RESEARCH ARTICLE

Young adult patients with type 1 diabetes have a higher risk of mortality than those of similar age with type 2 diabetes: A nationwide analysis in Hungary

Zoltán Kiss1 | György Rokszin2 | Zsolt Abonyi-Tóth2,3 | György Jermendy4 | Péter Kempler5 | László Barkai6,7 | István Wittmann1

Abstract

BACKGROUND: There are few papers comparing complications of type 1 diabetes with those of a similarly young age with type 2 diabetes. The aim of our nationwide study was to compare the risks of mortality and morbidities between the two types of diabetes (age ≤ 40).

METHODS: We identified all young adult patients with type 1 diabetes who were recorded in the database of the Hungarian National Health Insurance Fund between 2001 and 2014 (n = 11 863) and compared them with a population of similar age with young adult type 2 diabetes (n = 47 931). The incidence of all-cause mortality, myocardial infarction, stroke, any type of cancer, diabetic ketoacidosis, and hypoglycemia was followed from the onset of diabetes to the date of death or end of study period.

RESULTS: The risks of all-cause mortality were significantly higher in patients with type 1 compared with patients with type 2 diabetes (hazard ratio, 95%CI: 2.17, 1.95-2.41; P < .0001). The risks of myocardial infarction (0.90, 0.71-1.13; P = 0.36) and stroke (1.06, 0.87-1.29; P = .582) were not significantly different in type 1 compared with type 2. In contrast, the risk of cancer (1.35, 1.15-1.59; P = .0003), dialysis (2.20, 1.76-2.75; P < .0001), hypoglycemia (7.70, 6.45-9.18; P < .0001), and ketoacidosis (22.12, 19.60-25.00; P < .0001) was higher among patients with type 1 compared with those with type 2 diabetes.

CONCLUSIONS: A comparatively higher incidence of diabetic ketoacidosis and hypoglycemia and higher risk of cancer and dialysis in patients with type 1 diabetes than in those with type 2 may play a role in the higher risk of mortality.

KEYWORDS
all-cause mortality, cardiovascular morbidity, diabetic ketoacidosis, hypoglycemia, type 1 diabetes, type 2 diabetes

Correspondence
Prof. Dr István Wittmann, 2nd Department of Medicine and Nephrological Center, Faculty of Medicine, University of Pécs, Pécs, Hungary

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INTRODUCTION

The two most common forms of diabetes mellitus are type 1 and type 2. Each has an effect on diabetic complications, but the degree of the effect may differ from the standpoint of cardiovascular and renal complications and with regard to cancer, hypoglycemia, and diabetic ketoacidosis.

1.1 Type 1 diabetes

Several observational studies showed substantially increased mortality and diabetes-related comorbidity in patients with type 1 diabetes.1 Data collected from the Swedish registry showed a 3.52 adjusted hazard ratio in patient with type 1 diabetes for death from any causes compared with that in the control population.2 Despite substantial improvement in diabetes care, a Danish analysis still demonstrated higher rates of mortality among patients with type 1 diabetes with lowest age at onset, and in men.3

Lung et al conducted a meta-analysis studying the risk of all-cause mortality in patients with type 1 diabetes and reported a 3.82 relative risk compared with the general population. However, they showed a significant improvement, because relative risk of mortality decreased from 5.8 in 1971 to 3.11 after 1990.4 Another analysis of the Swedish National Register presented a roughly 40% decrease in the mortality of patients with type 1 diabetes and in the incidence of cardiovascular morbidities.5 In Finland, the survival of patients with type 1 diabetes also improved, but in Estonia and Lithuania a significantly higher diabetic ketoacidosis-related mortality risk was found compared with that of Finland in the same study.6

1.2 Type 2 diabetes

While the prevalence of type 2 diabetes is higher among the elderly population, there is an increasing incidence and prevalence among younger people resulting in higher long-term cardiovascular morbidity as a consequence of the long exposure to hypoglycemia.7 Earlier diagnosis and manifestation of renal complications in type 2 diabetes were found in a Canadian clinical record-based study, but no difference in retinopathy was detected. In this study, macrovascular comorbidities were rare, while microvascular complications, eg, dialysis manifested within 10 years from the diagnosis of diabetes.8

In an Australian population, long-term morbidity and mortality risk was also the highest in patients with type 2 diabetes starting at younger age (15-31 years) compared with those with usual onset (40-50 years, HR 3.4).9

1.3 Comparison of type 1 and type 2 diabetes

Several studies compared morbidity and mortality of type 1 and type 2 diabetes in young cohorts.10,11 For type 1 compared with type 2 diabetes, lower risks of death from any cause and of cardiovascular morbidity were characteristic.5,10 Despite the presence of more severe comorbidities in young patients with type 2 diabetes, long-term survival was similar in both types of diabetes.12 Constantino demonstrated a mortality excess in patients with type 2 diabetes compared with type 1 (11% vs 6.8%, P = .03) and an elevated hazard risk for death from any causes (HR 2.0, P = .003). Cardiovascular mortality was also more frequent in the population of type 2 diabetes (HR 3.5, P = .004).13 Similarly, three-fold higher mortality rate was found in a 15 to 34 age group of patients with type 2 diabetes in a large, prospective, cohort-based, Swedish study.14 Dart found a significantly higher 10-year survival rate in patients with type 1 diabetes (aged 1-18 years) compared with patients with type 2 (99.5% and 91.4%), which further decreased to 97.6% and to 77.5% after 20 years.15

Dart also found a higher risk of end-stage renal failure in young patients with type 2 diabetes when compared with the risk of patients with type 1 diabetes (aged 1-18 years).15 This finding has been confirmed between the two types of diabetes in Chinese and Japanese studies.16,17

The prevalence of diabetic ketoacidosis was high in young patients with type 1 diabetes and was reported to be constant between 2002 and 2010 (2002-2003: 30.2%, 2004-2005: 29.1%, and 2008-2010: 31.1%; P for trend = 0.42), while in young patients with type 2 diabetes, the frequency was lower with decreasing incidence (11.7% in 2002-2003 to 5.7% in 2008-2010 [P for trend = 0.005]).18 Another report across three registries and five nations also presented a high (5.0% to 7.1%) frequency of diabetic ketoacidosis in young patients with type 1 diabetes.19 Barski evaluated the mortality risk of diabetes ketoacidosis in both types of diabetes and found that in type 2 diabetes it is more severe, with worse, outcomes compared with type 1 diabetes.20

The incidence of cancer in diabetes is increased among type 2 diabetic patients compared with that of the nondiabetic population and is well reported in case of type 2 diabetes.21 On the other hand, only a limited amount of data is available on cancer-related morbidity and the mortality of patients with type 1 diabetes.22,23

The aim of our nationwide analysis was to compare the mortality and morbidity risks of young patients with type 1 and type 2 diabetes, using data of the Hungarian National Health Insurance Fund.

METHODS

2.1 Study design

In our retrospective cohort study, patients aged 40 years or under and starting antidiabetic therapy (ATC A10) between 1 January 2001 and 31 October 2014 were extracted from the database of the National Health Insurance Fund as anonymized, aggregated patient data. We used data from this time frame of all listed Hungarian patients with type 1 diabetes. We compared two similarly young adult, but not matched populations, and the ratio of type 1 to type 2 was more than 1:4.
Codes of the version 10th of International Classification of Diseases (ICD) were used to define diabetes and comorbidities. The data source includes information of mortality from any causes, incidence of myocardial infarct (ICD-10 I21-24), ischemic and hemorrhagic stroke (ICD-10 I61-63, G4630, G4640), dialysis, cancer (ICD-10 C and D class), diabetes ketoacidosis (ICD-10 E1010, E1110, and E1410), and hypoglycemia (ICD-10 E1600, E1610, and E1620). As dialysis reimbursement is quite expensive, it is recorded in a separate database of Hungarian NHIF, where all dialysis is followed as an intervention based on patient ID, without using ICD codes. We investigated all dialysis intervention in this separate database.

We defined type 1 diabetes (T1DM) (a) as being when a patient was recorded as having an E10 ICD code, (b) the age of the patient was less than 40 years at the time of diagnosis, and (c) had no oral medication prescriptions during the first 6 months. Patients having antidiabetic treatment (ATC A10) but not matching previously detailed criteria were taken as having type 2 diabetes (T2DM). A detailed specification of type 1 and type 2 diabetes has been described in an earlier publication. Patients with polycystic ovary syndrome (ICD 10 E282) were excluded from our analysis.

The onset of diabetes was defined either as the first occurrences of the diabetes-related ICD code in the database for a patient or the first insulin/noninsulin diabetic treatment. We searched for previous stroke and myocardial infarction events as well. We only used events (myocardial infarction, stroke, dialysis, cancer, diabetes ketoacidosis, and hypoglycemia) from the in-hospital records and only those that occurred after the diagnosis of diabetes. Dates of death were also retrieved from the National Health Insurance Fund. However, because this database does not differentiate causes of death, we used only all-cause mortality for analysis.

All-cause mortality, as well as morbidities of patients with type 1 and type 2 diabetes, were compared.

This study was approved by the Pécs University School of Medicine’s Regional Ethics Committee of the Medical Center, Hungary (study licence number: 6962/2017) and ran without commercial sponsorship. The study protocol was also reviewed and confirmed by the National Health Insurance Fund (NHIF) (identification number: SO4/161/2016).

### 3 | STATISTICAL ANALYSIS

Survival analyses were implemented by Cox regression where diabetes type was the explanatory variable and the model was adjusted for baseline differences in gender and age. For the visualization of results, Kaplan-Meier curves were used. Data were stratified by sex, and results were adjusted to take into account the differences in proportion of males in the two groups. Mean of age and follow-up time were compared using Welch’s two-sample test. Follow-up period was counted from diabetes onset. Proportion prior to stroke and myocardial infarction was compared using the chi square test. All analyses were performed with the use of R Software, version 3.4.2 (2017-09-28), applying survival, survminer, and multcomp packages.24

### 4 | RESULTS

Baseline characteristics of the groups of patients are presented in Table 1. Among patients with type 1 diabetes, 35.4% were female, the mean age was 21.63 years (95%CI 21.42-21.85), and no prior cardiovascular event was recorded. We included 47 931, unmatched young adult patients of similar age with type 2 diabetes.

Based on the examined 2001 to 2014 period, patients with type 1 diabetes had a higher risk for all-cause mortality than those patients with type 2 diabetes (Figure 1, panel A) resulted in a 2.17 hazard ratio after adjustment (1.95-2.41; P < .0001) (Figure 2). Ten-year survival was 93.84% in T1DM and 95.23% in T2DM, which ended in a difference of 1.65% at the end of the 167 months of follow-up (90.61% vs 92.26%).

On the contrary, the risks for myocardial infarction, stroke, and cancer were higher in the patients with type 2 diabetes (Figure 1, panels B-D) showing (T1DM vs T2DM) a 99.08% vs 98.00% (MI), 98.64% vs 97.31% (stroke), and 97.90% vs 97.07% (cancer) 10-year event-free-survival accordingly. However, after age and sex adjustment of risks, we could not find significant difference between the two types of diabetes in case of myocardial infarction (0.90, 0.71-1.13; P = .3600) and stroke (1.06, 0.86-1.29; P = .5820), while adjusted hazard risk of cancer was higher in type 1 diabetes (1.35, 1.15-1.59; P = .0003). In parallel with the mortality, the risks for diabetic ketoacidosis, hypoglycemia and dialysis were higher in patients with type 1, compared with those patients with type 2 diabetes (Figure 1, panels E-G). Ten-year event-free-survival was (T1DM vs T2DM) 71.99% vs 99.08% for diabetic ketoacidosis, 91.89% versus 99.33% for hypoglycemia, and 98.62% versus 99.02% in case of dialysis; adjusted hazard ratios were 22.12, 7.70, and 2.20, respectively (Figure 2).

### Table 1 . Baseline characteristics of patients with type 1 and type 2 diabetes

|                         | T1DM | T2DM | P Value |
|-------------------------|------|------|---------|
| Number of population    | 11 863 | 47 931 |         |
| Woman (%)               | 4200 (35.4) | 23 528 (49.1) | <0.0001 |
| Mean age at diabetes onset (95% CI) (year) | 21.63 (21.42-21.85) | 33.47 (33.41-33.53) | <0.0001 |
| Mean follow-up from diabetes onset (95% CI) (year) | 6.52 (6.45-6.59) | 6.56 (6.62-6.69) | =0.0008 |
| Prior myocardial infarction (%) | 0 | 72 (0.2) | <0.0001 |
| Prior stroke (%)        | 0 | 74 (0.2) | <0.0001 |
FIGURE 1. Kaplan-Meier presentation of overall survival (panel A), myocardial infarction (panel B), stroke (panel C), cancer (panel D), diabetic ketoacidosis (panel E), hypoglycemia (panel F), and dialysis free survival (panel G) for patients with type 1 (T1DM) and type 2 diabetes (T2DM).

FIGURE 2. Events and hazard ratios of risks of mortality and morbidities.
In our long-term, retrospective, nationwide study, we assessed the differences in risk for mortality and morbidity, comparing adult patients with young age (below 40 years) and follow-up with type 1 and 2 diabetes.

In our analysis, the following main findings were assessed: (a) a higher risk was found for mortality in patients with diabetes type 1 compared with type 2; (b) no difference in risks were detected for cardiovascular diseases, while increased risks were verified for cancer, diabetic ketoacidosis, hypoglycemia, and dialysis in type 1 diabetes.

A study comparing patients with type 1 and type 2 diabetes reported a better and improving mortality risk in the type 1 group, which is opposite to our findings. In the Constantino report, an increased hazard ratio for death was proved in the case of young patients with type 2 diabetes (HR (95%CI), 2.0 (1.2-3.2)) compared with those patients with type 1, which was confirmed by a Swedish study, and in the analysis by Dart et al. On the contrary, in our study, a higher risk was found for all-cause mortality in patients with type 1 diabetes compared with those patients with type 2. These differences could be explained as a consequence of the divergent populations.

However, an unexpectedly higher mortality in the T1DM group was found despite the younger (12 years) mean age of this population. These outstanding results could be explained as follows. In the cardiovascular outcomes, we did not find difference between the two diabetic groups, but other main causes of diabetic mortality, eg, ketoacidosis and hypoglycemia, together with renal impairment and cancer may impact the higher mortality of T1DM. Indeed, our findings in size of mortality are similar to Estonian and Lithuanian results, which detected a higher mortality in patients with type 1 diabetes.6

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In another, comprehensive, population-based cohort study of Karges, where T1DM patients using insulin treatment (n = 9,814) were paired with those, using insulin pump therapy (n = 9,814), the incidence of DKA episodes (3.64 vs 4.26 per 100 patient-years) and hypoglycemic events (9.55 vs 13.97 per 100 patient-years) were lower at patients with insulin pump therapy. These findings showed evidence for improved clinical results associated with insulin pump therapy, which may improve the outcome of Hungarian T1DM patients as well.

Nevertheless, a recently published comprehensive research from Rawshani et al investigated age-related cardiovascular comorbidities and mortality of Swedish T1DM population between 1998 and 2012. They found that age at diabetes onset is an important prognostic factor of survival, as well as all cardiovascular events. For all-cause mortality, HR was 4.11 (3.24-5.22) at 0 to 10-year cohort, while only 2.83 (2.38-3.37) for group aged 26 to 30 years. Similar excess of risk for younger diabetes onset vs older was found at different cardiovascular events, HR for coronary heart disease, and stroke, 30.50 vs 6.08 and 6.45 vs 3.20. Excess risk in women was higher, most outstanding in case of myocardial infarction at age 0 to 10 cohort with HR 92.07, while this risk at male was only 15.11. This finding may partially also explain higher mortality at T1DM group in our result as this population had earlier onset of diabetes than T2DM group.

In spite of the Kaplan-Meier curve demonstration of the survival which suggest that in T2DM could be higher the risk of cancer, the age adjustment in the Cox analysis proved that the risk of cancer was higher in the T1DM. This finding also supports the higher mortality outcome for T1DM and emphasizes the need of further studies of cancer risk in young adult.

Our study contains a variety of strengths and weaknesses. The length of the follow-up period, size of patient groups with type 1 and type 2 diabetes, the analyses of many diabetes-related comorbidities, and the high number of events provided sufficient power for the analyses.

The limitation of our analysis is that it included patients with diabetes using antidiabetic drug therapy, while it did not involve patients with type 2 diabetes solely leading a modified lifestyle, without antidiabetic drugs. We are also emphasizing that the mean age was different in the two groups, in T1DM 21.63 (21.42-21.85) and in T2DM 33.47 (33.41-33.53). Further limitations of our trial are that NHIF data source has no specific cause of death, we were able to investigate only all-cause mortality leading to relevant weakness of our analysis as significant amount of the first CVD events is fatal.

Besides the high incidence of DKA, we also found high occurrence (HR 12.52) for hypoglycemia in T1DM. These unexpectedly high occurrence of two acute complications of type 1 diabetes may be the underlying cause of death in T1DM cohort and may lead to the higher risk (17%) versus T2DM.

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Based on these findings, in spite of the higher prevalence of cardiovascular and cancer morbidity in patients with type 2 diabetes, the higher prevalence of diabetic ketoacidosis and hypoglycemia found in our study may contribute to the higher mortality risk of patients with type 1 diabetes compared with those with type 2. A higher rate of dialysis, as a precipitation factor for both hypoglycemia and ketoacidosis, may sustain these differences in the long term.

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**CONFLICT OF INTEREST**
The authors declare that they have no conflicts of interest.

**AUTHORS’ CONTRIBUTIONS**
Z.K. participated in data collection. Gy.R. participated in data collection and prepared figures and tables. Zs.A.T. prepared figures and tables and performed the statistical analysis. Gy.J. wrote the manuscript and participated in the interpretation of data. P.K. wrote the manuscript and participated in the interpretation of data. L.B. participated in the interpretation of data of type 1 diabetic patients. I.W. designed the study, wrote the manuscript, and lead the author teamwork.

**ORCID**
István Wittmann https://orcid.org/0000-0001-5163-5733

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