KETOSIS-PRONE TYPE 2 DIABETES: CHALLANGES IN DIABETES CLASSIFICATION

Ph.D. Thesis Booklet

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1. INTRODUCTION

Diabetes mellitus represents a heterogeneous group of metabolic disorders that differ markedly in pathophysiology, clinical presentation, and long-term management. While traditional classification systems distinguish primarily between type 1 and type 2 diabetes, increasing evidence indicates that this dichotomy does not adequately capture the complexity of adult-onset diabetes, particularly in cases presenting with acute metabolic decompensation.

Ketosis-prone type 2 diabetes is a distinct phenotype characterised by diabetic ketoacidosis or ketosis at diabetes onset, absence of diabetes-related autoimmunity, and preserved endogenous insulin secretion. Although recognised as a hybrid form of diabetes in the 2019 World Health Organization classification, ketosis-prone type 2 diabetes remains underdiagnosed in routine clinical practice. Its acute presentation often leads to misclassification as autoimmune diabetes, resulting in unnecessary long-term intensive insulin therapy despite preserved beta-cell function.

Most available data on ketosis-prone type 2 diabetes originate from non-Caucasian populations, whereas evidence from European cohorts is limited. Clarifying its prevalence, clinical characteristics, and long-term course – particularly in Caucasian populations – is therefore essential for improving diagnostic accuracy and optimising treatment strategies.

2. OBJECTIVES

The primary aim of this thesis was to improve the recognition and characterisation of ketosis-prone type 2 diabetes and to clarify its clinical relevance in adults presenting with diabetic ketoacidosis or ketosis at diabetes onset.

The specific objectives were:

- To summarise the global prevalence of ketosis-prone type 2 diabetes among adults presenting with diabetic ketoacidosis or ketosis through a systematic review and meta-analysis.
- To compare the clinical characteristics of ketosis-prone type 2 diabetes with autoimmune diabetes at

diabetes onset based on systematically synthesised evidence.

- To determine the prevalence of ketosis-prone type 2 diabetes in a Hungarian cohort of newly diagnosed adults with diabetes.
- To characterise the clinical and metabolic features of ketosis-prone type 2 diabetes in this cohort and to evaluate the impact of autoantibody and C-peptide testing on diabetes classification.
- To assess long-term endogenous insulin secretion and treatment patterns in patients with ketosis-prone type 2 diabetes during extended follow-up.

3. METHODS

3.1 Study I – Systematic review and meta-analysis

A systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 guidelines. A comprehensive search of major biomedical databases was performed to identify studies reporting the prevalence and clinical characteristics of ketosis-prone type 2 diabetes in adults with diabetic ketoacidosis or ketosis. Eligibility

criteria required documentation of diabetes-related autoantibody status and assessment of beta-cell function. Two reviewers independently screened studies, extracted data, and assessed risk of bias using standardised appraisal tools. Pooled prevalence estimates and comparisons of clinical parameters between ketosis-prone type 2 diabetes and type 1 diabetes were calculated using a random-effects model, accounting for expected heterogeneity. The certainty of evidence was evaluated using GRADE methodology.

3.2 Study II – Hungarian follow-up cohort study

The second study was a retrospective longitudinal cohort study conducted at the 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary, including adult patients enrolled between 2001 and 2008, with longitudinal follow-up data available through 2022. The study was designed and reported in accordance with the STROBE 2007 guidelines. Patients presenting with newly diagnosed diabetes were identified from institutional records and classified according to the

presence of diabetic ketoacidosis or ketosis, diabetes-related autoantibodies, and fasting C-peptide levels.
Clinical and laboratory data were collected at diagnosis. Long-term follow-up data focused on endogenous insulin secretion and treatment modalities in patients with ketosis-prone type 2 diabetes. Statistical analyses included descriptive statistics and regression-based comparisons across diabetes types, with multivariable adjustment for relevant covariates, as well as longitudinal mixed-effects modelling of C-peptide trajectories; Bayesian regression models were applied as sensitivity analyses.

4. RESULTS

4.1 Study I – Systematic review and meta-analysis

The systematic review and meta-analysis of 2010 multiethnic patients demonstrated that ketosis-prone type 2 diabetes is a common phenotype among adults manifesting with diabetic ketoacidosis or ketosis at diabetes onset. Within this population, 35% (95% CI: 24%–49%) were classified as having ketosis-prone type 2

diabetes rather than autoimmune diabetes. Compared with type 1 diabetes, individuals with ketosis-prone type 2 diabetes were significantly older at diagnosis (mean difference: 11.55 years; 95% CI: 5.5–17.6) and had a higher body mass index (mean difference: 5.48 kg/m^2; 95% CI: 3.25–7.72). Based on these findings, we propose a simplified diagnostic approach to distinguish ketosis-prone type 2 diabetes from type 1 diabetes in adults showing diabetic ketoacidosis or ketosis at diabetes onset, incorporating autoantibodies, C-peptide, age, and body mass index.

4.2 Study II – Hungarian follow-up cohort study

In our Hungarian cohort of 183 adults with newly diagnosed diabetes, ketosis-prone type 2 diabetes accounted for approximately one quarter of ketosis-positive cases (22 of 86), representing one of the largest Caucasian cohorts reported. Patients with ketosis-prone type 2 diabetes were older at diagnosis than those with autoimmune diabetes (54.9±12.6 vs. 34.8±12.6 years; $p<0.0001$), had higher hemoglobin A_{1c} (13.3±3.1% vs.

10.8±3.2%; p=0.0047), higher body mass index (31.5±5.6 vs. 22.5±3.7 kg/m²; p<0.0001), and higher hepatic steatosis index (45.4±6.2 vs. 34.7±4.7; p<0.0001). In patients with ketosis-prone type 2 diabetes, fasting C-peptide levels remained within the reference range during long-term follow-up (5–10 years: 4.37±2.45 ng/mL; 10–15 years: 2.85±1.54 ng/mL), indicating sustained endogenous insulin secretion, although intensive insulin regimens initiated during the acute metabolic phase were continued in several patients.

5. CONCLUSIONS

This thesis demonstrates that ketosis-prone type 2 diabetes is a frequent and clinically relevant diabetes subtype that should be considered in adults presenting with diabetic ketoacidosis or ketosis at diabetes onset, including those of Caucasian ethnicity. Based on our findings, affected individuals are typically older and more obese than patients with type 1 diabetes. Systematic assessment of diabetes-related autoantibodies and C-peptide at diagnosis is essential for accurate classification

in all adults manifesting with diabetic ketoacidosis or ketosis at diabetes onset, regardless of ethnicity, and may prevent unnecessary long-term intensive insulin therapy. Notably, endogenous insulin secretion may remain preserved in the long term despite an acute presentation with diabetic ketoacidosis or ketosis. To improve recognition and management of ketosis-prone type 2 diabetes, internationally standardised diagnostic criteria and follow-up guidelines should be implemented, including uniform autoantibody and C-peptide assessment, with emphasis on safe insulin withdrawal and the appropriate incorporation of modern type 2 diabetes therapies.

6. BIBLIOGRAPHY

6.1 Publications Related to the Thesis

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