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Clinical Remission in Type 1 Diabetes: A Conceptual Model of Immunometabolic Recovery, C-Peptide Preservation, and Beneficial Clinical Effects

Laura Wilson[1], Sangameshwar Rawoor[1], Johnny Zhou[2], Walid Shouman[2], Ramandeep Kaur[2], Divya Pushkarna[2], Jean-Paul Collet[2]

[1]Sanofi, Bridgewater, NJ, USA; [2]Evidinno Outcomes Research, Vancouver, BC, Canada

Contact details: Laura Wilson| **Email:** Laura.Wilson@sanofi.com

INTRODUCTION

- Type 1 diabetes (T1D) is an autoimmune disease characterized by destruction of pancreatic beta (β)-cells.[1] Shortly after diagnosis, many patients experience a transient phase of reduced insulin requirements and improved glycemic control, sometimes referred to as the "honeymoon phase," reflecting residual β-cell function.[2-5]
- In the research literature, this phase is operationalized using varying quantitative definitions of partial remission (PR), such as insulin requirement <0.5 units/kg/day and HbA1c <7%.[6]
- These definitions differ from, and should not be conflated with, the partial and complete/clinical remission endpoints used in interventional trials (e.g., IDAA1c-based or insulin-dose-and-HbA1c-based thresholds intended to capture a deeper, potentially treatment-induced remission state).
- Observational cohorts applying PR definitions report associations with fewer retinopathy and nephropathy events, reduced triglyceride and LDL-cholesterol levels, less severe hypoglycemia, and improved long-term metabolic profiles.[7-9]
- The populations, remission definitions, and designs underlying these associations vary across studies, which limits direct comparability with the clinical remission construct addressed in this conceptual model.

OBJECTIVE

To synthesize the evidence from a systematic literature review on clinical remission in T1D and to propose a preliminary conceptual model of hypothesized pathways linking remission, preserved β-cell function and residual C-peptide secretion to clinical outcomes (e.g., glycemic stability, hypoglycemia, lipid profile and microvascular complications). The model is intended to be hypothesis-generating; the SLR was designed to map the available evidence, not to test causality.

METHODS

- **Systematic literature review (SLR):** An SLR was conducted to identify studies reporting predictors or clinical outcomes of clinical remission in stage 3 T1D. Medline, Embase and the Cochrane Database of Systematic Reviews were searched from inception to January 2026 for observational studies, clinical trials and guidelines in adults or children with stage 3 T1D. Two independent reviewers extracted relevant data and assessed study quality.
- **Preliminary conceptual model:** A preliminary, hypothesis-generating conceptual model was developed from the SLR findings and supplemented by a targeted, non-systematic literature review to address knowledge gaps on potential mechanisms. The targeted review drew largely on preclinical studies and trials of exogenous C-peptide; recurring factors and mechanisms were grouped into higher-level concepts representing hypothesized relationships, not demonstrated causal pathways.
- Targeted searches for the preliminary conceptual model covered:
  1. Factors associated with remission;
  2. Immunologic and immunometabolic mechanisms proposed to sustain remission and β-cell preservation (e.g., β-cell rest, regulatory immune dominance, anti-inflammatory and vascular effects attributed to C-peptide);
  3. Metabolic and physiologic studies linking remission, residual β-cell function, and C-peptide with glycemic control, vascular biology, and clinical outcomes.

RESULTS

Study characteristics

- A total of 88 publications pertaining to 82 unique studies were included in the SLR, including 69 cohort studies (35 retrospective and 34 prospective), 5 cross-sectional studies, 5 ambispective design studies, 2 randomized controlled trials, and 1 non-randomized clinical trial.
- Sample sizes of studies from SLR ranged from 18–14,292 (median: 154).

Participant characteristics

- Baseline characteristics were reported by overall T1D population and remitters (**Table 1**).
- Among studies reporting remitter characteristics, remitters were characterized by preserved β-cell function, reflected by random and stimulated C-peptide levels of 0.32 nmol/L and 0.50 nmol/L, respectively.
- In the overall T1D population, reported random and stimulated C-peptide levels were 0.21 nmol/L and 0.10 nmol/L, respectively.
- Median daily insulin requirements and HbA1c levels among remitters were 0.50 U/kg and 10.66%, respectively; corresponding values reported for the overall T1D population were 0.61 U/kg and 11.20%, respectively.

Table 1. Baseline characteristics reported across included studies

Characteristics	Study-reported values, overall T1D population* (44 studies)	Study-reported values, remitter subgroup (45 studies)
Age at T1D diagnosis (years)	8.9 (3.5–27.0)	8.5 (3.1–30.6)
Female sex (%)	47.8 (12.5–66.7)	45.3 (16.0–65.0)
Random C-peptide (nmol/L)	0.21 (0.12–0.32)	0.32 (0.15–0.74)
Stimulated C-peptide (nmol/L)	0.1 (0–0.22)	0.5 (0.25–0.60)
Daily insulin dose (U/kg)	0.61 (0.31–0.77)	0.50 (0.29–0.71)
HbA1c level (%)	11.20 (6.90–13.90)	10.66 (5.99–12.36)

*Remitters and non-remitters. Outcomes are reported in median (range)
Abbreviations: HbA1c = hemoglobin A1c; T1D = type 1 diabetes.

Table 2. Outline of hypothesized pathways within the T1D remission conceptual model

Left Panel (Upstream Determinants)	Central Panel (Pathways Linked to Remission)	Outcomes / Effects of Pathways
• **Higher β-cell function reflects higher endogenous insulin and C-peptide secretion**	**Pathway 1: Potential Effects of Preserved Endogenous Insulin**	
	• Better regulation of blood glucose • Decreased oxidative stress from hyperglycemia • Improved lipid metabolism (↓ triglycerides, ↓ LDL) • Supports β-cell preservation	• Improved glycemic control; fewer hyper/hypoglycemic episodes • Reduced acute events (severe hypoglycemia, DKA) • Reduced inflammation • Potentially favorable cardiovascular risk profile • Reinforces remission (positive feedback loop)
	Pathway 2: Potential Effects of Preserved C-peptide Based on Mechanistic Studies	
	• Suppresses oxidative stress • Improves endothelial nitric oxide synthase activity • Prevents endothelial and neural apoptosis • Effects depend on residual β-cell function (baseline C-peptide level)	• Potential anti-inflammatory and vascular protective effects • Improved tissue perfusion • Potential microvascular protective effects

Abbreviations: BMI = body mass index; DKA = diabetic ketoacidosis; HbA1c = hemoglobin A1c; IDAA1c = insulin-dose adjusted A1c; LDL = low-density lipoprotein; T1D = type 1 diabetes.

Preliminary Conceptual Model

- To develop the preliminary conceptual model, findings from the SLR were supplemented with targeted searches to address evidence gaps in hyperglycemia correction, insulin secretion, and C-peptide mechanisms during remission.
- Evidence from mechanistic and in-vitro/animal studies suggests that increased insulin and C-peptide secretion, along with rapid glycemic improvement and concurrent immune modulation, may help explain observed clinical benefits.
- The model proposes potential links between glycemic improvement, residual β-cell function, and immune modulation. These mechanisms remain untested during endogenous remission.

Outcomes

- **Table 2 and Figure 1** present a preliminary, hypothesis-generating conceptual model linking baseline clinical factors, clinical remission, and preserved C-peptide to glycemic and vascular outcomes reported in the SLR.
- Some studies indicated that partial remission is associated with preserved β-cell function and endogenous secretion of insulin and C-peptide in equimolar amounts and is partly defined by improved glucose metabolism and preserved β-cell function (e.g., via IDAA1c). These features should be read as overlapping with the definition of remission itself, not as independently demonstrated downstream effects.

Factors associated with remission

- Frequently reported factors associated with remission in T1D include male sex, higher body mass index, higher C-peptide levels, older age, lower insulin dose, absence of diabetic ketoacidosis, lower HbA1c levels at diagnosis, and less severe expression of T1D.
- These same factors (age, sex, DKA, HbA1c, insulin dose, C-peptide) are also associated with less severe disease at onset and are not adjusted for in most studies linking remission to clinical outcomes.

Preserved Secretion of Endogenous Insulin by β-Cells During Remission

- Preserved β-cell function maintains endogenous insulin secretion, which improves glycemic control and suppresses lipolysis and hepatic VLDL production.[10]
- These effects may improve lipid levels, reduce glycemic variability, and lower the risk of severe hypoglycemia and diabetic ketoacidosis.[11]
- Rapid correction of hyperglycemia may also reduce oxidative stress, β-cell stress, and inflammation, potentially helping preserve residual β-cell function.

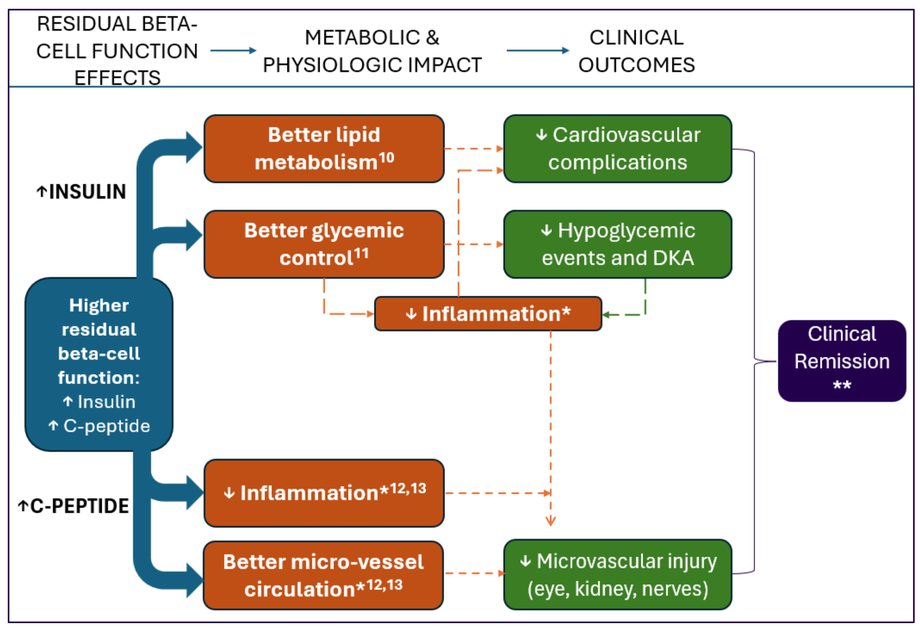
Potential Effects of C-peptide and Supporting Evidence

- Mechanistic and in-vitro/animal studies, largely preclinical or involving exogenous C-peptide, suggest potential effects on microvascular circulation and inflammatory pathways, including enhanced nitric oxide production, improved endothelial function, and reduced oxidative stress.[12,13]
- Together with endogenous insulin secretion and rapid glycemic improvement, these mechanisms could plausibly contribute to the favorable metabolic and vascular associations observed. **These pathways have not been tested directly during remission.**

Limitations of the approach

- Remission definitions (e.g., IDAA1c, partial and complete remission) partly incorporate β-cell function or C-peptide, so the remission-C-peptide relationship is partly circular by construction.
- Remitters differ from non-remitters in disease severity at onset (age, sex, DKA, HbA1c, insulin dose), and the available studies do not adjust fully for this. The model therefore identifies hypotheses and evidence gaps; it does not test mediation or causality.

Figure 1. Visual representation of the hypothesized T1D remission pathway and the trends observed between remission and glycemic control, clinical complications, and preservation of β-cell function



*Supporting evidence includes in-vitro/animal studies; the indicated mechanistic effects have not been established during endogenous clinical remission in humans.

**Clinical remission is heterogeneously defined across studies, with varying criteria and reported clinical outcomes. The model simplifies complex, potentially overlapping and interdependent pathways; the depicted relationships are hypothesis-generating and should not be interpreted as established causal effects.

Note: Dashed arrows indicate hypothesized relationships, not established causal effects, based on findings from mechanistic studies.

Abbreviations: DKA = diabetic ketoacidosis; IDAA1c = insulin-dose adjusted A1c

CONCLUSIONS

- In a heterogeneous, predominantly observational evidence base, clinical remission in T1D was associated with improved glycemic control. Evidence for other clinical outcomes, including hypoglycemia, lipid profiles, and microvascular complications, was limited or inconsistent.
- Because remission definitions partly incorporate β-cell function, insulin requirements and C-peptide, these features may reflect the definition rather than independent findings.
- The preliminary conceptual model proposes hypothesized pathways linking reduced glucotoxicity, endogenous insulin secretion, residual C-peptide, and immune modulation to glycemic stability and potential vascular benefits. Support comes mainly from mechanistic and in-vitro/animal studies.
- These pathways have not been tested directly during endogenous remission. Available clinical evidence does not establish these mechanisms or determine the direction or magnitude of causal effects.
- Standardized remission definitions and longitudinal studies are needed to evaluate the proposed pathways. Studies should adjust for disease severity at onset, test whether C-peptide mediates associations between remission and clinical outcomes and assess remission duration and patient-relevant outcomes.

DISCLOSURES:
This study was funded by Sanofi and conducted by Evidinno Outcomes Research Inc. Laura Wilson and Sangameshwar Rawoor are employees of Sanofi and may hold shares and/or stock options in the company. Divya Pushkarna, Jean-Paul Collet, Johnny Zhou, Ramandeep Kaur, and Walid Shouman report employment with Evidinno Outcomes Research Inc.

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