity.[3] A similar presence of adrenal insufficiency can be detected early in T1D by serum 21-hydroxylase autoantibodies positivity or by detecting impaired cortisol reserves on a 250 μg cosyntropin test.

Conventionally, the phenotype of T1D patients was considered to be lean due to weight loss and presentation in the emergency with ketosis. However, with the increasing prevalence of obesity in the general population and the easy availability of medical facilities, many T1D patients present early in the course of illness without clinical signs of excessive catabolism. With such a phenotype, it is often difficult to differentiate T1D from type 2 diabetes (T2D) in young. Measurement of pancreatic autoantibodies in such a situation gives an additional tool, besides serum C-peptide levels, to the treating physician to differentiate obese T1D from T2D of young.

In the study reported by Ferrell *et al*.,[4] in this issue, there was a 12.6% prevalence of pancreatic autoantibodies in a group of T2D patients attending a pediatric diabetes clinic in San Francisco, USA. Groups with and without antibodies were not significantly different in terms of age, sex, and body mass index. Interestingly, hemoglobin A1c (HbA1c) was significantly lower in the autoantibody-positive group. The lower HbA1c in autoantibody-positive cases of T2D could represent a temporary improvement observed in the pancreatic autoimmunity akin to early in the course of T1D as in the honeymoon phase in them. However, another interesting feature that is unique in their study was the prevalence of Zn transporter autoantibodies rather than the usual GAD65 autoantibodies. Six of the 10 T2D patients in their study had Zn transporter autoantibodies and only two had GAD65 autoantibodies. Such unusual positivity of zinc transporter autoantibodies in T2D would be a subject of further investigation in other populations. Nonetheless, the present study highlights that it is important to keep a watch on the occurrence of pancreatic autoimmunity in youth-onset diabetes even if the phenotype is T2D.

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