Current Perspective on Auto-antibodies in Type 1 Diabetes

Aberrant immune responses against specific β-cell autoantigens generates Islet autoantibodies (IA), like Glutamic Acid Decarboxylase (GADA), insulinoma antigen-2 (IA-2A), insulin (IAA), and most recently Zinc Transporter 8 (ZnT8A). IA are biomarkers of autoimmune Type 1 diabetes (T1DM) and help in its diagnosis.[1] IA can be present very early in the natural history of T1DM from normoglycemic and preT1DM to overt diabetes stage. IA can distinguish Latent Autoimmune Diabetes in Adults (LADA) from phenotypically type 2 diabetes.[1]

India accounts for most of T1DM in South East Asia with a rising incidence in recent years probably due to changing environment, prosperity, and microbial factors.[2] The hygiene hypothesis suggested changes in enterobiome may have triggered surge in autoimmunity leading to T1DM.[3] Bhatia *et al*. found 45% recent onset T1DM were negative for GADA and IA2A.[4] In this edition of IJEM, a study in children with T1DM found 97.8% antibody positivity, including GADA, IAA, IA2A, and ZnT8A. GADA was most common, 67.3% of T1DM had two antibodies, with the number of antibodies correlating with diabetes duration. Type, frequency and level of autoantibodies depend on age, onset, and duration of T1DM.[1,5-7] IAA is common in young children and may be associated with fulminant course due to total destruction of β cells and complete insulin deficiency with rapid onset of T1DM.[6] ZnT8A is more frequent in recent onset young (≤10 years) with acute-onset T1D, but it decreases with increasing duration of T1DM.[7] Although GADA is most common and most persistent IA in T1DM, it peaks later, being more common in older children and adolescent with T1DM and LADA, suggesting more persistent but less intense autoimmune process.[1] Among subjects with two autoantibodies, IA2A has higher risk of type 1 diabetes than GADA.[5] High level of multiple autoantibodies (mAbs) especially at earlier age is associated with loss of beta cell mass and progression to overt T1DM, thus predictive of early onset T1DM.[1,5] Detection of mAbs helps in early prediction and intervention for prevention and treatment of high risk T1DM subjects, but results may be inconsistent, as older children and adolescents with mAbs may have low risk of progression.[1,5,7]

IA levels fluctuate, with transient autoantibody positivity in adult onset autoimmune diabetes.[1] IAA peaks in first years of life and declines thereafter, losing IAA reactivity is associated with delayed progression to T1DM even in mAb positive children.[6] Reversion of mAb positivity, is rare (4.1%), but indicates immune remission with reduced risk of progressing to overt T1DM and is associated with older age, lower autoantibody titers, and fewer positive autoantibodies.[8]

IA may predict clinical outcomes in T1DM. GADA is associated with lower HbA_{1c}; IA2A was associated with lower severe hypoglycaemic episodes and both distal and autonomic neuropathy, while ZnT8A positivity was associated with higher total and LDL cholesterol.[7] No association between autoantibody positivity and C-peptide was observed.[7]

TDM is associated with other auto-immune diseases, either alone or in the context of autoimmune polyendocrine syndrome (APS). A meta-analysis in T1DM, found autoimmune hypothyroidism was most prevalent (9.8%) followed by celiac (4.5%), autoimmune gastric disease (4.3%), hyperthyroidism (1.3%), adrenal insufficiency in 0.2%.[9] Hypothyroidism prevalence increased by 4.6% for every 10-year increase in age of T1DM.[9] Multiple organ-specific organ-specific antibodies (OS-Ab) may be present even prior to T1DM, nesseciating regular screening.[10] The study reported in the current edition also reported a high prevalence of OS-Ab especially thyroid (anti-TPO-51%, anti-thyroglobulin-25%), and celiac disease (IgA anti-tissue transglutaminase-22.8%), anti TPO positivity correlated with age of onset of T1DM. Increasing age and diabetes duration and the presence of GADA is associated with increased risk of development of additional autoimmunity specially thyroid and gastric autoimmunity.[10]

There is controversy regarding OS-Ab in T1DM, represent an epiphenomenon or true expression of associated autoimmune disorders. A study in T1DM children found, 60% with positive anti-thyroid antibodies developed autoimmune thyroiditis, while 62.5% with anti-tTG IgA positive developed biopsy-confirmed celiac disease.[10] A longitudinal study in T1DM, found that the presence of thyroid antibodies or parietal cell antibodies was associated with dysfunction of corresponding organ.[11]

Previous studies suggest that autoimmune thyroiditis (AIT) peaks at puberty and was more common in girls, but hypothyroidism was more frequently in boys and developed only in presence of thyroid antibodies.[12] AIT in T1DM may increase the risk of neurovascular complications but no differences in growth and metabolic control.[12] Annual screening of thyroid antibodies in T1D is recommended, while serum TSH level should be measured in patients with detected thyroid antibodies.[12]

In conclusion, there is high prevalence of autoantibodies in T1DM, which may help in exploring natural history, disease prediction in at-risk individuals and also for diagnostics or prognostics of T1DM. There is a strong association of other OS-Ab organ specific antibody in T1DM. The presence of OS-Ab may predate T1DM and predict corresponding organ dysfunction, reinforcing the importance of regular screening of

OS-Ab and respective organ dysfunction especially for celiac disease and thyroid and adrenal dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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