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Beta cell mass versus function in type 1 diabetes: truth or dare?

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In a recent commentary by Professor Knip (Diabetes: Loss of β -cell mass - an acute event before T1DM presentation? (1)), a series of issues were raised with respect to our article (2) that deserve clarification.

Dr. Knip suggests, “no direct evidence indicates that beta cell mass remains intact before clinical disease onset” (1). However, as he states in the introduction, it is accepted that this is the case, at least at the stage of autoantibody positivity (AAb+) (single and double) in samples obtained from the Network for Pancreatic Organ donors with Diabetes (nPOD) program, a finding that has also been reported by other groups (3; 4). Based on these data, if beta cell mass is preserved at the multiple AAb stage, secondary prevention before onset is likely to be more effective than tertiary prevention in recent-onset patients, where the autoimmune process has already taken over and in most cases there is a critical loss of beta cell mass. The key question is whether or not *mass correlates with function* and if a decline in first phase insulin response (FPIR) early on might be a direct reflection of a decrease in beta cell mass? Future studies on longitudinal cohorts and available pancreata from patients and donors having a wide age range (at diagnosis) and at different stages of prediabetes will greatly help to answer these important questions.

To the question of insulin preservation in pre-type 1 diabetes (T1D; i.e., prediabetic), we observed a similar percentage of insulin positive area in pancreatic sections from non-diabetic and AAb+ non-diabetic individuals (2). This does not necessarily infer that insulin production is maintained during the prediabetic phase, as insulin secretion may be compromised despite its presence in the pancreas. In addition, a decline of the FPIR in prediabetic patients does occur several years before onset, as noted by Prof. Knip. However, it significantly accelerates approximately 1.5-0.5 years before diagnosis (5). Taken together, we believe the increase in proinsulin positive area in prediabetic individuals could represent an early sign of beta cell dysfunction that demonstrates itself as a poor proinsulin to insulin conversion, with a subsequent defect in insulin secretion along with a decrease in FPIR.

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Issues were also raised by Prof. Knip regarding nPOD donors representing “classic preclinical T1D”; especially whether these donors would have progressed to clinical disease. Here, we believe that T1D is a heterogeneous disease with the time of symptomatic onset occurring at different ages, dependent on a series of risk variables and various pathogenic mechanisms. To be clear, it is neither fair nor honest to compare our results with those obtained from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study as there are significant geographical and age differences, let alone ascertainment of different variables (e.g., pancreatic pathology with nPOD). Beyond this, the commentary by Prof. Knip falls short in recognizing that the donors recovered by nPOD may not recapitulate the “classic preclinical T1D”. Indeed, we believe it important to understand the pathogenesis of T1D diagnosed at later ages (>30 years old) (6) and to identify the true natural history and pathogenic mechanisms of this disease at any stage rather than effort to maintain long-standing dogmas that may, in fact, not represent reality.

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