

# Invincible $\beta$ -cells in type 1 diabetes

The classical definition of type 1 diabetes, of which the pathogenesis lies in the autoimmune destruction of  $\beta$ -cells that eventually leads to complete loss of insulin secretion capacity, has recently been revisited with the emerging concept of an endotype to address the heterogeneity of the disease<sup>1</sup>. In the Diabetes Control and Complications Trial, it was observed that some individuals retained a clinically meaningful C-peptide persistence years after diagnosis of type 1 diabetes; post-mortem studies of pancreas specimens of long-standing type 1 diabetes patients also showed insulin-containing  $\beta$ -cells<sup>2</sup>. These findings implicate the presence of functioning  $\beta$ -cells that have evaded apoptosis and/or have been newly formed, as suggested by the Joslin 50-Year Medalist Study. However, little is known about the effects of clinically detectable C-peptide in long-standing type 1 diabetes in adults. Furthermore, the minimum threshold of clinically meaningful C-peptide levels is also unspecified with limited data available. Accordingly, evaluation of adults with type 1 diabetes in terms of residual  $\beta$ -cell secretory capacity, as well as counterregulatory  $\alpha$ -cell function across the spectrum of detectable levels of C-peptide, was imperative.

Rickels *et al.*<sup>3</sup> recently assessed secretory hormone responses with stimulated C-peptide and its clinical implications using currently available gold-standard methods. They recruited a total of 63 adult participants with type 1 diabetes duration of  $\geq 2$  years and categorized according to the peak C-peptide levels during the mixed-meal tolerance test (MMTT) as follows: negative ( $<0.007$  pmol/mL or  $<0.02$  ng/mL), low

( $0.017$ – $0.200$  pmol/mL or  $0.05$ – $0.60$  ng/mL), intermediate ( $>0.200$ – $0.400$  pmol/mL or  $>0.60$ – $1.20$  ng/mL) and high ( $>0.400$  pmol/mL or  $>1.20$  ng/mL). A high level of residual C-peptide was positively correlated with increased C-peptide and proinsulin responses to hyperglycemia during the glucose-potentiated arginine test. It was also strongly correlated with glucagon release during the hyperinsulinemic-euglycemic clamp followed by a subsequent hypoglycemic clamp.

When evaluated as continuous variables, a strong linear relationship was noted between the MMTT peak C-peptide, the acute C-peptide response to glucose-potentiated arginine test and the decrease in C-peptide from the euglycemic to hypoglycemic clamp condition. As the glucose-potentiated arginine test and glucose clamp are inconvenient to carry out in routine clinical practice, this correlation proposes MMTT as a reliable method to estimate endogenous insulin secretion.

In the study by Rickels *et al.*<sup>3</sup>, patient characteristics were balanced between the C-peptide groups in terms of sex, age, body mass index and hemoglobin A1c (HbA1c). Duration of type 1 diabetes, however, differed across groups of C-peptide production, with the longest duration observed in the negative C-peptide group. Thus, potential questions might arise in interpreting the data as to whether the difference of  $\beta$ -cell secretory responses represented by C-peptide and proinsulin secretion to hyperglycemia, acute C-peptide and proinsulin responses to arginine, and suppression of C-peptide levels and increment of glucagon in the euglycemic clamp followed by hypoglycemic clamp could exclusively be attributed to the level of stimulated C-peptide or to the disease duration itself. The rate of  $\beta$ -cell destruction might vary widely, as exemplified by fulminant type 1 diabetes and slowly progressive

type 1 diabetes, although most often the levels of plasma C-peptide closely correlate with type 1 diabetes duration. Matching the duration of type 1 diabetes could possibly provide a clue to elucidation with a bigger sample size.

The clinical implication of acknowledging residual endogenous insulin secretion capacity in type 1 diabetes is that it might provide a guide to individualized management decisions in optimal glycemic control. As HbA1c is an indirect measure of average glycemia and does not provide a measure of glycemic variability, a tailored approach should be implemented to increase time in range while reducing hypoglycemia, or time below range. Every 10% increase in time in range is associated with a 0.5–0.8% reduction in HbA1c, and is associated with clinically significant benefits; that is, reduction of the risk of microvascular complication<sup>4</sup>. Rickels *et al.*<sup>3</sup> reported that integrating data generated from continuous glucose monitoring (CGM) showed that time in range was higher with an increasing MMTT peak C-peptide level. Thus, preserving underlying  $\beta$ -cell secretory capacity with residual C-peptide by peak MMTT response as a surrogate parameter might be a reasonable therapeutic target in improving glycemic control. Hitherto, the only proven strategy to retain this capacity in practice is early intensive insulin therapy, although the prolonged secretion is expected to last for just the first 4 years. A number of clinical trials involving immunotherapies have also proven successful in short-term C-peptide preservation, but whether it would durably shift the  $\beta$ -cell trajectory is yet to be seen. Nevertheless, as preserved C-peptide level, indicative of residual  $\beta$ -cell secretory function, has been shown to be associated with a decreased incidence of severe hypoglycemia and fewer diabetic complications in the Diabetes Control and Complications Trial, different

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approaches to preserve residual C-peptide secretion are currently under investigation.

Recently, utilization of CGM as an adjunctive measure to HbA1c has been shown to assess glycemic variability more accurately. Adopting CGM technology with appropriate patient education has been shown to be related to improved glycemic control, as direct visualization of glycemic excursions not only motivates the patients as a part of the medical intervention, but also modifies behavior with proper understanding of the data. Thus, although treatment goals should aim for preserving or restoring  $\beta$ -cell function, type 1 diabetes patients with low levels of C-peptide could also conversely benefit with the use of CGM metrics.

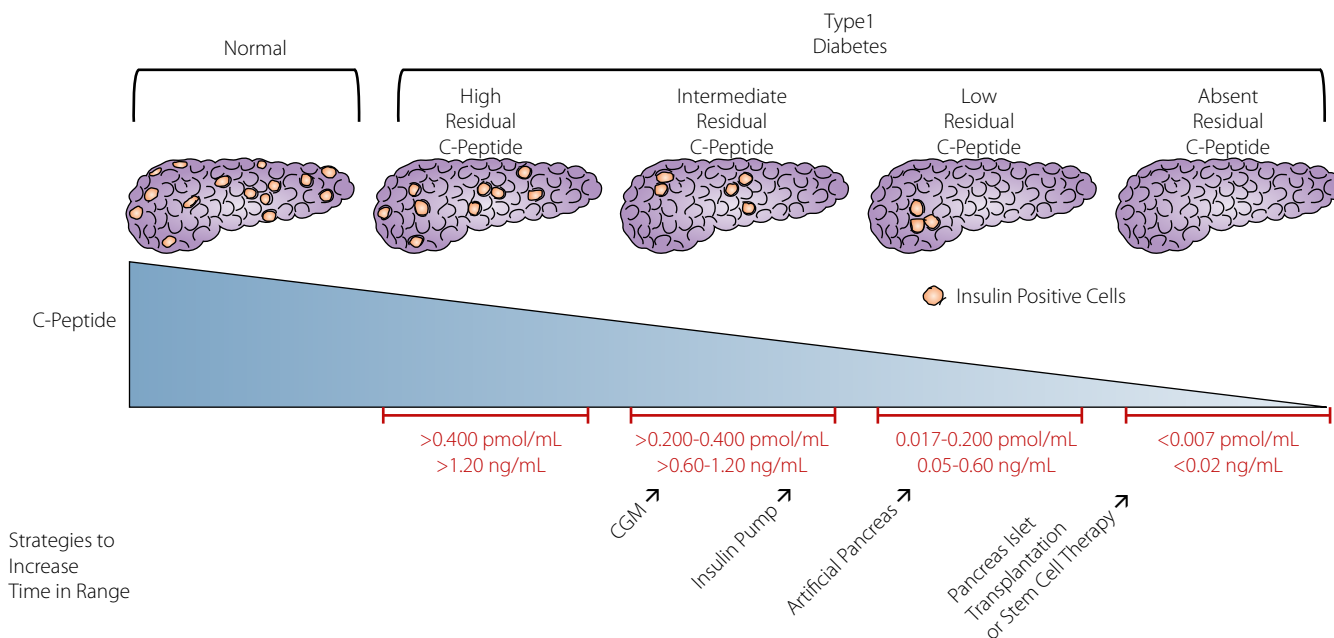
$\alpha$ -Cells are not subject to immune assault, as evidenced by the increased  $\alpha$ -to- $\beta$ -cell ratio in type 1 diabetes patients, but they lose responsivity to hypoglycemia, showing “glucose blindness”

early in the course of the disease. Rickels *et al.*<sup>3</sup> showed that type 1 diabetes patients with a high level of residual C-peptide retained  $\alpha$ -cell responsiveness to hypoglycemic insult. This preserved counterregulatory mechanism might provide a certain degree of protection against episodes of severe hypoglycemia. As type 1 diabetes patients lacking  $\beta$ -cell function are more vulnerable to severe hypoglycemia, additional means to restore  $\beta$ -cell function with a physiologically meaningful level of detectable C-peptide is paramount.

One conceivable solution to achieve improved metabolic stability with a concomitant decrease in time spent in hypoglycemia is to combine an insulin pump with CGM technology. By using algorithms to suspend and automatically restart insulin delivery predictively based on CGM data, hypoglycemic exposure can be safely reduced. The unprecedented advances in technology have led to the closed loop system, or “artificial

pancreas”; superiority of both single and bihormonal artificial pancreas over conventional insulin pump therapy has been shown in adults with type 1 diabetes, although studies with longer follow up should be pursued. In cases where less invasive treatments are ineffective in preventing severe hypoglycemia, human islet transplantation might also be a feasible option. Strategies to regenerate endogenous  $\beta$ -cells by replication of existing pancreatic  $\beta$ -cells or reprogramming of other pancreatic cells through transdifferentiation are alluring, but remain experimental<sup>5</sup>.

Figure 1 is a simplified model to propose the possible aforementioned approaches to confer improved metabolic control according to decreasing levels of residual C-peptide. Rickels *et al.*<sup>3</sup> showed that improving diabetes care is contingent on any level of detectable C-peptide. Absolute C-peptide deficiency militates against fine tuning of glycemic control, as  $\beta$ -cell secretory function can only be



**Figure 1** | Strategies to increase time in range and decrease hypoglycemic events in accordance with varying levels of C-peptide in type 1 diabetes. There is a growing body of evidence that very low, but clinically meaningful, insulin secretion persists in patients with long-standing type 1 diabetes. Complete loss of insulin secretion predisposes the risk of heightened glycemic fluctuation, which is commonly accompanied with frequent hypoglycemia. Recent advances in technology and cell biology could be deployed to address these risks in accordance with the stimulated C-peptide level, a practical measure of residual insulin secretion. Insulin-positive  $\beta$ -cells are shown in yellow circles. CGM, continuous glucose monitoring.

obtained from external sources with numerous challenges yet to be overcome. Could  $\beta$ -cells be rendered invincible from the autoimmune attack? Maybe the time has come to address different treatment strategies to preserve residual C-peptide function in type 1 diabetes patients.

#### DISCLOSURE

The authors declare no conflict of interest.

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#### REFERENCES

1. Battaglia M, Ahmed S, Anderson MS, *et al.* Introducing the endotype concept to address the challenge of disease heterogeneity in Type 1 diabetes. *Diabetes Care* 2020; 43: 5–12.
2. Oram RA, Jones AG, Besser RE, *et al.* The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. *Diabetologia* 2014; 57: 187–191.
3. Rickels MR, Evans-Molina C, Bahnson HT, *et al.* High residual C-peptide likely contributes to glycemic control in type 1 diabetes. *J Clin Invest* 2020; 130: 1850–1862.
4. Gibb FW, McKnight JA, Clarke C, *et al.* Preserved C-peptide secretion is associated with fewer low-glucose events and lower glucose variability on flash glucose monitoring in adults with type 1 diabetes. *Diabetologia* 2020; 63: 906–914.
5. Latres E, Finan DA, Greenstein JL, *et al.* Navigating two roads to glucose normalization in diabetes: automated insulin delivery devices and cell therapy. *Cell Metab* 2019; 29: 545–563.

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