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ORIGINAL ARTICLE

Kidney failure risk in type 1 vs. type 2 childhood-onset diabetes mellitus

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Abstract

Background Diabetic kidney disease (DKD) is becoming increasingly common among children. We aimed to estimate the risk of end-stage renal disease (ESKD) and mortality among adolescents with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) and normal renal function compared with non-diabetics. We hypothesized that childhood onset T1DM vs. T2DM would be associated with a different risk profile for developing ESKD and its complications.

Methods A nationwide, population-based, retrospective cohort study, including 1,500,522 adolescents examined for military service between 1967 and 1997, which were classified according to the presence and type of diabetes. Data were linked to the Israeli ESKD registry. Cox proportional-hazards models were used to estimate the hazard ratio (HR) for ESKD.

Results At study enrolment, 1183 adolescents had T1DM and 196 had T2DM. ESKD developed in 2386 non-diabetic individuals (0.2%) compared with 72 individuals (6.1%) with T1DM and 8 individuals (4.1%) with T2DM. Participants with T1DM were younger at ESKD onset than participants with T2DM (median age, 36.0 vs. 40.5 years, $P < 0.05$). In a multivariate model adjusted for age, sex, paternal origin, enrollment year, BMI, and blood pressure, T1DM and T2DM were associated with HR of 36.4 (95% CI 28.3–46.9) and 19.3 (95% CI 9.6–38.8) for ESKD, respectively. Stratification according to sex, ethnicity, immigration, and socioeconomic status did not materially change the HR. During the follow-up period, mortality rates were higher in T2DM as compared with T1DM and controls (8.7 %, 2.2%, and 2.7% respectively).

Conclusions T1DM and T2DM in adolescents with normal renal function confer a significantly increased risk for ESKD. T1DM is associated with younger age at ESKD onset while T2DM is associated with higher mortality rate.

Keywords Type 1 diabetes mellitus · Type 2 diabetes mellitus · End-stage kidney disease (ESKD) · Chronic kidney disease (CKD)

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Introduction

Type 2 diabetes mellitus (T2DM) is becoming increasingly more common among children and adolescents, with recent estimates of 12.5 cases per 100,000 youths in the USA [1]. In contrast to type 1 diabetes mellitus (T1DM) and despite its importance, T2DM diagnosed during childhood is a relatively new disease, whose natural history is largely unknown, with respect to both mortality and long-term complications, such as diabetic kidney disease (DKD).

Few studies have directly compared mortality and long-term risk of end-stage kidney disease (ESKD) between childhood-onset T1DM and childhood-onset T2DM, in comparison with non-diabetic subjects. These yielded conflicting results, in part because of different cohort ages [2–5]. Hence, data is lacking with regard to the long-term renal outcome and risk of mortality in T2DM with respect to the general population.

Herein, we were interested in delineating the comparative risk of future ESKD and all-cause mortality in childhood-onset T1DM, childhood-onset T2DM, and a cohort without a history of childhood diabetes. We hypothesized that childhood onset T1DM vs. T2DM would be associated with a different risk profile for developing ESKD and its complications. To test this hypothesis, we carried out a nationwide, population-based retrospective cohort study among 1,500,522 Israeli adolescents evaluated for military service who were followed for 30 years. We assessed the risk for ESKD and mortality in adolescents with either T1DM or T2DM as compared with non-diabetic controls.

Material and methods

Study participants, clinical assessment, and diagnosis

One year prior to their conscription into military service, all eligible Israeli adolescents undergo mandatory medical board examination for health status assessment that includes reviewing the medical file obtained from the primary care physician on a structured form, taking a medical history and conducting a physical examination (including routine urinalysis), and, if indicated, providing referral for further evaluation. All potential recruits undergo baseline measurement of height, weight, heart rate, and a sphygmomanometric blood pressure measurement obtained in the right arm in the seated position [6]. All conscripts with glycosuria or participants for whom diabetes mellitus cannot be ruled out based on the medical record or examination undergo additional tests and are referred to a board-certified endocrinologist. All diabetic conscripts are referred to a board-certified endocrinologist for diagnosis confirmation. Classification to T1DM or T2DM was based on a letter from the primary physician/endocrinologist and following approval by the IDF medical board committee. All diabetic participants enrolled into the study had a urinalysis not indicating the presence of kidney disease. Following this process at enrollment, participants were divided into three groups: (a) participants with T1DM (b) participants with T2DM, and (c) non-diabetic participants. The accuracy and completeness of the medical information with respect to each diagnosis are additionally assessed and verified by a committee of two trained military service physicians. Each diagnosis is assigned a numerical code and recorded in a central database. This process was uniform for all future conscripts.

Inclusion criteria for the current study were age 16–25 years at the time of medical board examination which took place between 1967 and 1997. Because military service is not mandatory for Israeli non-Jews, the study population included only Jewish recruits, for whom military service is compulsory. Exclusion criteria were the presence of cystic fibrosis, recurrent/chronic pancreatitis, systemic lupus erythematosus, vasculitis, hypertension, or any known past or current kidney disease at enrollment, including primary congenital or acquired anomalies of the kidneys or urinary tract, glomerulonephritis, nephrolithiasis, pyelonephritis, or cystic renal disease. In addition, we excluded participants with acute or chronic kidney injury or proteinuria.

The Israeli treated ESKD Registry

The Israeli treated ESKD database is a national registry maintained by the Ministry of Health [7]. It contains information on patients receiving any form of renal replacement therapy, i.e., hemodialysis, peritoneal dialysis, or kidney transplantation. All nephrology dialysis units in Israel, public and private, report to the Ministry of Health on new patients receiving renal replacement therapy and changes in treatment modality. The database includes demographic data, a primary diagnosis, and initial modality of renal replacement therapy, as well as dates of initiating dialysis, change of treatment modalities, renal transplantation, and death. Validation of the database includes periodic linkage with the Israeli population registry to update demographic and mortality data. Reports of cadaver donor transplants in Israel are crosschecked with the National Laboratory for Tissue Matching, and reports on living donor kidney transplants are crosschecked with the National Transplant Center. A single primary diagnosis is recorded for each new patient in the treated ESKD database [7]. The current study cohort was linked to the Israeli treated ESKD registry using the identification number given to all Israeli citizens at the time of birth or immigration. The institutional review board of the Israel Defense Forces approved the study

and waived the requirement for informed consent on the basis of preserving participants' anonymity.

Outcome variables and follow-up

Onset of treated ESKD was defined as the date of initiation of dialysis or transplantation, whichever came first, and all treated ESKD cases from January 1, 1980, to December 31, 2014, were included. Follow-up period was measured from initial medical board assessment until the initiation of renal replacement therapy (incidence of ESKD), death, or to December 31, 2014, whichever came first. In addition, the Israeli army data is continuously updated on the vital status of the potential recruits through an ongoing linkage with the Israeli Population Registry, which served as the source of mortality data.

Statistical analysis

Summary statistics for the study group were expressed as mean (SD) or percentage. Statistical significance was determined using the two-sample *t* test for metric variables or chi-squared test for categorical variables. Cox proportional hazards models [8] were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for comparing the incidence of treated ESKD among participant subgroups. The proportional hazards assumption was tested graphically using log-minus-log graphs. A model was constructed controlling for age, sex, paternal country of origin (Europe/Americas, West Asia, North Africa, and Israel), period of baseline examination by decade, body mass index (BMI) according to the accepted cutoffs for overweight and obesity (BMI of 25 and 30 kg/m^2, respectively), systolic blood pressure (categorized as below or above the sex-specific 95th percentile), and presence of hematuria. Multiple imputations for missing data were made with the use of SAS Enterprise Miner software, version 14.1 (SAS Institute). Two-sided P value < 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using SPSS version 24 (IBM).

Results

Study population

Figure 1 shows the study design. The cohort comprised 1,500,522 adolescents and young adults (61.7% male). Of the participants who met entry criteria, 1,499,143 were non-diabetic, 1183 (0.079%) had T1DM, and 196 (0.013%) had T2DM. The mean age at recruitment was 17.7 ± 1.1, with a similar male:female ratio in all subgroups, of approximately 60:40 (Table 1).

Childhood-onset diabetes mellitus and future risk of ESKD

During 45,531,560 person-years of follow-up (mean, 30.3 years), 2386 participants developed ESKD for an overall incidence of 5.24 per 100,000 person-years. Table 2 shows the crude associations between T1DM and T2DM and ESKD. ESKD incidence in non-diabetic participants was 5.1 per 100,000 person years, while participants with T1DM and T2DM showed incidence rates of 229.8 and 132.3 per 100,000 person-years, respectively. Accordingly, compared with non-diabetic participants, the unadjusted HR for ESKD in T1DM patients was 58.3 (95% confidence interval (CI) 46.1–73.7), whereas T2DM patients had a 28 times higher risk of ESKD (HR, 27.8 (95% CI 13.9–55.7)) compared with non-diabetic controls. Controlling for age, sex, paternal origin, and enrollment period reduced the HR to 41.5 (95% CI 32.2–53.4) in T1DM and 24.7 (95% CI 13.3–49.6) in T2DM (Table 2 and Fig. 2a). Further controlling for BMI, blood pressure, and microhematuria yielded HR of 36.4 (95% CI 28.3–46.9) in T1DM and 19.3 (95% CI 9.6–38.8) in T2DM (Table 2). Notably, when considering only the subgroup of patients with hypertension (systolic blood pressure above the 95th percentile), similar results were obtained, with T1DM and T2DM patients showing HR of 48.3 (95% CI 36.5–64.1) and 11.5 (95% CI 2.9–46.1), respectively.

To determine whether the increased ESKD risk in T1DM patients is related to an earlier disease onset, we reanalyzed the data, assuming a mean age of start of follow-up of 10 years for T1DM patients, which is the mean age of T1DM diagnosis in Israel [9]. Following adjustment for age, sex, paternal origin, enrollment period, BMI, blood pressure, and microhematuria, we found no significant difference in ESKD risk between T1DM and T2DM, yielding HR of 20.4 (95% CI 15.8–26.3) and 21.7 (95% CI 10.8–43.5), respectively.

Mortality in childhood-onset diabetes mellitus

Subsequently, we analyzed all-cause mortality. Whereas T1DM patients and non-diabetic patients had similar mortality rates (2.2% and 2.7%, respectively), T2DM patients exhibited a significantly higher death rate of 8.7%. Accordingly, the HR for death was 0.7 (95% CI 0.5–1.0) and 2.3 (95% CI 1.4–3.7) among participants with T1DM and T2DM, respectively, compared with non-diabetic participants. Figure 3 shows the survival curve for each subgroup.

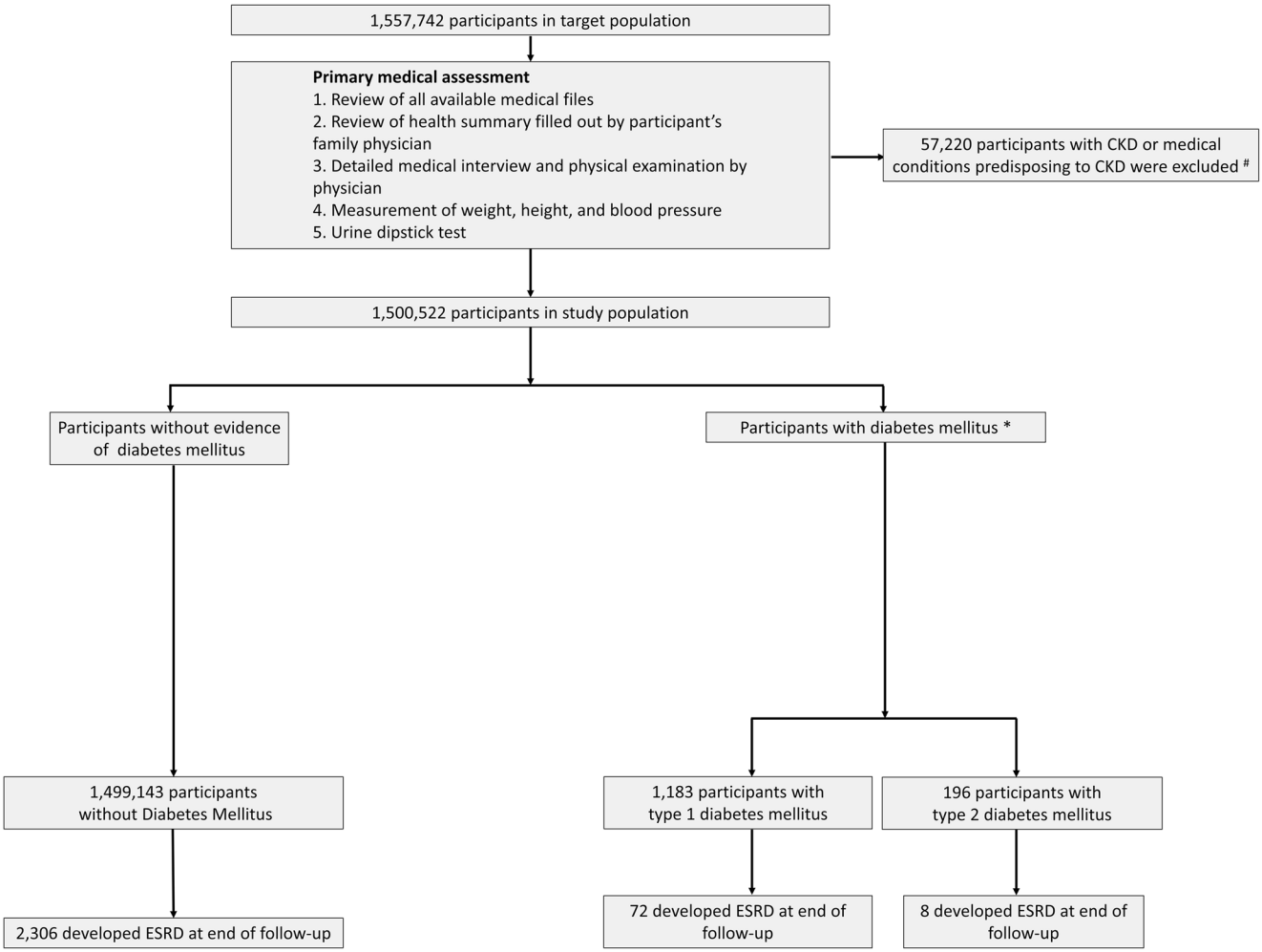

Fig. 1 Participant assessment, designation, and outcome. Asterisk symbol indicates the diagnosis and classification of diabetes mellitus were given following a full evaluation and assessment by a board-certified endocrinologist. Number sign indicates that these included proteinuria, persistent hematuria, CAKUT, and history of glomerulonephritis to history of acute pyelonephritis

Risk factors for ESKD in T1DM

So as to identify potential risk factors for ESKD in T1DM patients, we stratified participants according to (I) gender, (II) paternal origin (North Africa, West Asia, Europe/America, or Israel), (III) immigration status (immigrant or native Israeli), and (IV) socioeconomic status (as defined by the Israeli Central Bureau of Statistics, which grades each municipality's socioeconomic status on a scale of 1–10). These analyses did not reveal a specific subgroup of T1DM participants with increased ESKD risk.

Discussion

Numerous studies have evaluated the long-term renal consequences of T1DM in youth [10–13]. In contrast, despite its rapidly increasing incidence, T2DM among children and adolescents is still a poorly defined entity with regard to its long-term morbidity and mortality. We therefore set out to assess the long-term risk of ESKD and mortality among adolescents with each type of diabetes.

In this population-based study that encompassed approximately 1.5 million participants, we found that for adolescents at a mean age of 17 years, the cumulative incidence of ESKD after 30 years of follow-up is significantly higher for T1DM (6.1%) compared with T2DM (3.8%), even after accounting for age, sex, blood pressure, BMI, enrollment period, and paternal country of origin. Our sensitivity analysis, whereby the earlier age of onset of T1DM was taken into consideration, revealed that the difference in risk is attributable mostly to the longer disease duration in T1DM compared with T2DM.

The figure reported herein for ESKD risk among T1DM patients is within the range reported in other countries for similar follow-up periods [10–13]. In contrast, very few studies have evaluated this risk among young T2DM.

Several studies demonstrated a higher prevalence of albuminuria in youth with T2DM compared with youth with

Table 1 Baseline characteristics of 1,500,522 participants examined between 1967 and 1997 According to the presence and type of diabetes mellitus

Characteristic	All participants (N = 1,500,522)	Non-diabetic (N = 1,499,143)	Type 1 DM (N = 1183)	Type 2 DM (N = 196)	P value
Age at assessment, mean (SD) (years)	17.7 (1.1)	17.7 (1.1)	18.0 (1.4)	18.6 (1.7)	< 0.001
Male, sex, no. (%)	926,209 (61.7)	925,362 (61.7)	730 (61.7)	117 (59.7)	0.843
Father's place of birth, no. (%)					< 0.001
Europe/Americas	642,945 (42.8)	642,337 (42.8)	497 (42.0)	111 (56.6)	
West Asia	376,075 (25.1)	375,884 (25.1)	163 (13.8)	28 (14.3)	
North Africa	363,379 (24.2)	363,206 (24.2)	143 (12.1)	30 (15.3)	
Israel	68,184 (4.5)	68,130 (4.5)	44 (3.7)	10 (5.1)	
Unknown	49,939 (3.3)	49,586 (3.3)	336 (28.4)	17 (8.7)	
Systolic blood pressure, no. (%)					0.001
< 95th percentile	1,389,096 (92.6)	1,387,850 (92.6)	1075 (90.9)	171 (87.2)	
≥ 95th percentile	111,426 (7.4)	111,293 (7.4)	108 (9.1)	25 (12.8)	
Body mass index, no. (%)					< 0.001
< 25	1,329,802 (88.6)	1,328,716 (88.6)	951 (80.4)	135 (68.9)	
25–29	139,491 (9.3)	139,332 (9.3)	118 (10.0)	41 (20.9)	
≥ 30	31,229 (2.1)	31,095 (2.1)	114 (9.6)	20 (10.2)	
Period of enrollment, no. (%)					< 0.001
1967–1979	503,372 (33.5)	503,032 (33.6)	253 (21.4)	87 (44.4)	
1980–1989	479,038 (31.9)	478,644 (31.9)	332 (28.1)	62 (31.6)	
1990–1997	518,112 (34.5)	517,467 (34.5)	598 (50.5)	47 (24.0)	

T1DM at various disease time points [14, 15]. Hence, our results indicate that the rate of progression from early CKD to ESKD is significantly lower in T2DM, which has been previously suggested [16], although to date no study has directly compared ESKD risk in the two types of DM over long follow-up periods using a population-based cohort of adolescents. A study from Japan, which examined all cases of early-onset (age < 30 years) T2DM diagnosed between 1970 and 1990 in a diabetes clinic, and followed-up until 1996, reported a cumulative incidence of 4.7% for renal failure requiring dialysis after approximately 8 years [17]. In a prospective study, Luk et al. reported similar rates of ESKD among patients with young-onset T2DM and T1DM, once adjusted for BMI and other metabolic indices [4], again relying on a relatively short follow-up, of 9 years. In contrast, Dart et al. reported that young (< 18 years) T2DM patients were significantly more likely to develop ESKD after a mean follow-up period of 5.3–7.9 years, while Cowie et al., studying American diabetic patients, reported that T1DM patients were more likely to develop ESKD than T2DM patients, although

Table 2 Association between diabetes mellitus and treated end-stage kidney disease according to the cox proportional hazards model

	Type 1 DM	Type 2 DM	Non-diabetic
Incidence rate of ESD—no. of cases per 100,000 person-years	229.8	132.3	5.1
Total years of follow-up	31,330	6045	45,494,185
Age at end of follow-up (year)	44.5 ± 8.9	49.4 ± 8.6	48.0 ± 9.3
Died—no. (%)	26 (2.2)	17 (8.7)	40,178 (2.7)
Hazard ratio (95% CI) for ESKD from any cause in adulthood			
Unadjusted	58.3 (46.1–73.7)	27.8 (13.9–55.7)	Reference
Adjusted[ǂ]	41.5 (32.2–53.4)	24.7 (13.3–49.6)	Reference
Fully adjusted[¶]	36.4 (28.3–46.9)	19.3 (9.6–38.8)	Reference
Fully adjusted[ϕ]	20.4 (15.8–26.3)	21.7 (10.8–43.5)	Reference

[ǂ] Adjusted for age, sex, paternal origin, and period of enrollment

[¶] Adjusted for age, sex, paternal origin, period of enrollment, body mass index, and blood pressure

[ϕ] Adjusted for age, sex, paternal origin, period of enrollment, body mass index, and blood pressure, assuming a mean age of start of follow-up of 10 years for T1DM patients

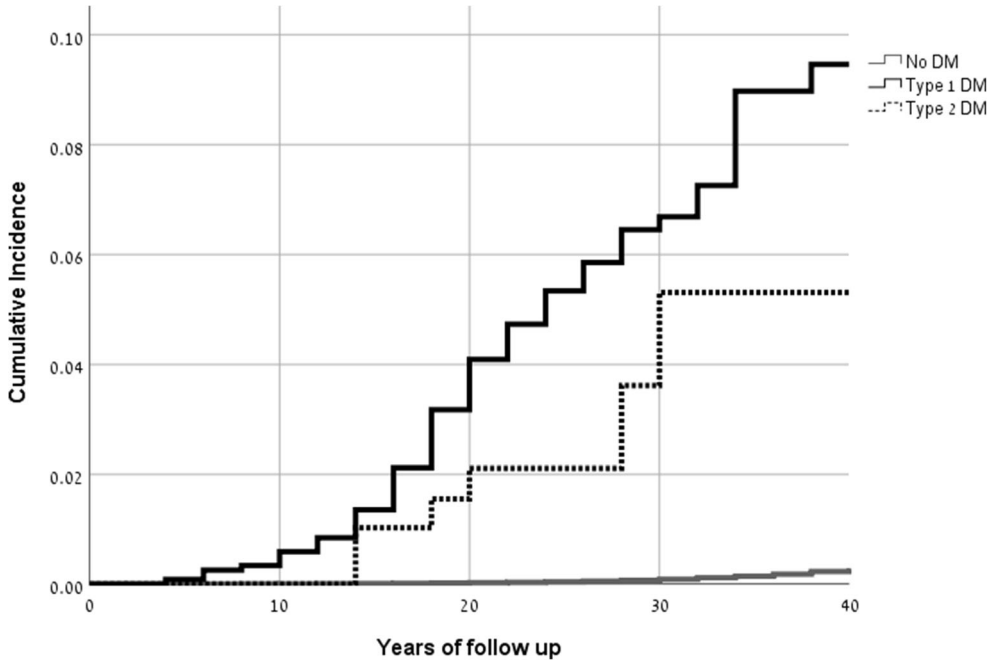

Fig. 2 Cumulative incidence of treated ESKD among study participants

the study was not restricted to young patients. The similar risk of DKD between T1DM and T2DM patients is an interesting finding considering the different pathogenetic mechanisms of renal damage in each of the two disorders. While T1DM-related DKD is mostly related to the damages of hyperglycemia, T2DM-related DKD might be more influenced by other factors, such as dyslipidemia [18, 19], visceral fat [20], and low-grade inflammation [21, 22].

Another important observation in our study is the significantly higher mortality rate among patients with T2DM compared with those with T1DM (8.7% vs. 2.2%, respectively). While various studies examined mortality rates in childhood-onset T1DM [23–25], only few directly compared mortality rates in the two types of diabetes over long periods. Constantino et al. previously reported a similar difference, albeit with higher mortality rates, of 11% and 6.8%, respectively, after follow-up periods of approximately 20 years. The lower survival in that study can be attributed to the older cohort. Interestingly, most patients died from vascular complications, and none of the patients died of a renal etiology.

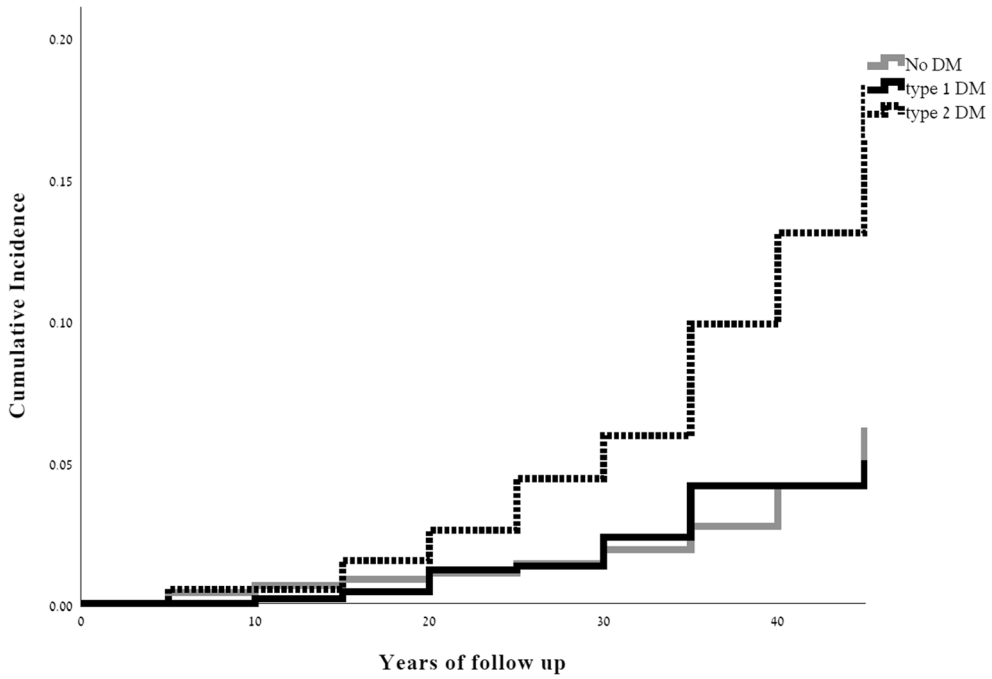

Fig. 3 Cumulative mortality rates in participants with type 1 diabetes mellitus (DM), type 2 DM, and no diabetes mellitus

Similarly, the study by Luk et al. found mortality rates of 2.4% and 22.5% after 20 years of follow-up in young T1DM and T2DM patients, respectively. The extraordinarily high mortality rate among the latter may be attributed to a genetic predisposition or other factors. Importantly, it would be interesting to assess this issue using more recent data, by carrying out a prospective study or by analyzing data from more recent years, following the advent of tight glycemic control, continuous glucose monitors, insulin pumps, and sodium-glucose transport protein 2 inhibitors (SGLT2i) and assess whether this might affect the trends in mortality.

Notably, we found no significant difference in mortality during the study period between T1DM patients and controls. This is in line with several previous observations [24] and may imply that DM-related complications (e.g., vascular disease) reach life-threatening levels after more than 30 years of adulthood. Moreover, it is possible that T1DM patients, who are usually diagnosed at a young age, benefit from a tighter follow-up, more frequent medical evaluations, and possibly higher awareness to possible complications, in comparison with the general population. Furthermore, since diabetic participants in our cohort were already diagnosed upon entry into the study, deaths related to acute T1DM complications (e.g., diabetic ketoacidosis), which represent 10–15% of mortality cases over long follow-up periods in some reports, were not fully reflected in our mortality data. Hence, we cannot exclude the option of a slight underestimate of death rates among T1DM participants.

Interestingly, various epidemiological factors did not prove to be associated with ESKD risk in our cohort of T1DM patients, including paternal origin, immigration, and socioeconomic status. The former two are particularly remarkable considering the significant variability in ESKD incidence reported in different countries among T1DM patients. The most likely explanation is the similar genetic background and universal access to health services in Israel. Notably, similar results were reported in a study carried out in Germany [26], which demonstrated an association between socioeconomic status and DKD only in T2DM, but not in T1DM. In accordance with some previous studies [13, 27], we did not find a difference in the risk of ESKD between men and women with T1DM. While historically men were thought to be at a greater risk than women [28, 29], most recent studies were unable to show any difference between the sexes [13, 27].

Several limitations of the current study should be considered. First, data on DM were collected from 1967 onwards, whereas data on treated ESKD were collected from 1980 onwards. Second, clinical information, such as normal creatinine levels and diagnosis of DM, were reported rather than measured. Hence, we are unable to ascertain the exact evaluation carried out by the treating physicians and endocrinologist that resulted in the diagnosis of DM. In addition, renal ultrasound was probably not carried out in some participants, such that not all cases of CAKUT were detected. Nonetheless, this should include similar numbers in both groups of DM and control group. Moreover, no data about clinical events during the follow-up period were available. Nonetheless, this is true for both the study and control populations. Third, the exact time of DM diagnosis at childhood was not available to us. Fourth, our study was limited to Jewish recruits, thereby limiting its generalizability. In addition, our cohort included a nationally representative group of Jewish men but not of Jewish women, since orthodox women are exempt from military service. Lastly, it is possible that the introduction of the newer anti-diabetic medications could have an effect on the risk for ESKD and mortality, which would have to be assessed in a prospective study.

The main strengths of this study are the reliance on very large cohorts with detailed clinical assessment parameters alongside a long follow-up period and comprehensive documentation of ESKD. These allowed us to determine the risk for this disease with relatively low incidence. In addition, the routine assessment of a large part of the population at a young age allowed us to study young T2DM patients, a currently under-studied disease.

In summary, we report that childhood-onset T2DM may be associated with higher mortality rates than T1DM over the course of 30 years, although the rate of ESKD is lower in this disease due to a shorter disease duration. These findings are of value to the clinician treating diabetic patients in their first years of adulthood and should be used to direct follow-up and management decisions.

Compliance with ethical standards

The institutional review board of the Israel Defense Forces approved the study and waived the requirement for informed consent on the basis of preserving participants' anonymity.

Conflict of interest The authors declare that they have no conflict of interest.

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