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Reply to 'Slowly progressive insulin dependent diabetes mellitus in type 1 diabetes endotype 2'

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We are grateful to Tetsuro Kobayashi and Takashi Kadowaki for their correspondence on our Review (Redondo, M. J., Morgan, N. G. Heterogeneity and endotype of type 1 diabetes mellitus. *Nat. Rev. Endocrinol.* **19**, 542–554 (2023))[1], their insights into the immunopathology of slowly progressive type 1 diabetes mellitus (SPIDDM) (Kobayashi, T. & Kadowaki, T. Slowly progressive insulin-dependent diabetes mellitus in type 1 diabetes endotype 2. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-024-00975-z (2024)[2]) and their suggestion that the features of this disease might assist in defining more fully an endotype we refer to as T1DE2 (ref. 1), in accord with our 2020 study[3].

We agree with Kobayashi and Kadowaki that obesity and other diabetogenic mechanisms characteristic of type 2 diabetes mellitus (T2DM) are not necessarily present in slowly progressive forms of diabetes mellitus, in which development of clinical diabetes mellitus might result solely from autoimmune loss of β-cells over time. However, we believe the coexistence of T2DM-related factors in an individual with slowly progressive islet autoimmunity could hasten the onset of clinical diabetes mellitus by disturbing the balance between insulin secretion and sensitivity[4]. Importantly, we also note that the definition of SPIDDM was established and revised using criteria from Japan[5] and that these criteria might differ in other populations.

The relationship between SPIDDM and T1DE2 remains unclear. Kobayashi and Kadowaki characterize SPIDDM as an atypical form of T1DM, while we propose that T1DE2 is the predominant endotype of T1DM among the adolescent-onset and adult-onset population in Western countries[3,6]. T1DE2 is also the form identified most often in histological studies of new-onset instances of T1DM worldwide, since very few samples come from young children where T1DE1 predominates. Kobayashi and Kadowaki also report persistent enteroviral infection in endocrine and exocrine pancreatic cells in SPIDDM, contrasting it with fulminant type 1 diabetes mellitus (FT1DM), which involves more acute enteroviral infection and extensive islet cell lysis[7]. Currently, there is no evidence that T1DE1 and T1DE2 are distinguished by differences in enteroviral infection of islets cells. Hence, our view is that SPIDDM and FT1DM do not align completely with T1DE2 and T1DE1, respectively. Compared with T1DE1, seen in young children, T1DE2 shows slower progression, less intense infiltration of islets by $CD8^+$ T cells, fewer $CD20^+$ B cells, and a greater proportion of residual insulin-containing islets at onset. However, T1DE1 does not display all of the features of FT1DM as, unlike in FT1DM, there is little evidence of islet cell lysis and the aggressive autoimmune-mediated demise of β-cells seems to account for the rapid disease progression and early age at onset[8].

Kobayashi and Kadowaki also report the depletion of the intracellular dsRNA sensor, MDA5 in the β-cells of individuals with long-duration SPIDDM, although MDA5 levels are increased in short-duration SPIDDM[9]. Studies have shown higher levels of islet cell MDA5 in people with T1DE2 compared with individuals without diabetes mellitus, but this increase was more pronounced in individuals with shorter T1DE2 duration[10]. Therefore, MDA5 levels might decrease with time and studies that compare diabetes mellitus type while accounting for this factor are needed. Whether the disease course, environmental influences or genetic background explain the differences between SPIDDM and T1DE2, or if SPIDDM represents a distinct endotype, remains unanswered. Overall, however, we concur with Kobayashi and Kadowaki that a deeper understanding of T1DM endotypes is crucial for effective therapeutic intervention.

References

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Competing interests

The authors declare no competing interests.