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KETOSIS-PRONE TYPE 2 DIABETES: CHALLANGES IN DIABETES CLASSIFICATION

Ph.D. Thesis

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Budapest

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“Absence of evidence is not evidence of absence”

– Carl Sagan –

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

ADA	American Diabetes Association
ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
CGM	Continuous glucose monitoring
CoCoPop	Condition-Context-Population framework
DKA	Diabetic ketoacidosis
FFA	Free fatty acids
FIB-4	Fibrosis-4 index
GAD-65	Glutamic acid decarboxylase-65 autoantibody
GDT	GRADEpro Guideline Development Tool
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HbA_{1c}	Hemoglobin A_{1c}
HLA	Human leukocyte antigen
HOMA2-B	Homeostatic model assessment 2 of beta-cell function
HOMA2-IR	Homeostatic model assessment 2 of insulin resistance
HSI	Hepatic steatosis index
ICA	Islet cell autoantibodies
JDFU	Juvenile Diabetes Foundation unit
KPT2D	Ketosis-prone type 2 diabetes
LADA	Latent autoimmune diabetes in adults
MAFLD	Metabolic-associated fatty liver disease
MARD	Mild age-related diabetes

MD	Mean difference
MOD	Mild obesity-related diabetes
OR	Odds ratio
PECO	Population-Exposure-Comparison-Outcome framework
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
QUIPS	Quality in prognosis studies
SAID	Severe autoimmune diabetes
SD	Standard deviation
SEM	Standard error of the mean
SIDD	Severe insulin deficient diabetes
SIRD	Severe insulin resistant diabetes
STROBE	Strengthening the reporting of observational studies in epidemiology
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TCF7L2	Transcription factor 7-like 2
WHO	World Health Organization
WHR	Waist-to-hip ratio

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve the recognition of ketosis-prone type 2 diabetes through accurate classification at diagnosis, thereby reducing unnecessary long-term intensive insulin therapy. My mission is to clarify the true prevalence of this condition – particularly in Caucasian populations – and to characterise its clinical features to enable reliable differentiation from type 1 diabetes, despite an initial presentation characterised by diabetic ketoacidosis. The goals of my research are to determine its global prevalence, assess its prevalence in a Hungarian cohort, and describe its clinical characteristics and long-term disease course.

2.2. Scientometrics

Number of all publications:	3
Cumulative IF:	12.4
Av IF/publication:	4.1
Ranking (SCImago):	D1:1, Q1:2
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9.4
Av IF/publication:	4.7
Ranking (SCImago):	D1:1, Q1:1
Number of citations on Google Scholar:	29
Number of citations on MTMT (independent):	17
H-index:	2

The detailed bibliography of the student can be found on page 49.

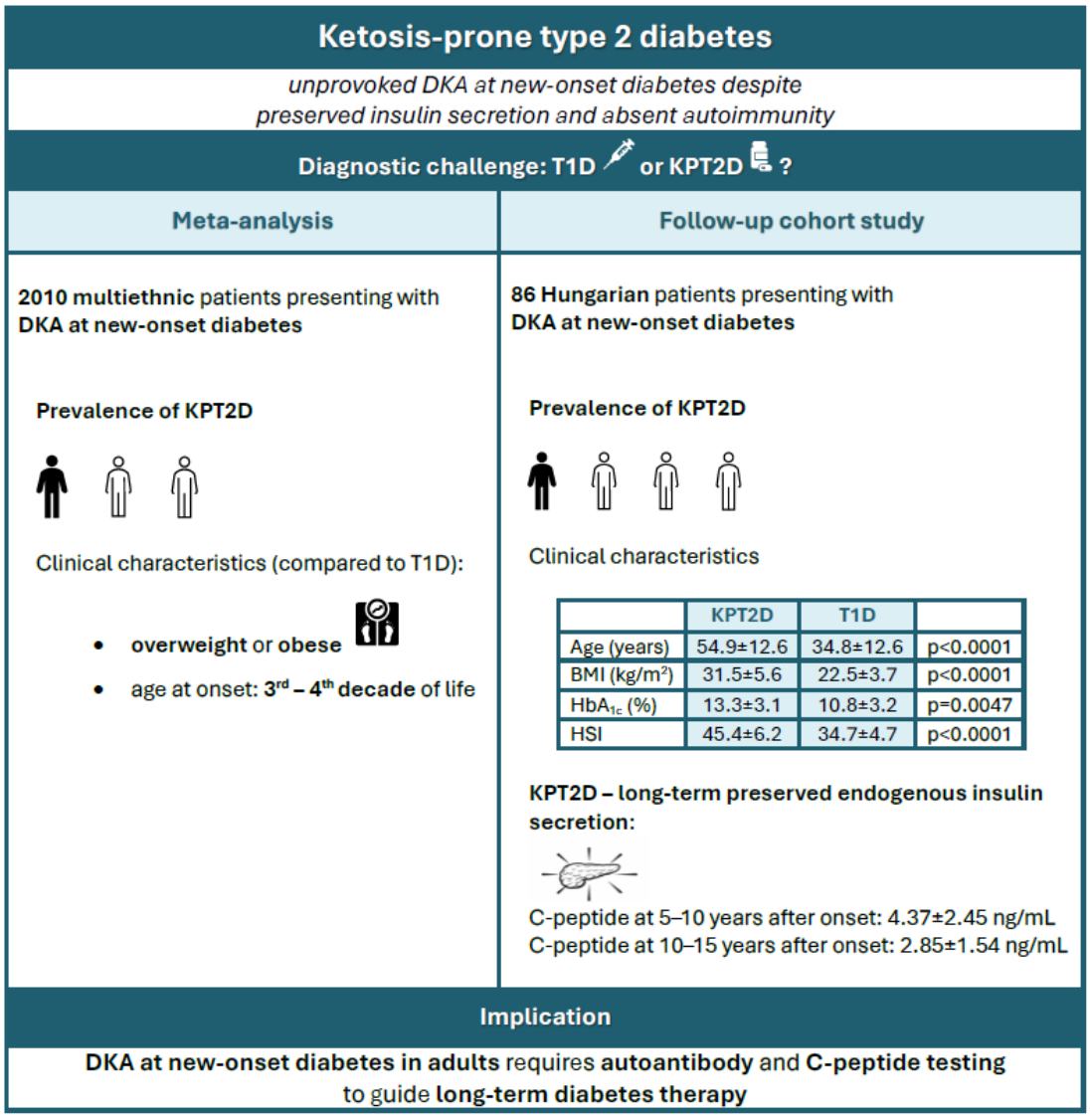
2.3. Future plans

In the near future, I plan to focus on clinical practice, while the scientific and methodological foundations gained during my PhD remain central to how I work. I value translational medicine because it allows research evidence to have an immediate and tangible impact on both patient care and the health care system.

3. SUMMARY OF THE THESIS

This thesis investigates the epidemiology, clinical phenotype, and long-term course of ketosis-prone type 2 diabetes, a distinct diabetes subtype characterised by unprovoked diabetic ketoacidosis or ketosis, absent diabetes-related autoimmunity, and preserved endogenous insulin secretion. Despite its recognition in the 2019 World Health Organization diabetes classification, ketosis-prone type 2 diabetes remains underdiagnosed – particularly in Caucasian populations – owing to its overlap with autoimmune diabetes at clinical presentation. The first part of this work comprises a systematic review and meta-analysis of 11 studies including 2010 patients, demonstrating that approximately one-third of adults presenting with diabetic ketoacidosis or ketosis at new-onset diabetes has ketosis-prone type 2 diabetes rather than type 1 diabetes. Compared with type 1 diabetes, affected individuals were on average 11.5 years older, exhibited a 5.48 kg/m² higher body mass index, and showed significantly higher fasting and stimulated C-peptide levels, while hemoglobin A_{1c} values at admission were comparable. Based on these findings, a simplified diagnostic approach integrating age, body mass index, autoimmune markers, and C-peptide was proposed. The second part of the thesis presents a retrospective longitudinal cohort analysis of 183 Hungarian adults with newly diagnosed diabetes. Among the 86 ketosis-positive patients, 22 (26%) fulfilled the diagnostic criteria for ketosis-prone type 2 diabetes, providing one of the largest Caucasian cohorts described to date. These individuals were older, had a worsened glycemic state – evidenced by elevated HbA_{1c} – and displayed more advanced metabolic-associated fatty liver disease than those with autoimmune diabetes. Human leukocyte antigen genotyping confirmed a low prevalence of type 1 diabetes-associated susceptibility alleles, and long-term follow-up up to 21 years showed sustained endogenous insulin secretion despite heterogeneous therapeutic regimens. Together, these findings confirm that ketosis-prone type 2 diabetes is a common and clinically relevant diabetes subtype across diverse populations, including Caucasians. The thesis strengthens the evidence for a distinct phenotype, supports routine evaluation of autoantibodies and C-peptide in all adults with new-onset diabetes presenting with diabetic ketoacidosis or ketosis, and provides novel long-term data indicating sustained endogenous beta-cell function, clarifying that continued intensive insulin therapy is often unnecessary.

4. GRAPHICAL ABSTRACT



	KPT2D	T1D	
Age (years)	54.9±12.6	34.8±12.6	p<0.0001
BMI (kg/m²)	31.5±5.6	22.5±3.7	p<0.0001
HbA_{1c} (%)	13.3±3.1	10.8±3.2	p=0.0047
HSI	45.4±6.2	34.7±4.7	p<0.0001

DKA: Diabetic ketoacidosis; T1D: Type 1 diabetes; KPT2D: Ketosis-prone type 2 diabetes; HSI: Hepatic steatosis index

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

The topic of this thesis is the prevalence and clinical characteristics of ketosis-prone type 2 diabetes, a distinct diabetes subtype characterised by unprovoked diabetic ketoacidosis (DKA) or ketosis at diabetes onset, absence of autoimmune markers, and preserved endogenous insulin secretion. This is addressed through a systematic review and meta-analysis, complemented by a follow-up cohort study conducted in Hungarian adults from our clinical practice.

5.1.2. What is the problem to solve?

Significant gaps persist in our understanding of the epidemiology, phenotype, and long-term clinical course of ketosis-prone type 2 diabetes. Evidence from Caucasian populations is particularly limited, as most existing studies focus on African, Asian, or multiethnic cohorts. Lack of diagnostic clarity at diabetes onset also remains a major challenge, as this condition characteristically presents with diabetic ketoacidosis or ketosis in a manner that closely resembles autoimmune type 1 diabetes.

5.1.3. What is the importance of the topic?

The importance of this topic lies in ensuring that clinicians consider ketosis-prone type 2 diabetes in Caucasian adults presenting with diabetic ketoacidosis or ketosis at diabetes onset, a subgroup in whom this phenotype may otherwise be overlooked and multiple daily insulin therapy unnecessarily continued beyond the acute phase.

5.1.4. What would be the impact of our research results?

Our work highlights the clinical relevance of ketosis-prone type 2 diabetes in adults showing diabetic ketoacidosis or ketosis at diabetes onset, particularly in settings where this subtype has traditionally received limited consideration. By clarifying its key clinical features, the study provides a more coherent and integrated diagnostic framework that can support more accurate classification and guide more appropriate therapeutic decisions, ultimately reducing unnecessary treatment burden for both individuals and the wider health care system.

5.2. Recent challenges of diabetes classification

Diabetes mellitus represents a broad spectrum of metabolic conditions that share the hallmark feature of chronic hyperglycemia. While the diagnostic criteria rely uniformly on elevated blood glucose levels, long-term therapeutic strategies and disease trajectories differ substantially among the various forms of diabetes (1,2). The most recent classification proposed by the American Diabetes Association (ADA) delineates four principal categories: 1) type 1 diabetes, encompassing autoimmune-mediated destruction of pancreatic beta-cells, which may occur rapidly or follow a more indolent course, as well as less common idiopathic variants; 2) type 2 diabetes, characterised by a progressive decline in endogenous insulin secretion in combination with insulin resistance; 3) specific types of diabetes, in which a clearly identifiable underlying cause can be determined; and 4) gestational diabetes, defined as glucose intolerance first recognised during pregnancy (2).

In 2019, the World Health Organization (WHO) established a distinct subgroup referred to as hybrid forms of diabetes. This category includes both the slowly progressive adult-onset autoimmune form previously termed latent autoimmune diabetes in adults (LADA) and ketosis-prone type 2 diabetes (1).

Accumulating evidence demonstrates substantial heterogeneity in clinical presentation, underlying pathophysiology, and immunogenetic background across the various diabetes subtypes (3). This increasing recognition of complexity has contributed to the development of data-driven clustering approaches in adult-onset diabetes, designed to more accurately reflect the multidimensional heterogeneity that conventional classifications are unable to encompass (4). The most influential data-driven attempt to refine adult-onset diabetes classification was published by *Ahlqvist et al.* in 2018 (5). The authors integrated six routinely available clinical variables – glutamic acid decarboxylase antibodies (GADA) status, age at diagnosis, body mass index (BMI), hemoglobin A_{1c} (HbA_{1c}), and homeostatic model assessment 2 of beta-cell function and insulin resistance (HOMA2-B and HOMA2-IR, respectively) – and identified five reproducible diabetes subgroups with distinct metabolic profiles and complication risks. These included severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD) (5). Subsequent studies across multiple populations have broadly

replicated the clustering structure, with notable ethnic differences in both cluster frequencies and within-cluster phenotypes (4,6). Phenotypic clustering currently shows its strongest translational relevance in predicting differences in complication risk between subgroups, whereas its role in guiding treatment decisions remains limited and requires further evidence (7). Genotypic clustering offers complementary insights into underlying disease mechanisms, yet current evidence remains limited, and its clinical applicability has not been demonstrated (7).

Reflecting two core pathophysiological dimensions, a recent *Lancet* proposal has introduced a simplified, clinically actionable subclassification of type 2 diabetes into insulin-resistant (type 2A), insulin-deficient (type 2B), and mixed (type 2AB) forms (8). Ultimately, diabetes is more accurately conceptualised as a continuum rather than a collection of discrete categories, and ketosis-prone type 2 diabetes illustrates how precise phenotypic characterization can identify biologically meaningful subgroups within this spectrum (9).

5.3. Ketosis-prone type 2 diabetes

Ketosis-prone type 2 diabetes was first recognised between the 1960s and 1980s through case reports describing individuals – predominantly of African or African-American descent – who presented with diabetic ketoacidosis despite lacking the classical features of type 1 diabetes (10,11). These early observations revealed an unfamiliar clinical pattern in which patients exhibited marked hyperglycemia and ketosis at onset, yet a substantial proportion subsequently achieved prolonged insulin independence without evidence of autoimmune beta-cell destruction (10,11). Later studies in larger cohorts confirmed that this phenotype is more widespread, with ethnicity influencing its prevalence but not defining the syndrome; nevertheless, Caucasian populations remain underrepresented in current research (12,13). Clinically, individuals are typically diagnosed in the third to sixth decade of life and are most often overweight or obese, frequently with central adiposity (10,11). Men are overrepresented, and a positive family history of diabetes is common (10,11). Features of insulin resistance, such as acanthosis nigricans, are frequently observed (10,11). The clinical course resembles that of type 2 diabetes, with periods of insulin dependence during metabolic decompensation followed by remission phases characterised by restored endogenous insulin secretion (10,11). Remission from

insulin dependence has been associated with favourable post-decompensation glycemic control (e.g. achieving HbA_{1c} <7% at least six months after the diagnosis), biochemical evidence of preserved beta-cell functional reserve (reflected by a high C-peptide-to-glucose ratio), and the absence of HLA (Human leukocyte antigen) class II alleles linked to type 1 diabetes susceptibility (14).

Recent data have highlighted several biochemical and clinical tools that may support the early identification of ketosis-prone type 2 diabetes. A metabolomics study showed that a specific panel – including beta-hydroxybutyrate, C-peptide, glucagon, and selected amino-acid and lipid metabolites – can distinguish this subtype from type 1 and type 2 diabetes during hyperglycemic crises (15). One clinical study reported that a HbA_{1c} threshold of 10.15% identified ketosis-prone type 2 diabetes with 92.7% sensitivity and 70.5% specificity (16). A second study by *Min et al.* developed a four-factor nomogram (age, family history, HbA_{1c}, free fatty acids (FFA)) with excellent discrimination for predicting ketosis risk in newly diagnosed type 2 diabetes (17). Complementing these findings, *Zheng et al.* proposed a five-parameter prediction model (age, fasting C-peptide, FFA, HbA_{1c}, proteinuria) (18). Together, these studies demonstrate the growing interest in metabolic and clinical predictors of ketosis-prone type 2 diabetes, while underscoring the need for broader population-level data.

6. OBJECTIVES

6.1. Study I. – The prevalence of ketosis-prone type 2 diabetes

Given the scarcity of robust data on the global prevalence of ketosis-prone type 2 diabetes, we performed a systematic review and meta-analysis to summarise the existing evidence across diverse ethnic populations. We also aimed to describe its clinical characteristics in a quantitative manner.

6.2. Study II. – Ketosis-prone type 2 diabetes in a Hungarian cohort

Given the underrepresentation of Caucasian cohorts in the literature – and our clinical experience suggesting that ketosis-prone type 2 diabetes does occur among Hungarian patients – we conducted a cohort study of newly diagnosed adults with diabetes mellitus. Our objective was to establish its prevalence in this population and to describe the associated clinical phenotype and long-term course to facilitate accurate diagnosis.

7. METHODS

7.1. Study I.

7.1.1. Methodology and Protocol

The systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 recommendations (19), and the study design followed the methodological guidance outlined in the Cochrane Handbook (20). The protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews; CRD42021283369) prior to initiating the review, and it was carried out without modifications.

7.1.2. Eligibility Criteria

Eligibility criteria were defined using the CoCoPop (Condition, Context, Population) framework for prevalence outcomes and the PECO (Population, Exposed group, Comparison group, Outcomes) framework for clinical characteristics. We included studies of patients with newly diagnosed diabetes presenting with DKA or ketosis, where ketosis-prone type 2 diabetes was defined by autoantibody negativity and preserved C-peptide. No age restrictions were applied. Studies lacking autoantibody or C-peptide data or that included populations not solely presenting with diabetic ketoacidosis or ketosis, as well as reviews and case reports, were excluded.

7.1.3. Information Sources and Search Strategy

A systematic search was carried out on 15 October 2021 using five major databases (MEDLINE, Embase, Web of Science, Scopus, and CENTRAL), and no search filters were applied. To ensure completeness, the reference lists of the studies meeting the inclusion criteria were also reviewed for additional relevant publications.

7.1.4. Study Selection and Data Extraction

All records identified through the database search were imported into EndNote (Clarivate Analytics, Philadelphia, PA, USA), where duplicates were removed both automatically and manually. Study selection was carried out independently by two reviewers, first based on titles and abstracts and then through full-text assessment. Interrater agreement was quantified using Cohen’s kappa. Any discrepancies were resolved by a third reviewer.

Data extraction was performed by one reviewer and independently checked by another. When studies reported overlapping populations, we retained the publication with the larger sample size and more complete outcome data.

From each eligible study, we collected publication details, study characteristics, sample sizes, prevalence data, and clinical and laboratory parameters (age, sex, BMI, fasting or stimulated C-peptide, HbA_{1c}, lipid profile, and insulin dependence at follow-up). Family history of diabetes was also extracted. Laboratory units were standardised where necessary (C-peptide in ng/mL, lipid values in mmol/L).

7.1.5. Risk of Bias and Quality of Evidence Assessment

The risk of bias of the included studies was assessed independently by two reviewers, with disagreements resolved by discussion. For the prevalence outcomes, we used the Joanna Briggs Institute Critical Appraisal Tools (JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data) (21), and for the clinical characteristics, the Quality In Prognosis Studies (QUIPS) tool (22). The certainty of the evidence was evaluated using the GRADEpro Guideline Development Tool (GDT), in line with the recommendations of the Cochrane Handbook (23).

7.1.6. Data Synthesis and Analysis

Categorical outcomes were summarised as prevalence estimates and odds ratios with 95% confidence intervals (CI), where the odds ratio was defined as the odds in the ketosis-prone type 2 diabetes group divided by the odds in the type 1 diabetes group. Continuous variables were pooled as mean differences (MD) with 95% CIs, calculated as the mean value of the ketosis-prone type 2 group minus that of the type 1 diabetes group.

Given the expected heterogeneity across studies, effect sizes were pooled using a random-effects model. Statistical significance was assumed when the 95% CI did not include the null value. Heterogeneity was quantified with Higgins and Thompson's I^2 statistic, and results were presented in forest plots. Influence analyses were performed using leave-one-out procedures. Publication bias was evaluated by Egger's test (at a significance level of 10%) and visual inspection of funnel plots. All analyses were conducted in R (R Core Team 2021, v4.1.1) (24) using the meta (v5.2.0) (25) and dmetar (v0.0.9000) packages (26). We report 95% confidence intervals as CI.

7.2. Study II.

7.2.1. Study Design and Setting

This investigation was conducted as a retrospective longitudinal cohort study in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) 2007 guidelines (27). Consecutive adult patients manifesting with new-onset diabetes mellitus between 2001 and 2008 at the 3rd Department of Internal Medicine, Semmelweis University (Budapest, Hungary) were identified from institutional archives. Baseline characteristics and long-term clinical outcomes were obtained retrospectively from routine medical documentation available until 2022.

7.2.2. Ethics and Patient Consent

Ethical approval for the study was obtained from the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SERKEB 92/2023). No additional interventions or diagnostic procedures were performed beyond routine clinical practice. The study was based exclusively on information contained in existing medical records.

7.2.3. Participants

The study population consisted of Caucasian adults (≥18 years) with newly diagnosed diabetes mellitus. New-onset diabetes was defined as a diagnosis made during the inclusion period in individuals without previous diabetes or glucose-lowering treatment. No restrictions were applied regarding sex or comorbidities. Patients were excluded if a secondary cause of diabetes was identified (e.g., exocrine pancreatic disease, steroid-induced hyperglycemia) or in the case of gestational diabetes.

Diabetes mellitus was diagnosed according to the ADA recommendations (2). Diabetic ketoacidosis was defined by arterial pH ≤7.30 or serum bicarbonate ≤18 mEq/L, with plasma glucose >13.9 mmol/L (>250 mg/dL), and positive urine ketones (28). Ketosis was defined as hyperglycemia (≥13.9 mmol/L) with positive urine ketones (28). All newly diagnosed adults were first categorised as ketosis-positive or ketosis-negative based on their clinical presentation. Among ketosis-positive patients, the presence of diabetes-related autoantibodies indicated type 1 diabetes. Autoantibody-negative cases were further stratified by beta-cell function; those with fasting C-peptide within the

reference range were diagnosed with ketosis-prone type 2 diabetes. In the ketosis-negative group, autoantibody positivity indicated LADA, while autoantibody-negative individuals were classified as type 2 diabetes.

7.2.4. Variables and Data Sources

The following clinical and laboratory parameters were collected for comparison across diabetes subtypes: number of patients, sex distribution, age, plasma glucose (mmol/L), arterial pH, urine ketones, ICA (islet cell autoantibodies, JDF units), GAD-65 (glutamic acid decarboxylase-65 autoantibody, U/mL), BMI (kg/m^2), waist-to-hip ratio (WHR), fasting C-peptide (ng/mL), HbA_{1c} (%, mmol/mol), lipid profile (cholesterol, triglyceride, HDL, mmol/L), and liver enzymes; bilirubin (µmol/L), AST (U/L), ALT (U/L), ALP (U/L), GGT (U/L), LDH (U/L). Metabolic-associated fatty liver disease (MAFLD) was assessed using HSI (Hepatic steatosis index) and FIB-4 (Fibrosis-4 index), and insulin resistance was estimated using HOMA2-IR and HOMA2-B.

Genetic analyses included HLA genotyping (DQB1*0201, DQB1*0302, DR3, and DR4) as markers of type 1 diabetes susceptibility and TCF7L2 (Transcription factor 7-like 2) rs7903146 as a marker of type 2 diabetes predisposition. The cut-off values applied were 10 JDFU for ICA, 0.9 U/mL for GAD-65, and a laboratory reference range of 0.8–4.2 ng/mL for fasting C-peptide.

For treatment comparison, patients with ketosis-prone type 2 diabetes were stratified into three groups: 1) diet ± oral glucose-lowering medication; 2) basal insulin-supported oral therapy ± GLP-1 (glucagon-like peptide 1) receptor agonist; 3) multiple daily insulin injections. Long-term follow-up of endogenous insulin secretion (C-peptide) is provided in 5-year intervals.

Data were retrieved retrospectively from the hospital information system and verified for completeness and consistency before analysis. Further details on data measurement and data quality are provided in the supplementary material of our original publication (29).

7.2.5. Bias and Confounding

Given the retrospective, single-centre design and the recruitment of patients from a national referral centre, selection bias cannot be excluded, and the study population may not fully represent the distribution of diabetes subtypes in the general population. To reduce this risk, both inpatients and outpatients were consecutively included. Follow-up

information was limited because many patients were transferred to primary or secondary care after diagnosis; therefore, the analyses primarily focused on baseline characteristics with complete availability. Follow-up data were summarised descriptively and interpreted cautiously.

7.2.6. Statistical Methods

Comparisons of clinical parameters across diabetes types were conducted using linear regression models, initially without adjustment and subsequently adjusted for age, sex, and BMI (with BMI and HSI models adjusted only for age and sex). The overall effect of the diabetes type was evaluated using ANOVA (analysis of variance). Pairwise differences between diabetes types were examined through estimated marginal means with Tukey-adjusted p-values. Bayesian regression models were fitted as a sensitivity analysis, and the resulting median differences with 95% credible intervals closely aligned with the frequentist estimates. All analyses were performed in R (v4.2.1) (30) using the car (v3.1.0) (31,32), emmeans (v1.8.0) (33), and brms (v2.23.0) packages (34). Univariate group comparisons are illustrated using violin plots. Estimated marginal means with their 95% confidence intervals were visualised using a marginal means plot, in which arrows indicate pairwise comparisons (non-overlapping arrows denote statistically significant differences). Longitudinal C-peptide trajectories were analysed via a mixed-effects regression model incorporating a random intercept and a linear tail-restricted cubic spline (three degrees of freedom) to model temporal change. Given the limited sample size within several subgroups, the statistical results should be considered exploratory.

8. RESULTS

8.1. Study I: The prevalence of ketosis-prone type 2 diabetes - Meta-analysis

8.1.1. Study Search and Selection

Of 16962 records identified, 9278 were excluded after title and abstract screening, and 106 full texts were assessed. Eleven studies met the eligibility criteria and were included in the systematic review and meta-analysis (**Figure 1**) (35). Altogether, 2010 patients were analysed. Most studies were observational and conducted in Asian (36–42) and African (43,44) populations; one involved Caucasian participants (13) and one study predominantly included African-American and Hispanic patients (45). Basic characteristics of eligible studies are shown in **Table 1** (35).

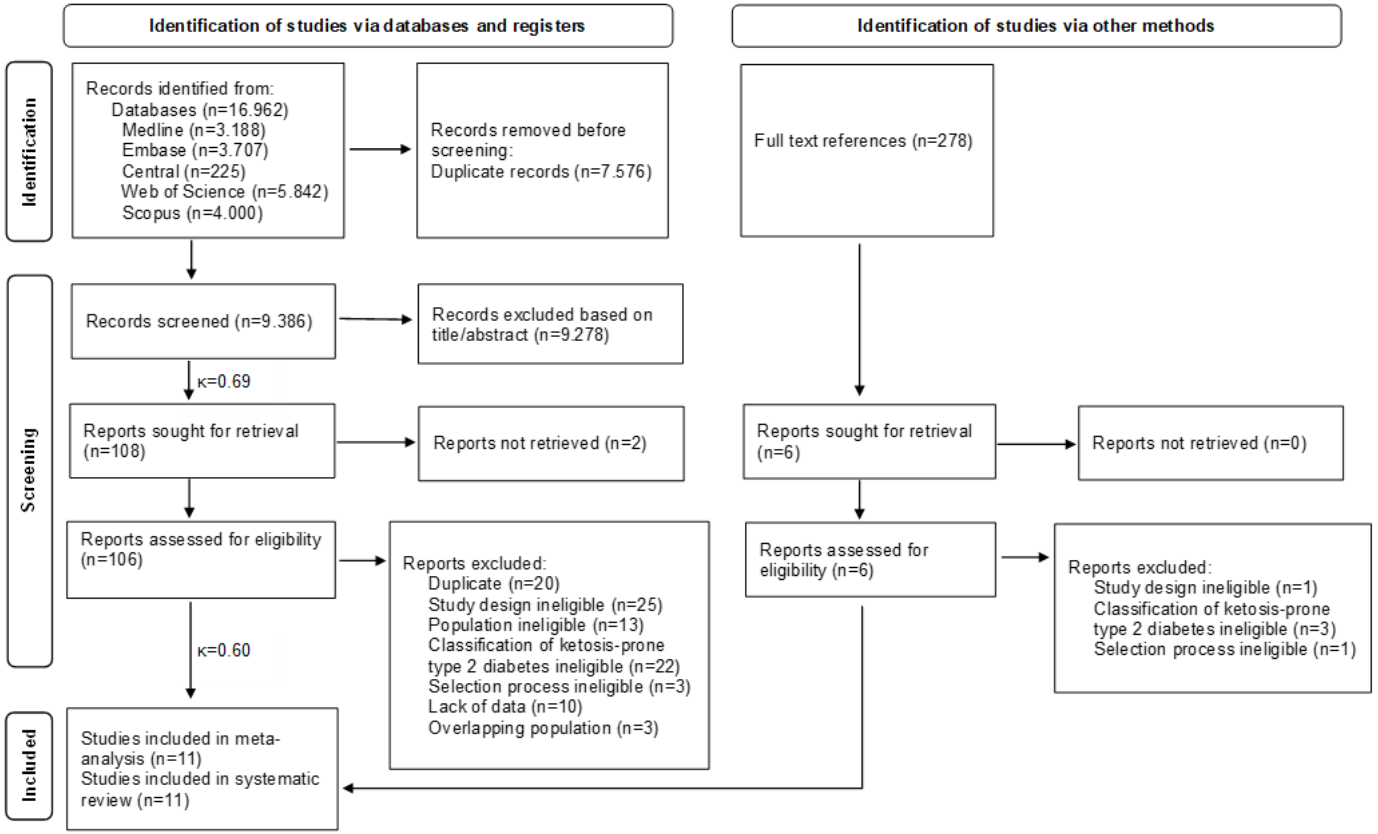


Figure 1. PRISMA 2020 flowchart representing the study selection process (35)

Table 1. Baseline characteristics of the eligible studies (35)

Study	Study design	No of patients (female %)	Age (years)[a]	KPT2D (%)	Diabetes classification	Diabetes-related autoantibodies	Definition of DKA or ketosis	Assessment of acidosis[b]		Assessed outcomes
								KPT2D	T1D	
Barkai et al. (13)	prospective cohort	90 (N/A)	N/A	23.3	Aß	ICA, GAD	DKA or ketosis by ketonuria	N/A	N/A	N/A
Du et al. (41)	retrospective cohort	304 (27.6)	26.7	62.2	Aß	ICA, GAD, IAA	DKA by ADA criteria or ketosis by urine ketone body ≥50 mg/dL or capillary ß-hydroxybutyrate >1 mmol/L with hyperglycaemia	DKA proportion 30%; pH 7.20±0.02; serum HCO3 11.7±0.5 mmol/L	DKA proportion 54%; pH 7.12±0.02; serum HCO3 8.2±0.5 mmol/L	BMI, HbA_{1c}, and lipid profile at admission; family history of diabetes
Ekpebegh et al. (43)	cross-sectional	71 (46.5)	34.7±15.3	46.5	Aß	GAD	DKA by ADA criteria	N/A	N/A	family history of diabetes
Gupta et al. (39)	prospective cohort	51 (N/A)	N/A	21.6	Aß[c]	GAD, IA-2A	DKA by ADA criteria	pH 7.14±0.08; serum HCO3 15.4±6.1 mmol/L	pH 7.26±0.11; serum HCO3 17.8±5.5 mmol/L	BMI, HbA_{1c}, and lipid profile at admission; family history of diabetes; HbA_{1c}, C-peptide, and insulin dependence at 1-year follow-up

Study	Study design	No of patients (female %)	Age (years)[a]	KPT2D (%)	Diabetes classification	Diabetes-related autoantibodies	Definition of DKA or ketosis	Assessment of acidosis[b]		Assessed outcomes
								KPT2D	T1D	
Harzallah et al. (44)	case series	63 (36.5)	46.0±11.6	39.7	Aß	ICA, GAD, IA-2A	ketosis defined by ketonuria with hyperglycaemia	N/A	N/A	BMI, and lipid profile at admission; family history of diabetes
Liu et al. (42)	cross-sectional	79 (35.4)	27.4±20.8	50.6	Aß	GAD, IA-2A	DKA or ketosis defined by ketonuria (urine ketone body above 2+)	N/A	N/A	BMI, HbA_{1c}, and lipid profile at admission
Nalini et al. (45)	prospective cohort	292 (N/A)	N/A	28.4	Aß	GAD, IA-2A, ZnT8	DKA by ADA criteria	N/A	N/A	N/A
Seok et al. (37)	retrospective cohort	60 (35.0)	37.1±13.1	35.0	Aß	GAD	DKA by ADA criteria	pH 7.16±0.12	pH 7.18±0.10	BMI, and HbA_{1c} at admission; family history of diabetes; HbA_{1c}, C-peptide, and insulin dependence at 1-year follow-up

Study	Study design	No of patients (female %)	Age (years)[a]	KPT2D (%)	Diabetes classification	Diabetes-related autoantibodies	Definition of DKA or ketosis	Assessment of acidosis[b]		Assessed outcomes
								KPT2D	T1D	
Tan et al. (36)	retrospective cohort	263 (41.6)	48.7	10.6	treatment history+Aß	ICA, GAD, IAA	DKA by ADA criteria	pH 7.35±0.13; serum HCO3 8.30±0.30 mmol/L	pH 7.34±0.16; serum HCO3 9.99±0.99 mmol/L	BMI, HbA_{1c}, and lipid profile at admission; family history of diabetes
Thewjitcharoen et al. (38)	retrospective cohort	94 (56.0)	47.4±20.4	8.5	treatment history+Aß	N/A	DKA by ADA criteria	serum HCO3 18.1±4.6 mEq/L	serum HCO3 13.3±6.1 mEq/L	BMI, and HbA_{1c} at admission
Xu et al. (40)	retrospective cohort (multicentre)	643 (47.7)	39.4	3.7	treatment history+Aß[d]	ICA, GAD, IAA	DKA by ADA criteria	N/A	N/A	N/A

A: Diabetes-related autoantibodies; ß: Beta-cell function (measured by fasting/stimulated serum C-peptide level); DKA: Diabetic ketoacidosis; ADA: American Diabetes Association; KPT2D: Ketosis-prone type 2 diabetes mellitus; N/A: Not applicable or available; BMI: Body mass index; HbA_{1c}: Hemoglobin A_{1c}

[a]Reported in mean±SD, where available

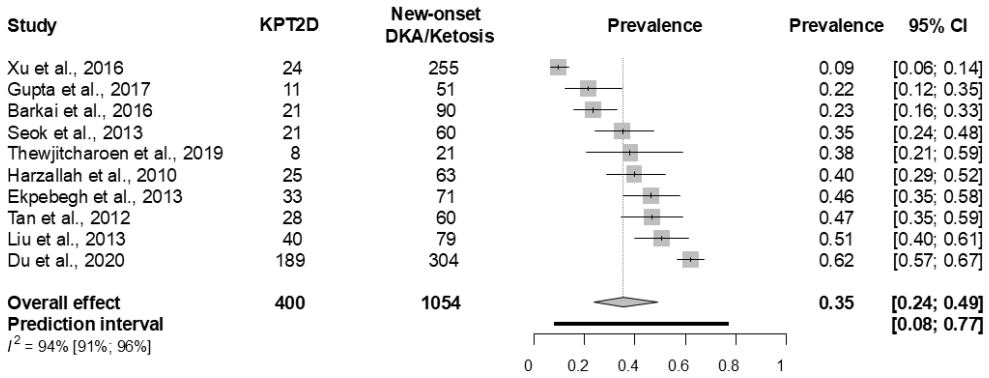
[b]Available data are reported in mean±SD; except for Du et al, where mean±SEM is reported

[c]Additional criteria: insulin independence at 1-year follow-up

[d]Islet cell autoantibodies not prerequisite for type 1 diabetes due to low prevalence of autoantibodies in Chinese ethnicity

8.1.2. Primary Outcomes

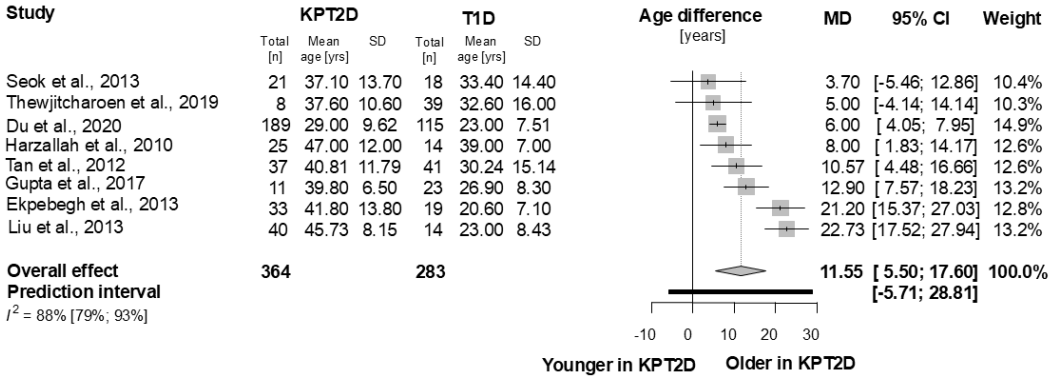
Overall, 1054 patients showing diabetic ketoacidosis or ketosis at diabetes onset were included in the prevalence analysis, of whom 400 had ketosis-prone type 2 diabetes. The pooled prevalence was 35% (CI: 24–49%; I^2=94% [CI: 91–96%]; n=10) (**Figure 2**) (35).



KPT2D: Ketosis-prone type 2 diabetes mellitus; DKA: Diabetic ketoacidosis

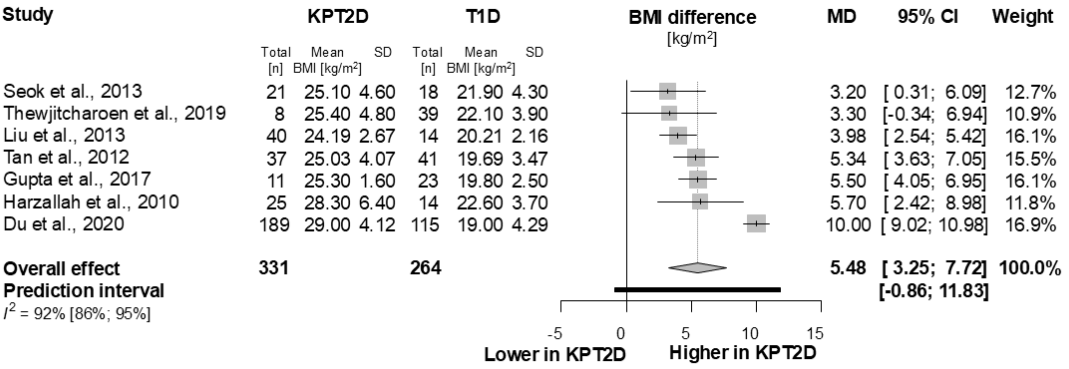
Figure 2. One-third of patients admitted with diabetic ketoacidosis or ketosis at diabetes onset had ketosis-prone type 2 diabetes (35)

Regarding clinical differences between ketosis-prone type 2 and type 1 diabetes, significant results were found for age and BMI. Patients with ketosis-prone type 2 diabetes were, on average, 11.5 years older than those with type 1 diabetes (n=364 vs. n=283; CI: 5.5–17.6; I^2=88% [CI: 79–93%]) (**Figure 3**) (35). They also had a higher BMI (n=331 vs. n=264), with a mean difference of 5.48 kg/m² (CI: 3.25–7.72; I^2=92% [CI: 86–95%]) (**Figure 4**) (35).



KPT2D: Ketosis-prone type 2 diabetes mellitus; T1D: Type 1 diabetes mellitus; MD: Mean difference

Figure 3. Patients with ketosis-prone type 2 diabetes were older than patients with type 1 diabetes (35)



KPT2D: Ketosis-prone type 2 diabetes mellitus; T1D: Type 1 diabetes mellitus; BMI: Body mass index; MD: Mean difference

Figure 4. Higher BMI in ketosis-prone type 2 diabetes compared to type 1 diabetes (35)

Table 2 summarises our proposed diagnostic approach for distinguishing ketosis-prone type 2 diabetes from type 1 diabetes in adults with diabetic ketoacidosis or ketosis at diabetes onset (35). This simplified framework integrates the main findings of our meta-analysis, highlighting the most discriminative clinical features; diabetes-related autoantibody, C-peptide, BMI and age. Although individual variability exists, the pattern outlined here may support clinicians in the early differentiation of these two entities (35).

Table 2. Proposed diagnostic approach in new-onset diabetes with diabetic ketoacidosis or ketosis (35)

Clinical parameters		T1D	KPT2D
1	DKA/ketosis	+	+
2	Diabetes related autoantibodies	+	−
3	C-peptide	in low normal or under the reference range	in reference range
4	Mean weight status[a]	normal	overweight or obese
5	Mean age	20s –30s	30s – 40s

DKA: Diabetic ketoacidosis; T1D: Type 1 diabetes mellitus; KPT2D: Ketosis-prone type 2 diabetes mellitus
[a]Categorised by BMI (adjusted for the Asian population)

8.1.3. Secondary Outcomes

For outcomes not suitable for quantitative synthesis, the main findings are summarised in **Table 3** (35). Across the available studies, dyslipidemia at admission tended to be more pronounced in patients with ketosis-prone type 2 diabetes (35). Follow-up data showed that both fasting and stimulated C-peptide levels remained within the normal range and were higher in the ketosis-prone type 2 diabetes group at 1 year after the diagnosis, accompanied by better glycemic control (35). Long-term insulin dependence appeared uncommon: in one study, only 23% of patients remained on insulin therapy at 1-year follow-up (37).

Table 3. Systematic review of lipid parameters, beta-cell function, long-term glycemic control and insulin dependence (35)

Outcome	Study	KPT2D		T1D		p-value
		Mean±SD	No of patients	Mean±SD	No of patients	
LDL at admission (mmol/L)	Du et al. 2020	2.69±0.10[a]	189	2.59±0.17[a]	115	0.670
	Gupta et al. 2017	2.53±0.31	11	2.61±0.49	23	0.450
	Tan et al. 2012	2.70 (0.96-3.72)[b]	37	2.50 (0.23-4.41)[b]	41	N/A
HDL at admission (mmol/L)	Du et al. 2020	1.07±0.04[a]	189	1.39±0.05[a]	115	0.005
	Harzallah et al. 2010	0.96±0.26	25	1.16±0.23	14	<0.070
	Tan et al. 2012	1.06 (0.51-1.70)[b]	37	1.39 (0.56-2.85)[b]	41	N/A
Total cholesterol at admission (mmol/L)	Du et al. 2020	4.80±0.20[a]	189	4.00±0.20[a]	115	0.010
	Harzallah et al. 2010	4.91±0.72	25	3.75±0.85	14	<0.001
	Tan et al. 2012	5.08 (2.07-9.99)[b]	37	5.04 (2.92-20.69)[b]	41	N/A
Triglyceride at admission (mmol/L)	Du et al. 2020	3.90±0.30[a]	189	1.00±0.30[a]	115	<0.0001
	Gupta et al. 2017	1.80±0.29	11	1.68±0.36	23	0.650
	Harzallah et al. 2010	2.08±0.89	25	1.15±0.34	14	<0.005
	Liu et al. 2013	2.87±1.73	40	2.70±2.23	14	N/A
	Tan et al. 2012	3.48 (0.67-14.77)[b]	37	2.39 (0.45-21.87)[b]	41	0.000
Fasting C-peptide at 1-year (ng/mL)	Gupta et al. 2017	1.36±0.09	11	0.09±0.03	23	<0.010
	Seok et al. 2013	2.91±1.53	21	0.12±0.18	18	<0.001
Stimulated C-peptide at 1-year (ng/mL)[c]	Gupta et al. 2017	3.42±0.47	11	0.41±0.18	23	<0.010
	Seok et al. 2013	4.74±4.05	21	0.33±0.54	18	<0.001
HbA_{1c} at 1-year (%)	Gupta et al. 2017	6.10±0.30	11	8.20±1.50	23	0.010
	Seok et al. 2013	7.10±2.80	13	8.20±1.80	16	<0.050
Insulin dependence at 1-year (%)	Gupta et al. 2017	0[d]	11	100	23	N/A
	Seok et al. 2013	23	13	100	16	N/A

KPT2D: Ketosis-prone type 2 diabetes mellitus; T1D: Type 1 diabetes mellitus; SD: Standard deviation; HbA_{1c}: Hemoglobin A_{1c}; N/A: Not applicable or available
a: Reported in mean±SEM
b: Reported in mean (range)
c: Stimulation by glucagon or mixed meal tolerance test
d: Insulin independence at 1-year follow-up was diagnostic criteria for KPT2D

At admission, fasting and stimulated C-peptide levels – used as internal validation of our eligibility criteria – were significantly higher in the ketosis-prone type 2 diabetes group (MD=0.89 ng/mL; CI: 0.19–1.59; I^2=97% [CI: 96–98%] and MD=1.42 ng/mL; CI: 0.42–2.43; I^2=95% [CI: 92–97%], respectively) (35).

Further non-significant tendencies were observed for several clinical parameters, including a higher proportion of male patients (OR=2.10; CI: 0.83–5.33; I^2=79% [CI: 59–89%]) and a more frequent family history of diabetes (OR=2.52; CI: 0.88–7.21; I^2=67% [CI: 21–86%]) among individuals with ketosis-prone type 2 diabetes (35). HbA_{1c} levels at admission did not differ statistically or clinically between the two groups, as indicated by our analysis (MD=−0.19%; CI: −1.54–1.16%; I^2=65% [CI: 17–86%]) (35). The corresponding forest plots are available in the supplementary material of the original article (35).

Sensitivity analyses are summarised in the supplementary material of the original publication (35). Although a few studies were identified as potentially influential, their exclusion did not meaningfully affect the pooled effect sizes (35).

8.1.4. Risk of Bias Assessment

Most studies included in the prevalence analyses were judged to have a high risk of bias, mainly due to tertiary-centre settings and small sample sizes. For the analyses of clinical characteristics, the overall risk of bias was low, except for family history of diabetes, where the risk was moderate because of inconsistent assessment methods across studies. Detailed risk-of-bias figures are available in the supplementary material of our original publication (35).

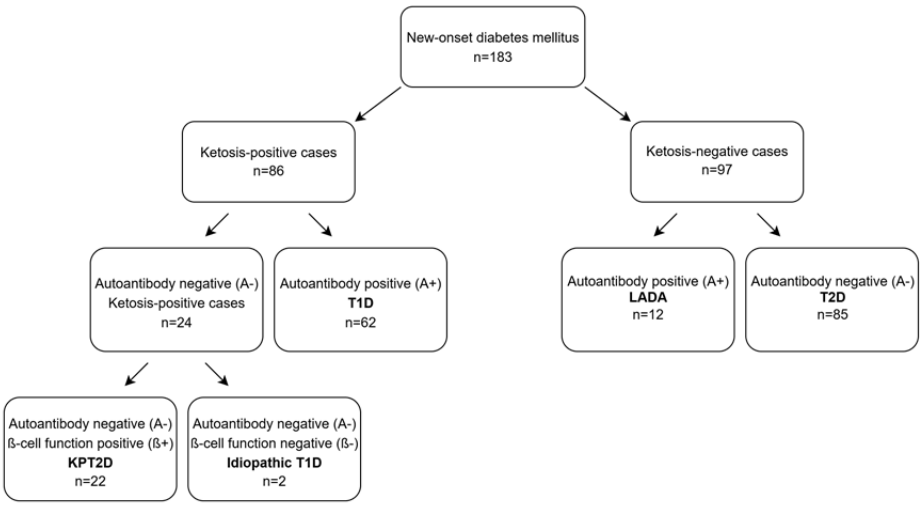
8.1.5. Quality of Evidence

The certainty of evidence was very low for all outcomes, reflecting the observational study design, substantial between-study heterogeneity, and the limited number of enrolled patients. The full GRADE assessment can be found in the supplementary material of our published article (35).

8.2. Study II: Ketosis-prone type 2 diabetes in a Hungarian cohort – Retrospective analysis with long-term follow-up

8.2.1. Study Population

We enrolled 183 patients with new-onset diabetes mellitus (**Figure 5**) (29), including 86 ketosis-positive and 97 ketosis-negative cases. Among the ketosis-positive patients, 62 fulfilled the diagnostic criteria for type 1 diabetes and 22 for ketosis-prone type 2 diabetes; 2 individuals with idiopathic type 1 diabetes were excluded. The ketosis-negative group comprised 85 patients with type 2 diabetes and 12 with LADA.



T1D: Type 1 diabetes; T2D: Type 2 diabetes; LADA: Latent autoimmune diabetes of adults; KPT2D: Ketosis-prone type 2 diabetes

Figure 5. Flowchart of diabetes classification (29)

8.2.2. Primary Outcomes

Demographic and anthropometric characteristics of the enrolled participants, along with admission laboratory parameters, are presented in **Table 4** (29).

Table 4. Baseline characteristics of the diabetes types

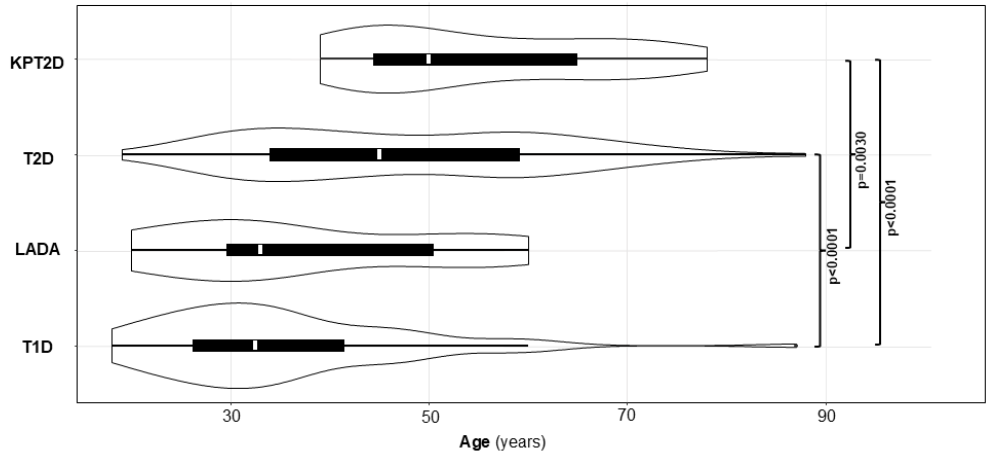
		T1D (n=62)	**T2D** (n=85)	**LADA** (n=12)	**KPT2D** (n=22)	**Overall** (n=181)	**p-value**
Female (%)		42	31	17	36	34	N/A
Age (years)	mean (SD)	34.8 (12.6)	47.4 (15.3)	37.2 (14.1)	54.9 (12.6)	43.3 (15.6)	N/A
	median (Q1, Q3)	32.5 (26.3, 41.3)	45.0 (34.0, 59.0)	33.0 (29.8, 50.3)	50.0 (44.5, 64.8)	41.0 (32.0, 56.0)	
	min, max	18.0, 87.0	19.0, 88.0	20.0, 60.0	39.0, 78.0	18.0, 88.0	
BMI (kg/m^2)	mean (SD)	22.5 (3.7)	29.2 (5.4)	25.4 (4.7)	31.5 (5.6)	26.8 (6.0)	<0.0001
	median (Q1, Q3)	22.5 (20.2, 24.7)	28.8 (26.0, 31.4)	24.3 (21.7, 30.1)	30.6 (28.6, 32.9)	26.2 (22.7, 30.2)	
	min, max	14.2, 33.7	17.9, 47.2	19.4, 31.8	23.1, 43.5	14.2, 47.2	
C-peptide (ng/mL)	mean (SD)	0.7 (0.6)	2.9 (1.4)	1.6 (1.2)	2.4 (1.0)	2.0 (1.5)	<0.0001
	median (Q1, Q3)	0.7 (0.3, 1.1)	2.7 (1.9, 3.8)	1.4 (0.7, 2.2)	2.5 (1.7, 3.0)	1.8 (0.8, 2.8)	
	min, max	0, 2.7	0.3, 7.2	0.2, 4.0	1.1, 5.1	0, 7.2	
HbA_{1c} (%) (mmol/mol)	mean (SD)	10.8 (3.2)	10.2 (2.7)	8.0 (2.6)	13.3 (3.1)	10.6 (3.2)	<0.0001
		95 (11)	88 (6)	64 (5)	122 (10)	92 (11)	
	median (Q1, Q3)	10.3 (8.2, 12.8)	10.3 (8.2, 11.9)	7.3 (5.8, 10.0)	12.5 (11.4, 14.3)	10.6 (8.2, 12.5)	
		89 (66, 116)	89 (66, 107)	56 (40, 86)	113 (101, 133)	92 (66, 113)	
	min, max	5.3, 20.0	5.4, 17.0	4.5, 12.5	6.5, 22.3	4.5, 22.3	
		34, 195	36, 162	26, 113	48, 220	26, 220	
Cholesterol (mmol/L)	mean (SD)	5.0 (1.3)	5.70 (4.4)	4.7 (0.8)	5.6 (1.7)	5.4 (3.1)	0.5931
	median (Q1, Q3)	4.7 (4.0, 5.7)	5.2 (4.3, 6.3)	4.6 (4.0, 5.5)	5.6 (4.2, 7.0)	5.0 (4.1, 6.1)	
	min, max	2.6, 8.3	2.6, 41.9	3.8, 6.1	2.7, 9.1	2.6, 41.9	
Triglyceride (mmol/L)	mean (SD)	1.8 (2.5)	3.2 (4.9)	1.4 (1.2)	3.9 (4.6)	2.7 (4.1)	0.5651
	median (Q1, Q3)	1.1 (0.7, 1.7)	1.7 (1.2, 3.3)	0.8 (0.6, 2.0)	1.7 (1.5, 4.3)	1.5 (0.9, 2.8)	
	min, max	0.3, 17.7	0.4, 32.1	0.5, 3.9	0.9, 19.0	0.3, 32.1	
HDL (mmol/L)	mean (SD)	1.4 (0.4)	1.2 (0.5)	1.4 (0.6)	1.2 (0.2)	1.3 (0.4)	0.6811
	median (Q1, Q3)	1.4 (1.2, 1.6)	1.1 (0.9, 1.4)	1.2 (1.1, 1.7)	1.1 (1.0, 1.3)	1.2 (1.0, 1.5)	
	min, max	0.7, 3.3	0.6, 3.0	0.6, 2.4	0.7, 1.6	0.6, 3.3	
Bilirubin (μmol/L)	mean (SD)	15.6 (10.6)	12.3 (5.7)	15.8 (5.5)	15.6 (6.9)	14.3 (8.1)	0.2190
	median (Q1, Q3)	12.0 (9.2, 17.3)	11.5 (8.3, 15.5)	17.0 (14.8, 18.0)	15.1 (9.7, 18.7)	12.0 (8.4, 17.0)	
	min, max	3.4, 46.6	3.8, 32.3	8.0, 21.0	7.5, 28.4	3.4, 46.6	
AST (U/L)	mean (SD)	19.6 (8.7)	27.2 (17.1)	22.7 (10.2)	34.4 (28.6)	25.3 (17.2)	0.0406
	median (Q1, Q3)	17.0 (15.0, 20.5)	21.5 (17.0, 30.3)	18.0 (17.0, 22.5)	26.0 (18.0, 39.0)	20.0 (16.0, 29.0)	
	min, max	11.0, 52.0	12.0, 108.0	17.0, 45.0	13.0, 147.0	11.0, 147.0	

		T1D (n=62)	T2D (n=85)	LADA (n=12)	KPT2D (n=22)	Overall (n=181)	p-value
ALP (U/L)	mean (SD)	113.0 (74.2)	95.1 (56.3)	107.0 (48.2)	104.0 (36.8)	103.0 (61.1)	0.2445
	median (Q1, Q3)	93.5 (65.3, 120.0)	82.0 (59.5, 108.0)	90.5 (73.3, 134.0)	92.5 (77.8, 127.0)	88.0 (64.5, 118.0)	
	min, max	37.0, 412.0	36.0, 304.0	62.0, 185.0	54.0, 205.0	36.0, 412.0	
GGT (U/L)	mean (SD)	22.2 (13.4)	49.3 (80.9)	38.7 (24.3)	72.3 (69.5)	42.6 (64.1)	0.6479
	median (Q1, Q3)	18.0 (13.0, 23.0)	30.0 (20.3, 50.8)	35.0 (21.5, 46.5)	50.0 (29.0, 62.5)	26.0 (17.0, 45.0)	
	min, max	5.0, 64.0	8.0, 657.0	15.0, 85.0	16.0, 267.0	5.0, 657.0	
Waist-to-hip ratio	mean (SD)	0.8 (0.1)	0.9 (0.1)	0.9 (0.0)	1.0 (0.1)	0.9 (0.1)	0.6253
	median (Q1, Q3)	0.8 (0.8, 0.9)	0.9 (0.9, 1.0)	0.9 (0.8, 1.0)	1.0 (0.9, 1.0)	0.9 (0.8, 1.0)	
	min, max	0.7, 1.2	0.7, 1.2	0.8, 1.0	0.8, 1.1	0.7, 1.2	
Hepatic steatosis index	mean (SD)	34.7 (4.7)	44.5 (7.9)	39.3 (6.8)	45.4 (6.2)	40.8 (8.1)	<0.0001
	median (Q1, Q3)	34.2 (31.9, 37.3)	43.8 (39.9, 49.4)	36.9 (35.9, 44.6)	45.5 (43.1, 49.0)	40.3 (34.3, 46.2)	
	min, max	25.0, 50.9	29.0, 67.7	28.9, 48.0	30.8, 58.5	25.0, 67.7	
Fibrosis-4 index	mean (SD)	0.7 (0.6)	0.9 (0.5)	0.9 (0.6)	1.2 (0.6)	0.9 (0.6)	0.5116
	median (Q1, Q3)	0.6 (0.4, 0.8)	0.7 (0.5, 1.2)	0.7 (0.4, 1.4)	1.2 (0.9, 1.4)	0.7 (0.5, 1.1)	
	min, max	0.2, 4.7	0.2, 3.4	0.4, 1.7	0.4, 2.8	0.2, 4.7	
HOMA2-IR	mean (SD)	1.2 (1.1)	4.5 (8.7)	2.2 (2.3)	3.6 (2.4)	3.4 (6.6)	0.5110
	median (Q1, Q3)	0.8 (0.6, 1.3)	2.8 (1.8, 4.8)	1.1 (0.8, 2.3)	3.4 (2.1, 6.5)	1.9 (0.9, 3.7)	
	min, max	0.4, 6.7	0.9, 71.4	0.5, 7.0	1.0, 9.5	0.4, 71.4	
HOMA2-B	mean (SD)	31.0 (29.2)	63.8 (49.0)	49.0 (41.3)	32.8 (29.8)	47.2 (42.8)	0.0001
	median (Q1, Q3)	17.5 (9.3, 47.6)	50.2 (24.1, 87.1)	33.6 (23.8, 63.8)	21.9 (15.8, 38.2)	33.0 (15.4, 68.6)	
	min, max	3.2, 131.0	6.2, 228.0	9.7, 126.0	6.8, 128.0	3.2, 228.0	

Data are presented as mean (standard deviation); median (first and third quartiles); and minimum, maximum for each group. Anova likelihood-ratio p-values from multivariable models adjusted for sex, age, and BMI.

T1D: Type 1 diabetes; T2D: Type 2 diabetes; LADA: Latent autoimmune diabetes of adults; KPT2D: Ketosis-prone type 2 diabetes; HOMA2-IR: Homeostatic model assessment 2 of insulin resistance; HOMA2-B: Homeostatic model assessment 2 of beta-cell function

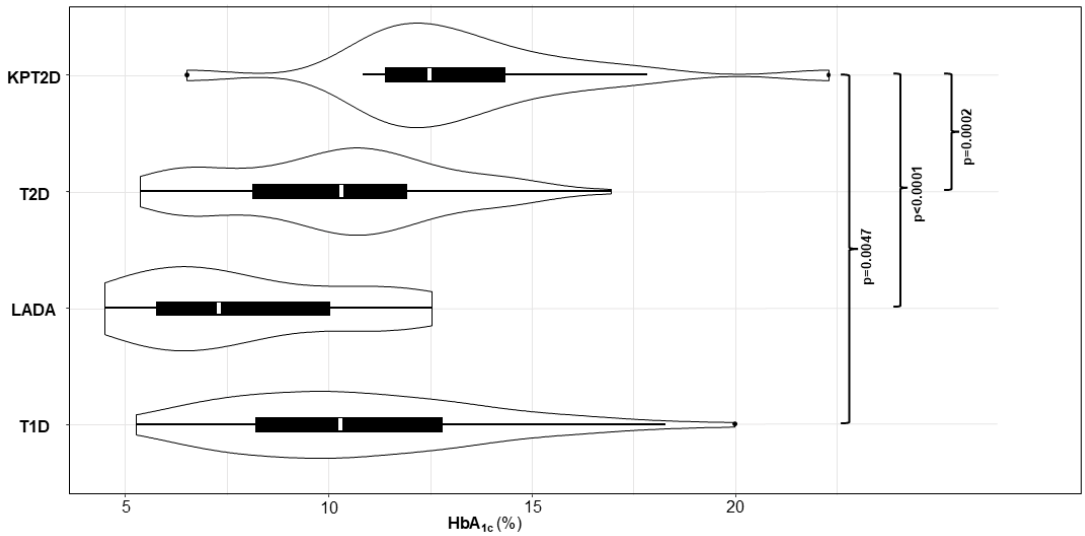
Patients with ketosis-prone type 2 diabetes were the oldest at disease onset (54.9±12.6 years), with significantly higher age compared with type 1 diabetes (34.8±12.6 years) and LADA (37.2±14.1 years; unadjusted p<0.0001 and p=0.0030, respectively) (29), whereas no significant difference was observed relative to non-ketotic type 2 diabetes (47.4±15.3 years; unadjusted p=0.1176) as shown in **Figure 6** (29).



T1D: Type 1 diabetes; T2D: Type 2 diabetes; LADA: Latent autoimmune diabetes of adults; KPT2D: Ketosis-prone type 2 diabetes. KPT2D: n=22; T2D: n=85; LADA: n=12; T1D: n=62.

Figure 6. Patients with ketosis-prone type 2 diabetes were older than those with autoimmune-mediated diabetes (29)

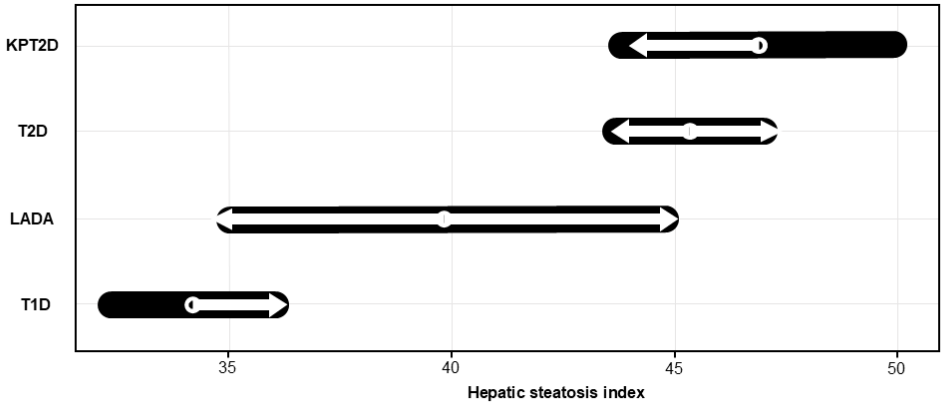
Patients with ketosis-prone type 2 diabetes showed markedly worse glycemic control (HbA_{1c}: 13.3±3.1%) than those with type 1 diabetes (10.8±3.2%; unadjusted p=0.0047), non-ketotic type 2 diabetes (10.2±2.7%; unadjusted p=0.0002), or LADA (8.0±2.6%; p<0.0001) as illustrated in **Figure 7** (29).



T1D: Type 1 diabetes; T2D: Type 2 diabetes; LADA: Latent autoimmune diabetes of adults; KPT2D: Ketosis-prone type 2 diabetes. KPT2D: n=22; T2D: n=85; LADA: n=12; T1D: n=62.

Figure 7. HbA_{1c} at diagnosis was higher in ketosis-prone type 2 diabetes than in other diabetes types (29)

After adjustment for age and sex, hepatic steatosis index (HSI) was substantially higher in individuals with ketosis-prone type 2 diabetes (46.86 [43.78–49.93]) than in those with type 1 diabetes (34.21 [32.38–36.04]; p<0.0001; **Figure 8**) (29). A comparable pattern was observed for BMI, which was significantly elevated in the ketosis-prone group (32.09 [29.86–34.33] kg/m²) relative to both type 1 diabetes (22.18 [20.89–23.46] kg/m²; p<0.0001) and LADA (25.22 [22.30–28.13] kg/m²; p=0.0017) (29).



T1D: Type 1 diabetes; T2D: Type 2 diabetes; LADA: Latent autoimmune diabetes of adults; KPT2D: Ketosis-prone type 2 diabetes

Figure 8. Hepatic steatosis index was higher in ketosis-prone type 2 diabetes compared to type 1 diabetes (29)

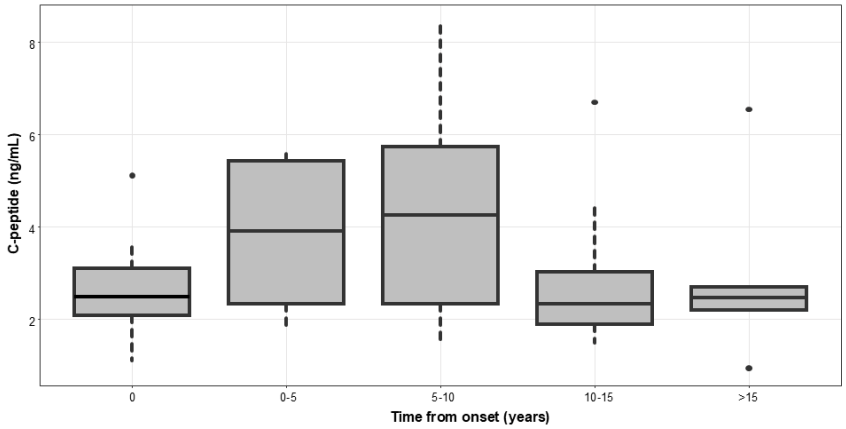
The proportion of genotypes associated with middle or high risk for type 1 diabetes exceeded 70% in patients with type 1 diabetes, compared with approximately 13% in those with ketosis-prone type 2 diabetes (**Table 5**) (29).

Table 5. HLA genotypes indicating low type 1 diabetes risk in ketosis-prone type 2 diabetes (29)

	KPT2D (n=15)	**T1D** (n=545)
Protective	4 (26.6 %)	27 (5.0 %)
Neutral	9 (60.0 %)	134 (24.6 %)
Middle risk	2 (13.3 %)	230 (42.2 %)
High risk	0 (0 %)	154 (28.3 %)

KPT2D: Ketosis-prone type 2 diabetes; T1D: Type 1 diabetes

As shown in **Figure 9** (29), fasting C-peptide levels remained within reference range throughout follow-up, with mean±SD values of 3.82±1.63 ng/mL (0–5 years, n=8), 4.37±2.45 ng/mL (5–10 years, n=10), 2.85±1.54 ng/mL (10–15 years, n=12), and 2.96±2.11 ng/mL (>15 years, n=5) (29).



At "0" time point (=disease onset) n=14; 0-5 years n=8; 5-10 years n=10; 10-15 years n=12; >15 years n=5

Figure 9. Fasting C-peptide remained in reference range on long-term follow-up in ketosis-prone type 2 diabetes (29)

8.2.3. Secondary Outcomes

The distribution of the TCF7L2 rs7903146 polymorphism was comparable between ketosis-prone and non-ketotic type 2 diabetes, and these findings should be interpreted as exploratory (**Table 6**) (29).

Table 6. TCF7L2 rs7903146 allele frequency was similar in ketosis-prone and non-ketotic type 2 diabetes (29)

	Genotype (n, %)			**Allele frequency** (2n, %)	
	CC	**CT**	**TT**	**C**	**T**
KPT2D (n=15)	7 (46.67 %)	7 (46.67 %)	1 (6.66 %)	21 (70.00 %)	9 (30.00 %)
T2D (n=1297)	585 (45.11 %)	582 (44.87 %)	130 (10.02 %)	1752 (67.54 %)	842 (32.46 %)

KPT2D: Ketosis-prone type 2 diabetes; T2D: Type 2 diabetes

During long-term follow-up (range: 5–21 years), patients with ketosis-prone type 2 diabetes generally maintained adequate endogenous insulin secretion, although treatment

regimens varied, with 13 individuals using insulin and 7 managed with oral glucose-lowering agents (**Table 7**) (29).

Table 7. Long-term follow-up of patients with ketosis-prone type 2 diabetes (29)

Patient	**C-peptide at onset** (ng/mL)	**C-peptide at follow-up** (ng/mL)	**Follow-up time** (yrs)	**Treatment at follow-up**[a]
1	1,09	1,09	21	2
2	2,07	1,63	19	0
3	1,32	N/A	9	2
4	2,8	1,89	19	1
5	1,65	N/A	18	2
6	3,62	2,69	19	0
7	2,08	1,83	12	2
8	1,59	5,81	16	0
9	3,21	7,35	19	2
10	2,99	N/A	5	2
11	1,33	2,57	19	2
12	2,84	N/A	N/A	N/A
13	1,8	N/A	6	0
14	1,12	N/A	12	2
15	3,2	5,53	6	0
16	2,14	4,97	16	0
17	3,16	N/A	14	2
18	2,32	1,85	18	2
19	2,91	N/A	N/A	N/A
20	2,63	2,9	13	1
21	2,72	2,25	16	0
22	5,1	2,07	13	1

[a]Treatment: 0: Diet ± glucose-lowering oral medication; 1: Basal supported oral therapy ± Glucagon-like peptide 1 receptor agonist; 2: Multiple daily insulin injections

8.2.4. Sensitivity Analysis

Given the limited sample size – most notably within the LADA subgroup – the stability of frequentist multivariable regression estimates and between-group comparisons could not be fully ensured. Therefore, Bayesian counterparts of these models were fitted as a sensitivity analysis. As the Bayesian results were highly concordant with the frequentist estimates, they are presented separately in the supplementary material of the original publication (29).

9. DISCUSSION

9.1. Summary of Findings, International Comparisons

Recent developments underscore that diabetes is not a collection of discrete categories but a heterogeneous continuum with considerable variation in clinical presentation, pathophysiology, and immunogenetic background (4,9,46). Emerging classification frameworks – such as the WHO's hybrid forms and data-driven clustering – reflect this complexity and highlight the need for more precise subclassification, a necessity exemplified by ketosis-prone type 2 diabetes as a clinically meaningful subgroup (1,5).

Our systematic review and meta-analysis showed that approximately one-third of adult patients manifesting with diabetic ketoacidosis or ketosis at diabetes onset had ketosis-prone type 2 diabetes rather than type 1 diabetes, based primarily on evidence from non-Caucasian populations (35). It was also demonstrated that individuals with ketosis-prone type 2 diabetes were, on average, 11.5 years older and had a BMI higher by 5.48 kg/m² than those with type 1 diabetes (35).

In our Hungarian cohort, one in four adults with diabetic ketoacidosis or ketosis at diabetes onset fulfilled the diagnostic criteria for ketosis-prone type 2 diabetes (29). These patients were older, had higher BMI and HbA_{1c} levels, and showed more advanced metabolic-associated fatty liver disease than those with classical type 1 diabetes presenting with ketosis at onset. These findings remained consistent after adjustment for age and sex (29). The frequency of HLA DQ/DR susceptibility alleles for type 1 diabetes was low in the ketosis-prone type 2 diabetes group. During long-term follow-up, endogenous insulin secretion remained preserved, although therapeutic management varied and included multiple daily insulin injections in several cases despite adequate beta-cell function (29).

A synthesis of previously published cohort studies with similar designs – but conducted in ethnically heterogeneous populations – indicates that patients with ketosis-prone type 2 diabetes are typically diagnosed in mid-adulthood, frequently present with moderate to severe obesity, and exhibit pronounced hyperglycemia at onset, findings that are concordant with the phenotype observed in our cohort (29,36–39,41–45,47). Early follow-up data from these studies consistently demonstrate preserved endogenous insulin secretion, and our long-term results extend this evidence by showing sustained C-peptide

levels over several decades despite considerable variability in therapeutic regimens (29,37,39,45). The continued use of intensive insulin therapy in individuals with preserved beta-cell function likely reflects earlier post-ketosis treatment practices or factors such as clinician preference, patient adherence, glycemic variability, and comorbidities, thereby underscoring the need for more individualised management strategies. Further details of these cohort studies are summarised in a table provided in the supplementary material of the original publication (29).

Ketosis-prone type 2 diabetes was acknowledged as a distinct entity in the 2019 WHO diabetes classification (1). In contrast, the ADA classification system – most commonly used in clinical practice – does not explicitly incorporate this subtype (2). This gap may lead to the misclassification of ketosis-prone type 2 diabetes as idiopathic type 1 diabetes, a form typically observed in lean patients of African or Asian ancestry with autoantibody negativity and markedly impaired beta-cell function (48–50). The pathophysiology of ketosis-prone type 2 diabetes remains incompletely understood. Current models suggest that threshold-dependent glucotoxicity may trigger transient beta-cell dedifferentiation that reverses with glycemic control, while lipotoxicity appears less central (51,52). Metabolomic data further indicate a distinct metabolic profile marked by impaired ketone oxidation, altered branched-chain amino acid metabolism and disrupted fatty-acid utilisation, with hyperglycemia-induced reductions in arginine availability contributing to blunted insulin secretion (53,54). Furthermore, the continued inadequacy of glucagon suppression indicates ongoing beta-cell dysfunction and impaired intraislet signalling that persists well beyond the acute hyperglycemic crisis (55,56).

Although the diagnosis of diabetes mellitus is established based on elevated blood glucose levels, accurate classification at disease onset is essential, as it determines long-term therapeutic management. Older age and higher BMI may assist clinicians in distinguishing ketosis-prone type 2 diabetes from type 1 diabetes, a differentiation of considerable importance given its major therapeutic implications. Accordingly, we propose that all adult patients showing diabetic ketoacidosis or ketosis at diabetes onset should undergo classification using diabetes-related autoimmune markers together with an assessment of endogenous beta-cell function (C-peptide).

9.2. Strengths

Our meta-analysis is the first to provide a quantitative estimate of the proportion of ketosis-prone type 2 diabetes among patients presenting with diabetic ketoacidosis or ketosis at diabetes onset, and to characterise this entity in comparison with type 1 diabetes (35). We used a rigorous methodological approach aligned with the Cochrane Collaboration's guidance and the PRISMA 2020 Statement (19,20). Given the limited availability of data on the prevalence of ketosis-prone type 2 diabetes in individuals of Caucasian ancestry (12,13), our cohort study offers a uniquely large number of affected patients from this population (29). Additionally, we contribute novel insights into the genetic background and long-term beta-cell function of ketosis-prone type 2 diabetes (29). Overall, we also advocate for a classification approach in which every newly diagnosed adult presenting with diabetic ketoacidosis or ketosis at diabetes onset is evaluated using autoantibody testing and assessment of beta-cell function, supported by the clinical parameters we identified, thereby enhancing clinicians' awareness and diagnostic precision.

9.3. Limitations

However, several important limitations should be acknowledged. First, the literature uses multiple definitions for ketosis-prone type 2 diabetes; although we applied an extended search strategy in our meta-analysis and carefully reviewed the classification methods of each study, some heterogeneity may still be present (35). Second, most included studies originated from university-affiliated tertiary centres, which could limit the generalisability of the estimated prevalence to the broader population (35). Third, the predominance of retrospective observational designs and the relatively small sample sizes warrant cautious interpretation of the results (35). Furthermore, our cohort data originate from a single national referral centre, a setting that is likely to introduce selection bias – potentially overestimating the proportion of ketosis-prone type 2 (29). The limited sample size of certain subgroups, particularly LADA and ketosis-prone type 2 diabetes, may reduce the overall statistical robustness of our analyses; therefore, these findings should be considered exploratory (29). The retrospective nature of data collection also raises the possibility of information bias, and follow-up data were incomplete and highly variable in duration, restricting the interpretability of long-term outcomes (29).

10. CONCLUSIONS

Our findings demonstrate that ketosis-prone type 2 diabetes represents a substantial proportion of adults manifesting with diabetic ketoacidosis or ketosis at diabetes onset, accounting for approximately one third of cases in the reviewed literature and one quarter in our Hungarian cohort (29,35). Individuals with this diabetes subtype typically present in their third to fourth decade of life and are generally overweight or obese, with higher BMI and – based on our cohort study – elevated HbA_{1c} values compared with those with type 1 diabetes (29,35). These clinical features, together with preserved or recoverable beta-cell function during follow-up, should heighten clinical suspicion for ketosis-prone type 2 diabetes in adults presenting with diabetic ketoacidosis or ketosis at diabetes diagnosis. To improve diagnostic accuracy, we recommend an integrative classification approach for all cases showing diabetic ketoacidosis or ketosis at diabetes onset, regardless of ethnicity, incorporating both islet autoantibody testing and C-peptide measurement to distinguish between type 1 diabetes and ketosis-prone type 2 diabetes and to guide appropriate, individualised long-term management.

11. IMPLICATIONS FOR PRACTICE

Our findings have several practical implications for the clinical management of adults with diabetic ketoacidosis or ketosis at diabetes onset. First, clinicians should be aware that a considerable proportion of such cases fulfil the criteria for ketosis-prone type 2 diabetes even among Caucasians, particularly in individuals in their third to fourth decade of life who are overweight or obese (35). Recognition of this phenotype, based on the absence of diabetes-related autoantibodies and preserved endogenous insulin secretion, is crucial, as its long-term treatment strategy differs from that of autoimmune diabetes. Despite preserved beta-cell function, many patients in our cohort remained on long-term insulin therapy (29). This persistent insulin use likely reflects historical post-ketosis treatment practices, as well as clinician or patient preferences. More tailored management can be enabled through regular reassessment of beta-cell function, diagnostic use of continuous glucose monitoring (CGM) to evaluate glycemic stability, and structured patient education to support safe de-escalation of insulin when appropriate. Modern glucose-lowering therapies may also offer benefit in this population. GLP-1 receptor agonists and dual GLP-1/GIP (glucose-dependent insulinotropic polypeptide) receptor agonists represent promising options for improving glycemic control and supporting weight management in overweight or obese individuals with ketosis-prone type 2 diabetes. Overall, increased clinical awareness, structured diagnostic evaluation, and modern, individualised therapeutic approaches may substantially improve the long-term management of ketosis-prone type 2 diabetes.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and Study Design

Future research should aim to confirm the prevalence of ketosis-prone type 2 diabetes through large, multicentre, population-based studies. More detailed clinical characterisation, as well as a clearer understanding of long-term metabolic status and beta-cell function, requires prospective cohort studies with standardised follow-up. The timing and safety of insulin withdrawal, together with the factors associated with remission and relapse, should be evaluated in adequately powered randomised controlled trials. The effectiveness of incretin-based therapies in improving glycemic stability and supporting weight management should be examined in both prospective cohorts and interventional trials. Finally, it is important to emphasize that comprehensive genetic investigations and focused pathophysiological studies are needed to clarify the biological processes underlying this diabetes subtype.

12.2. New Areas

Future research should focus on better understanding patient-related and behavioural factors influencing remission, insulin withdrawal, and long-term adherence, as these determinants remain insufficiently characterised. Advances in digital technologies and precision phenotyping may help identify metabolic profiles that more accurately stratify risk and predict clinical trajectories. Moreover, investigating ketosis-prone type 2 diabetes as a model of reversible beta-cell dysfunction could provide broader insights into mechanisms of dedifferentiation, metabolic stress, and recovery. Further important directions include exploring how circadian disruption, chronic stress, and gut microbiome interactions modulate metabolic transitions, as well as mapping long-term cardiometabolic and immunometabolic patterns that may shape susceptibility to ketosis and the potential for sustained remission.

13. IMPLICATIONS FOR POLICY MAKERS

To improve the recognition and management of ketosis-prone type 2 diabetes, policy makers should support the development of internationally standardised diagnostic criteria, including a consistent autoimmune antibody panel and a uniform C-peptide assessment protocol. Clear, evidence-based guidelines for structured follow-up and long-term management are also needed to harmonise clinical practice, guide decisions regarding insulin withdrawal, and reduce variability in care. Importantly, accurate diagnosis enabling timely de-escalation from multiple daily insulin injections, when appropriate, may substantially reduce disease burden for patients and lessen demands on health care systems, particularly with respect to diabetes education and long-term management. Establishing these standards would enhance diagnostic accuracy and promote more consistent, effective patient care across health systems.

14. FUTURE PERSPECTIVES

Ketosis-prone type 2 diabetes offers an opportunity to better understand patterns of beta-cell dysfunction and recovery, insights that may also inform care across other diabetes types. As evidence accumulates, its place within modern diabetes classification is likely to become clearer, leading to more consistent diagnostic criteria and well-defined clinical pathways. Advances in diagnostic tools, monitoring approaches, and patient-centred care may further support earlier recognition and more individualised management. Ultimately, translating scientific knowledge into meaningful community benefits is essential (57,58), and incorporating emerging findings into international guidelines may help ensure accurate diagnosis and effective long-term care.

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Kovács Adrienn, Teutsch Brigitta, Veres Dániel S., Pánczél Pál, Lukács Krisztina, Sipter Emese, Hegyi Péter, Hosszúfalusi Nóra

Ketosis-prone type 2 diabetes in Caucasian adults: a follow-up cohort analysis

DIABETES AND METABOLIC SYNDROME: CLINICAL RESEARCH AND REVIEWS

20: 1 Paper: 103360, 9 p. (2026)

Article (Journal Article) | Scientific [36597141]

Scopus - Medicine (miscellaneous) **SJR indikátor: Q1**

Scopus - Endocrinology, Diabetes and Metabolism SJR indikátor: Q2

Scopus - Internal Medicine SJR indikátor: Q2

IF (2024): 3,4

Kovács Adrienn, Bunduc Stefania, Veres Dániel S., Pálinkás Dániel, Gagyi Endre B., Hegyi Péter J., Erőss Bálint, Mihály Emese, Hegyi Péter, Hosszúfalusi Nóra

One third of cases of new-onset diabetic ketosis in adults are associated with ketosis-prone type 2 diabetes-A systematic review and meta-analysis

DIABETES-METABOLISM RESEARCH AND REVIEWS

40: 3 Paper: e3743, 10 p. (2024)

Survey paper (Journal Article) | Scientific [34227657]

Scopus - Endocrinology **SJR indikátor: Q1**

Scopus - Endocrinology, Diabetes and Metabolism SJR indikátor: Q1

Scopus - Internal Medicine SJR indikátor: Q1

IF (2024): 6,0

16.2. Publications not Related to the Thesis

Zahariev Olga Júlia, Bunduc Stefania, **Kovács Adrienn**, Demeter Dóra, Havelda Luca, Budai Bettina Csilla, Veres Dániel Sándor, Hosszúfalusi Nóra, Erőss Bálint Mihály, Teutsch Brigitta, Juhász Félix Márk, Hegyi Péter

Risk factors for diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis

FRONTIERS IN MEDICINE

10 Paper: 1257222, 18 p. (2024)

Survey paper (Journal Article) | Scientific [34536097]

Scopus - Medicine (miscellaneous) SJR indikátor: Q1

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