Age Ain't Nothing But a Number . . . or Is It?

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Type 1 diabetes (T1D) can develop at different stages in life, from infancy (1) to older adulthood (2). Younger children are more prone to diabetic ketoacidosis (DKA) (3) and a shorter partial remission period ("honeymoon") (4) compared with older individuals presenting with T1D. These clinical indicators of poor β-cell function correlate with lower serum C-peptide levels in young children with new-onset T1D (5) and are consistent with the histopathological observation of more profound loss of β-cells in the pancreas in children with T1D under 7 years of age (6). In addition, there is an inverse correlation between age of onset and the burden of T1D-associated genes (7). Longitudinal studies with autoantibody-positive pediatric and adult participants initially without diabetes have demonstrated that the risk of progression from single to multiple islet autoantibody positivity and then to clinical T1D is higher in younger individuals (8). In contrast with this aggressive disease course, there is a phenotype of slowly progressive autoimmune T1D that presents in adults who initially, but only transiently, respond to noninsulin agents (9). This phenotype is often misdiagnosed as type 2 diabetes (T2D) until insulin dependence becomes apparent, which frequently prompts autoantibody testing to confirm a T1D diagnosis. The fact that the incidence of T2D increases dramatically with age, from rare cases before puberty (10) to overwhelming predominance of diabetes types in adult life, contributes to diagnostic challenges. Taken together, these clinical and research observations have led to the common misconceptions that, after middle age, T1D is almost nonexistent and that, when it presents, its prognosis is mild, with slow loss of insulin secretory capacity and only late development of insulin dependence. These erroneous assumptions may result in older adults with T1D receiving a misdiagnosis of T2D and, even when diagnosed with T1D, not being prescribed insulin until extreme hyperglycemia or DKA develop.

In the current issue of *Diabetes Care*, Thomas et al. (11) assess the relationship between diagnosis age and the presentation characteristics, genetic susceptibility, and progression of recent-onset T1D in adults. To this end, the authors make use of the prospective StartRight study, which is a multicenter study in the U.K. that included nearly 1,800 adults with recent-onset diabetes (<12 months since diagnosis, median 5 months). For the present analysis, the authors defined T1D as diabetes and either *1*) multiple (two or more) islet autoantibody positivity (out of GAD, ZnT8, or IA-2) (n = 385 [group 1]) or *2*) single islet autoantibody positivity, a clinical diagnosis of T1D, and insulin initiation within 2 weeks of diagnosis (n = 180 [group 2]). The median age of diagnosis in group 1 (35 years) was selected as the cutoff to split both autoantibody groups into younger and older age categories. As control, the authors included participants with T2D defined according to self-reported clinical diagnosis of T2D, absence of insulin treatment within 2 weeks of diagnosis, and negativity for autoantibodies (n = 715).

With a follow-up of up to 30 months postdiagnosis, there was substantial annual decline in C-peptide secretion measured as urine C-peptide–to–creatinine ratio: ∼40% loss per year regardless of T1D definition (i.e., group 1 or group 2). Importantly, in neither group did age of onset (younger or older than 35 years) affect the rate of C-peptide loss or clinical presentation with respect to HbA_{1c}, plasma glucose concentrations, BMI, or presence of DKA. The T1D genetic risk score (a weighted sum of 67 genetic variants associated with T1D) was not different between the two age categories either in the multiple autoantibody or in the single autoantibody groups. Despite these similarities, participants with multiple autoantibody–positive T1D received different diagnosis and clinical management based on age of presentation: those >35 years of age, compared with those who were younger, were less likely to be admitted (40% vs. 60%), treated with insulin (73% vs. 93%), or given a diagnosis of T1D (87% vs. 96%) at onset. Among multiple autoantibody–positive T1D case participants, C-peptide was lower at onset in participants who received insulin at diagnosis than in those who did not, but annual decline rates were similar. Consequently, 2 years

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after onset, 88% of multiple autoantibody–positive T1D case subjects not treated with insulin at diagnosis had started insulin treatment (as opposed to 3% of participants with T2D).

Thomas et al. provide robust evidence that T1D can present over the age of 35 years with similar genetic burden and characteristics as aggressive as in younger adults, including rapid loss of insulin secretory capacity, very elevated HbA_{1c} and glucose concentrations, and DKA. However, older individuals are less likely to be managed as insulin insufficient, although it is important to note that the far majority still received insulin treatment. This study has clear and important clinical implications because the observed delay in correct treatment increases the risk of poor glucose control and, thus, acute and chronic diabetes complications.

The authors acknowledged that the StartRight cohort was purposely enriched for participants diagnosed after age 50 years receiving exogenous insulin at enrollment, i.e., with rapid loss of β-cell function. In addition, to avoid cases of false islet autoantibody positivity, single autoantibody positive–participants were excluded from the analysis if they had not started insulin treatment within 2 weeks of diagnosis. It was noted that almost 30% of participants (n = 513) in the StartRight study were not included in the present analysis because they had T1D and no autoantibodies, or single autoantibody positivity and no insulin treatment within the first 2 weeks (n = 217); uncertain diabetes type and none or single autoantibody positivity (n = 130); or T2D treated with insulin at diagnosis or single autoantibody positivity (n = 166). As a result, this analysis tended to exclude adults with T1D and slower decline in β-function, especially if they had single or no autoantibody positivity.

Future studies should focus on individuals with adult-onset T1D, single autoantibody positivity, and a natural history of a slower decline in β-cell function, for whom the clinical course remains uncertain and the diagnosis may be more challenging (9). Furthermore, a better understanding of the meaning of single autoantibody positivity will be important. To minimize the potential pitfall of false results, which is more likely with single autoantibody positivity, islet autoimmunity should be confirmed by methods such as repetition of the test or use of high-affinity assays (12) and variants that afford enhanced prediction (13). Although the risk of progression to T1D associated with single autoantibody positivity is much lower than with multiple positivity, 20% of TrialNet Pathway to Prevention participants who progress to T1D expressed a single autoantibody (14). Since positivity was confirmed on a separate sample and participants have a family history of T1D, the likelihood of a laboratory or biological false positive is low. However, single autoantibody positivity was associated with older age and markers of insulin resistance (14). These and other data (reviewed in 15) suggest that T2D-associated mechanisms may be important drivers in the ultimate development of diabetes in a subset of individuals with islet autoimmunity. However, the relative contribution of different diabetogenic pathways, their interactions, and how to target them for prevention and treatment are still unclear.

In sum, in our view, Thomas et al. demonstrated that individuals over 35 years old can develop T1D with a clinical course similar to that of younger-onset T1D, requiring early insulin treatment. This message is important for clinicians caring for these patients. Due to their inclusion criteria, uncertainty remains on the natural history and optimal treatment of T1D with slower β-cell function decline, presenting with insulin independence, and possibly with single autoantibody positivity. A longitudinal cohort of adults with insulin-deficient diabetes and comprehensive genetic, immunologic, and metabolic data, including measures of insulin sensitivity, could help to shed more light on this T1D subtype and response to noninsulin therapies. Then, singer Aaliyah's "Age Ain't Nothing But a Number" can be fully questioned in the context of adult-onset T1D.

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