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β-Cell mass versus function in type 1 diabetes mellitus: truth or dare?

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In a recent article by Mikael Knip (Loss of β-cell mass — an acute event before T1DM presentation? *Nat. Rev. Endocrinol.* **13**, 253–254 (2017))[1], a series of issues were raised with respect to our article[2] that we would like to address.

Knip suggests that "…no direct evidence indicates that β-cell mass remains intact before clinical disease onset…" (REF. 1). However, it is accepted that this is the case, at least at the stage of autoantibody positivity (single and double), in samples obtained from the Network for Pancreatic Organ Donors with Diabetes (nPOD) — a finding that has also been reported by other groups[3,4]. On the basis of these data, we suggest that, if β-cell mass is preserved at the multiple autoantibody stage, secondary prevention before clinical onset will probably be more effective than tertiary prevention in patients with recent-onset disease (in whom the autoimmune process has already taken over and a critical loss of β-cell mass is often present). The key questions are whether or not β-cell mass correlates with function and whether an early (before symptomatic onset) decline in first phase insulin response (FPIR) could be a direct reflection of a decrease in β-cell mass.

To address the question of preservation of insulin production in preclinical type 1 diabetes mellitus (T1DM), we observed a similar percentage of insulin positive area in pancreatic sections from non-diabetic and autoantibody-positive individuals without diabetes[2]. This observation does not necessarily infer that insulin production is maintained during the prediabetic phase, as insulin secretion might be compromised despite its presence in the pancreas. In addition, as noted by Knip, a decline in the FPIR in patients with prediabetes does occur several years before clinical onset. However, FPIR decline markedly accelerates approximately 1.5–0.5 years before diagnosis[5]. Taken together, we believe that the increase in proinsulin positive area in individuals with preclinical T1DM could represent an early sign of β-cell dysfunction that manifests as impaired conversion of proinsulin to insulin, with a subsequent defect in insulin secretion and a decrease in FPIR.

Issues were also raised by Knip regarding whether nPOD donors represent "…classic preclinical T1DM…", particularly whether these donors would have progressed to clinical T1DM within a time frame consistent with that of preclinical T1DM. We believe that T1DM is a heterogeneous disease with the time of symptomatic onset occurring at different ages, dependent on a series of risk variables and various pathological mechanisms. We feel that it is unfair to compare our results[2] with those obtained from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, as there are important geographical and age differences between these studies, as well as differences in the variables subject to investigation (for example, FPIR in DIPP, pancreatic pathology in nPOD). Furthermore, the commentary falls short in recognizing that the nPOD donors might not recapitulate the "…classic preclinical T1DM…". Indeed, we believe that it is important to understand the pathogenesis of T1DM diagnosed at later ages (>30 years old)[6] and to identify the true natural history and pathological mechanisms of this disease at any stage, rather than attempt to uphold long-standing dogmas that might not be definitive.

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Competing interests statement
The authors declare no competing interests.