

# Is type 2 diabetes an autoimmune disorder of gradual onset?

**Abbreviations:** T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; IL, interleukin; Th1/Th2, T-helper 1/T-helper 2; GAD, glutamic acid decarboxylase; IA-2, anti-insulinoma-associated protein 2; LADA, latent autoimmune diabetes of the adult

## Editorial

Type 2 Diabetes Mellitus (T2DM) has been traditionally considered a purely metabolic disorder as opposed to type 1 Diabetes Mellitus (T1DM) that is a result of an autoimmune attack in genetically susceptible individuals. However, loss of self-tolerance may occur in T2DM and may be a result of tissue damage releasing 'self' antigens, which were previously not accessible to T cells and thus may promote autoimmune activation.<sup>1</sup>

Obesity-associated insulin resistance has been linked to activation of innate immunity and chronic low-grade inflammation.<sup>2</sup> Production of  $\beta$  cell attacking cytokines (like interleukin (IL)-1 $\beta$ ) is characteristic of the chronic inflammatory state in T2DM.<sup>2</sup> To unravel the pathogenetic role of autoimmunity in T2DM other factors like apoptosis-related molecules Fas and Fasligand and defects in B-cell tolerance, defects in active suppression of self-reactivity by regulatory T cells (Tregs) or immune deviations in the T-helper 1/T-helper 2 (Th1/Th2) ratio should also be considered.<sup>3-5</sup>

The model of autoimmunity presented by Matzinger<sup>6</sup> supports the idea of autoimmune activation in T2DM, as pathological alterations characteristic of this disease - such as chronic adipose tissue inflammation and  $\beta$ -cell damage induced by gluco- and lipotoxicity - provide antigens and signals which cause an activation of both innate and adaptive immunity.<sup>6</sup> If self-reactive T cells, which have escaped deletion in the thymus, encounter such a  $\beta$ -cell antigen presented in primary lymph nodes by dendritic cells, T-cell priming might occur, followed by further T-cell-mediated  $\beta$ -cell destruction.<sup>7</sup> Not only  $\beta$  cells but also other affected tissues in T2DM, such as adipose tissue or the vessel wall, may be involved in this inflammation process.<sup>8</sup>

Circulating autoantibodies are indicative of an active autoimmune process in T2DM. As a hallmark study in T2DM, UKPDS has provided evidence of autoimmunity in T2DM patients with the identification of glutamic acid decarboxylase (GAD) and islet cytoplasm autoantibodies in 12% of over 3,000 T2DM patients aged between 25 and 65 years.<sup>9</sup> Other studies have confirmed the UKPDS findings for patients with T2DM and islet cell autoantibodies.<sup>10,11</sup> In T2DM patients older than 65 years, anti-GAD and/or anti-insulinoma-associated protein 2 (IA-2) autoantibodies have been detected in 12% of patients.<sup>12</sup> GAD are the commonly detected autoantibodies with only a small subset of patients presenting other autoantibodies.<sup>13</sup>

As a result of these findings a novel clinical entity of latent autoimmune diabetes of the adult (LADA) or type 1.5 diabetes mellitus has emerged. The genetic background of patients with LADA shares features of both T1DM and T2DM.<sup>14</sup>

LADA patients form a diverse group with variable titers of antibodies, body mass index and frequency of progression to

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insulin independence.<sup>15</sup> Patients with high compared with low titers of GAD65 antibodies usually have a lower body mass index, less endogenous insulin secretion (as measured by stimulated serum C-peptide concentrations), and progress more quickly to insulin dependence.<sup>15,16</sup> Studies are underway to determine whether early treatment with insulin or use of immunomodulator therapy can prevent disease progression.<sup>17,18</sup>

Novel antidiabetic treatments for T2DM provide actions that go beyond insulin kinetics. Incretin mimetics and DPP-4 antagonists have been shown to mitigate the apoptosis process and modulate autoimmune processes at least in vitro. In a recent study LADA patients treated with sitagliptin and insulin maintained better  $\beta$ -cell function by comparison to insulin alone with no difference in the GAD titers however.<sup>19</sup>

The idea of addressing autoimmune processes involved in triggering or perpetuating  $\beta$ -cell destruction in T2DM is appealing but can hardly provide an answer to the treatment of this complex and devastating disease. The emerging similarities between T1DM and T2DM may shed light to a different approach preventing the initiation of inflammation and generation of destructive signals produced in obesity to emphasize once more that the best way is the old way involving a better way of life with less food and more exercise.

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## Conflict of interest

The authors have no conflicts of interest to disclose.

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