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Beta cell function in the early stages of type 1 diabetes: still a long way ahead of us

Funkcja komórek beta we wczesnym stadium cukrzycy typu 1: ciągle jeszcze długa droga przed nami

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The clinical onset of type 1 diabetes (namely stage 3 type 1 diabetes [T1D]) is preceded by a relatively prolonged pre-symptomatic phase featured by islet autoimmunity [1] with (Stage 2 T1D) or without (Stage 1 T1D) dysglycaemia. While islet autoimmunity is the hallmark of the underlying autoimmune process, very little evidence is available for the metabolic changes that accompany the loss of functional beta cell mass. Indeed, a steep decline of C-peptide – a surrogate marker of beta cell function – is measurable only ~6 months before the onset of Stage 3 T1D [2]. Disease modifier drugs have, therefore, a very limited window of intervention because we lack of effective methods to track beta cell function over time and to identify early changes of insulin secretion that precedes dysglycaemia [3, 4] and clinically symptomatic diabetes.

Herein, we will revise current approaches to longitudinally track beta cell function over time before the onset of Stage 3 T1D, which might be suitable for monitoring the risk for diabetes progression as well as the effectiveness of disease modifier treatments.

Quantifying beta cell function

Although fasting or dynamic measures (e.g. the area under the curve) of C-peptide have been largely used in clinical trials to quantify residual beta cell function in people at risk for type 1 diabetes, they remain largely biased by the absence of adjustments for the actual insulin action [5]. In other terms, beta cell function can only be defined by the contemporary assessment of insulin secretion and of insulin sensitivity, especially when this assessment is performed in a rapidly changing population, such as those at risk for T1D. The paediatric population faces physiological changes of insulin sensitivity, and of insulin secretion, which in the absence of a quantitative and unbiased measure of these two dimensions, limits our ability to detect the actual beta cell function. To this end, a composite measure such as the disposition index – the constant product of insulin secretion and sensitivity – could be seen as an almost ideal metric, although it is still marginal in clinical trials targeting those at risk for T1D progression. The disposition index has been largely used to quantify beta cell function in youths at risk for type 2 diabetes or with recent-onset disease. The index reflects the hyperbolic relationship between insulin secretion and sensitivity: the physiological decrease of insulin sensitivity (e.g. during pubertal transition) is accompanied by a relative increase of insulin secretion to maintain euglycaemia. This interplay results in a constant disposition index (healthy beta cell function). A reduction of the disposition index mirrors an unbalanced reduction of insulin secretion or sensitivity [6–8]. Simple ratios for insulin sensitivity and insulin secretion during basal (e.g. the homeostasis model assessment) or dynamic tests (e.g. the Matsuda index and $\text{insulin}_{0-30}/\text{glucose}_{0-30}$ ratio) have been investigated mainly in type 2 diabetes research [5]. These methods fail to describe the complexity of gastrointestinal transit and the insulin hepatic extraction, and therefore provides limited information in population studies. To this end, metabolic models accounting for specific population characteristics and validated against complex metabolic studies could provide more reliable and reproducible information [8–10].

Model-based metrics of beta cell function

The oral minimal model (OMM) for glucose and C-peptide has recently been used to dissect the components of beta cell function (insulin secretion and insulin sensitivity) in children with stage 1 T1D. The OMM includes a glucose-insulin model to quantify insulin sensitivity and a glucose-C-peptide model to identify insulin secretion and its dynamic and static components. The dynamic component relies on early glucose and C-peptide sampling while the static component does not resent of the early sampling. The OMM has been successfully

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adopted to demonstrate early impairment of both insulin secretion and sensitivity during the early stage 1 T1D in children as compared to their healthy peers without islet autoimmunity [11]. The major drawback of this approach is the need for frequent sampling during the OGTT and the measure of both insulin and C-peptide. Other metabolic models have been proposed to identify early changes of beta cell function and to longitudinally track disease progression [12]. The advantage of metabolic models is their ability to estimate beta cell function as a result of its two components – insulin secretion and sensitivity – as well as to identify subtle changes that are not quantifiable with other surrogate metrics such as the area under the curve of C-peptide and glucose.

OGTT-derived indices

The 2-h OGTT has been adopted to stage pre-symptomatic type 1 diabetes [1, 13]. However, OGTT-derived metrics have been explored to predict the risk for disease progression in retrospective analyses of longitudinal cohorts [14]. A delayed time to glucose peak (>30 min) and a time to C-peptide peak > 60 min have been associated with a higher risk of progression to stage 3 T1D regardless of the C-peptide concentration at peak [14]. This observation challenges the common concept that measuring C-peptide (or the AUC for C-peptide) can track beta cell function and diabetes risk over time. Although AUC C-peptide has been adopted as a primary outcome for several intervention studies aimed at preserving beta cell function in newly diagnosed youths [15–17], there is little evidence for its reliability as a linear marker of beta cell function decline over time [18]. Other indices that derive from the contextual measure of glucose and C-peptide have been shown to predict the risk for diabetes progression, including the Index60 [19, 20] and the Diabetes Prevention Trial Type 1 Risk Score (DPTRS) [21–23]. However, the risk indices cannot be directly translated into metabolic outcomes for clinical prevention trials. Indeed, as prevention trials in individuals with stage 1 T1D are underway, and with more trials planned, metabolic changes may go largely undetected with the classical OGTT as well as with OGTT-derived risk indices. The absence of metabolic outcomes largely limits the design of intervention trials [24]. For example, an intervention trial targeting a high-genetic risk group – e.g. carriers of HLA-DR3/DR4– with a 10 year T1D incidence of 10% – designed to detect a 40% effect in diabetes progression, would require a sample size of more than 2000 participants [25]; conversely, interventions targeting stage 2 T1D with an almost 70% rate of diabetes progression have been proven to require a much lower numerosity (e.g. ~144 participants to detect a 50% effect in stage 2 T1D [3]). This poses the major challenge of powering prevention studies in the early stages (stage 1 T1D or single antibody carriers), which would require a much higher numerosity for the outcome of diabetes progression.

CGM-derived metrics

Continuous glucose monitoring has been investigated as a screening tool for identifying those at risk for T1D progression, which could allow home-monitoring, thus limiting the invasiveness and the costs of a full OGTT. A percentage of time with sensor glucose ≥ 140 mg/dl ≥ 5% or ≥ 8% resulted in 80% specificity and 48% sensitivity and 90% specificity with 38% sensitivity, respectively, to predict progression to Stage 3 T1D. A higher glucose threshold (≥ 160 mg/dl) resulted in a lower sensitivity (28% and 14%, respectively) [26]. These findings suggest that CGM might be a complimentary tool for screening those at risk for progression.

Intravenous glucose tolerance test (IVGTT)

One of the earliest metabolic changes underlying the risk for T1D progression is the loss of first-phase insulin response (FPIR), which can be quantified through the use of the intravenous glucose tolerance test (IVGTT). The rapid response to an intravenous glucose bolus – FPIR – has been adopted to stratify diabetes risk in the early prevention trials [27]; however, this test is moderately invasive, requires a dedicated facility, and does not provide (as any other intravenous dynamic test) information on the gut-mediated incretin effect, whose role remains largely unexplored in those at risk for T1D progression. More recently, OGTT-derived metrics have been shown to be strongly associated with FPIR. The ratio of C-peptide change to glucose change during the first 30 minute of an OGTT has been proven to be a predictor of T1D progression, being highly correlated with FPIR in the Diabetes Prevention Trial-Type 1 Diabetes (DPT-1) [28].

Conclusion

The need to identify those at risk for T1D progression and tracking changes of the metabolic phenotype during clinical trials is growing; however, the available tools to quantify beta cell function remain limited and relatively invasive. Metabolic modelling of OGTT-derived data offers a still largely unexplored path; however, this approach requires multiple IV samples and is limited to those able to undergo an oral glucose tolerance test, thus limiting its feasibility in the youngest patients or in low-resource settings. Home-based methods relying on non-invasive or minimally invasive approaches [29] are mandatory to enable large population-based screening and to ensure a safe and accurate estimate of the metabolic response to disease modifier drugs [13].

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