The long-term incidence of hospitalization for ketoacidosis in adults with established T1D – a prospective cohort study

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Disclosure summary

P-H.G. reports receiving lecture honorariums from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, MSD, Novartis, Novo Nordisk, and Sanofi and being an advisory board member of AbbVie, Astellas, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, and Sanofi. M.T. reports receiving lecture honorariums from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Servier, Takeda, and Novartis. No other potential conflicts of interest relevant to this article were reported.

Abstract

Context

The long-term natural history of diabetic ketoacidosis (DKA) and its risk factors are poorly understood.

Objective

To determine the long-term incidence and predictors of DKA in adults with longstanding type 1 diabetes (T1D)

Design

All hospitalizations and deaths due to DKA between 1996 and 2016 were identified in 4758 adults with T1D from the Finnish Diabetic Nephropathy Study (FinnDiane), and a cohort of 16224 adults with T1D from the Finnish general population.

Results

Between 1996 and 2015, there were 1228 DKA events in the FinnDiane participants (1.4/100 person-years) and 4914 DKA events (1.8/100 person-years) in the adults with T1D from the general population. The majority were hospitalized only once. There was a modest increase in the frequency of DKA in the FinnDiane over the follow-up (~2.4%/year [95% CI 0.3-4.5%]; p=0.03). Predictors of DKA were glucose control, CSII, smoking and alcohol consumption, raised HDL cholesterol and triacylglycerides. Diabetic nephropathy and renal impairment were associated with DKA; patients with end-stage renal disease, macroalbuminuria and microalbuminuria had 2.09- (95% CI 1.40-3.12), 1.65- (1.23-2.19) and 0.87- (0.61-1.24) fold risk of DKA, compared to patients with normal albumin

excretion rate, respectively. Patients with an eGFR<60 ml/min/1.73m^2 were also more likely to be hospitalized for DKA (HR 1.71, [1.26-2.67]).

Conclusions

DKA remains a common cause of hospitalization in individuals with longstanding T1D. These data suggest that the goal to use SGLT2 inhibitors for their vasculo- and renoprotective actions may be problematic, as those most likely to benefit may also have the highest risk for DKA.

Introduction

Diabetic ketoacidosis (DKA) is one of the most important emergencies in T1D (T1D) and a common reason for hospitalization (1). Despite improving diabetes care and new technologies for insulin delivery and glucose monitoring, at least three in every hundred persons with T1D may be hospitalised annually in the United States (US) and this incidence appears to be increasing both in the US (2, 3) and in other countries (4). The total health care cost associated with DKA in the US has been estimated to be over 5 billion dollars annually (1). Although mortality rates from DKA are declining, it remains one of the biggest contributors to loss of life years associated with T1D (5, 6).

Many DKA events are observed in and around the time of the diagnosis of T1D, or during the first few years of management when titration, accidental omission or poor adherence may sometimes result in inadequate insulin therapy, especially in children and adolescents. Cross-sectional studies exploring the prevalence of DKA are therefore potentially dominated by newly-diagnosed cases of T1D, especially in young individuals and their associated risk factors. These risks may not be the same as older adults with well-established diabetes, in whom the annual incidence of acute DKA is lower (2) but likely remains significant over time (6).

The long-term natural history of DKA and its risks are poorly understood. Determining the ongoing risks for DKA in adults with established T1D is also now particularly important, as the future relevance of vasculo-protective outcomes of Sodium GLucose coTransporter (SGLT)2 inhibitors may be offset by an increased risk of DKA following treatment with these agents in this setting (7). In this study, we examine the long-term incidence and predictors of hospitalization for DKA in a prospective cohort study of 4,758 Finnish adults with T1D from the FinnDiane study, and a

retrospective cohort of 16,224 adults with T1D from the Finnish general population followed over the same time period.

Methods

The Finnish Diabetic Nephropathy Study (FinnDiane) is an ongoing, nationwide, multicenter study, initiated in order to identify genetic and environmental risk factors for diabetic complications, with special emphasis on diabetic kidney disease in patients with type 1 diabetes. A detailed description of the FinnDiane recruitment protocol has previously been presented (8). Briefly, adult patients (≥18 years old) with type 1 diabetes across Finland were asked to participate, and the participation rate was 78%. Type 1 diabetes was defined as insulin dependence and C-peptide <0.30 nmol/l, age at onset of diabetes <40 years and insulin treatment initiated within 1 year of diagnosis. The study protocol was in accordance with the principles of the Declaration of Helsinki as revised in 2000 and was approved by the Ethical Committee of Helsinki and Uusimaa Hospital District. Written informed consents were obtained from each FinnDiane patient.

The baseline visit for participants occurred between the years 1994 and 2015 (n=4758), at which time participants underwent a thorough clinical examination and blood and urine samples were collected. Information on the presence of diabetic complications including renal and cardiovascular disease were obtained from the medical files by the attending physician using a standardized questionnaire. In addition, albuminuria status was determined based on measurements of urinary albumin excretion rate (UAER) from at least two timed overnight (g/min) or 24h urine (mg/24h) collections. Normoalbuminuria was defined when in at least two out of three urinary samples UAER was <20 µg/min or <30 mg/24 h; microalbuminuria, when UAER ≥20 and <200 µg/min or ≥30 and <300 mg/24 h; or macroalbuminuria, when UAER ≥200 µg/min or ≥300 mg/24 h; end-stage renal disease (ESRD) as dialysis treatment or having received a kidney transplant. Serum creatinine was

determined at a central laboratory by a kinetic Jaffe method using a Hitachi 911 autoanalyzer until January 2002. Thereafter it was determined by a photometric enzymatic method using a Hitachi 917 or Modular analyser. We have taken account of this change in the measurement of creatinine by using the modifying coefficient (1/1.0465). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.

Patients filled in questionnaires regarding their lifestyle, including their smoking habits, alcohol consumption and socioeconomic status. Serial HbA_{1c} values from the medical files were obtained and intra-individual mean and coefficient of variation (CV) were calculated. The CV was calculated as a ratio of intra-individual standard deviation and mean.

Ascertainment of outcomes

For each participant in the FinnDiane cohort, the composite outcome of admission to hospital, attendance at an emergency department or specialized outpatient care with a diagnosis of DKA or death from DKA (hitherto denoted as DKA hospitalization) was determined. Hospitalization for DKA was ascertained from the Finnish Care Register for Health Care (HILMO) database that collects all discharges from Finnish hospitals (including specialized outpatient care) and associated diagnosis and treatment codes. All events in which the International Classification of Disease (ICD) 9th Revision code of 2501B (1987-1995 for prevalent cases before visit) and the 10th Revision code of E10.1 (1996-2015) were used were designated as DKA. However, if there were several successive admissions within less than five days they were calculated as one event. Fatal DKA events were drawn from the Finnish Cause of Death Register.

For determining the frequency of DKA hospitalization in FinnDiane participants, all DKA events between 1996 and 2015 were determined, including events that occurred prior to enrollment and baseline visits. All DKA hospitalization events that occurred before the age of 18 or within the first

two years of their diabetes were excluded, as a recent diagnosis, honeymoon phases and subsequent titration of insulin may confound an analysis of DKA incidence in these cases. Outcomes follow-up commenced from the start of their third year of diabetes, from 18 years of age or the year 1996, whichever was most recent. For analysis of the predictors of incident DKA, only DKA events that occurred after the baseline visit were considered as the outcome. A history of prior DKA was determined as a coded diagnosis for hospitalization between 1987 and baseline visit in the HILMO dataset and used as a predictive variable.

Retrospective cohort validation

The frequency of hospitalization for DKA over the same time period was also determined in a larger retrospective cohort of adults with type 1 diabetes in Finland. To do this, all adults (age >18) with T1D (defined by a diagnosis of diabetes under the age of 30 years and ongoing insulin requirements) present on January 1st 1994 were identified using the National Institute for Health and Welfare database, as previously described (9-11). Admission to hospital for DKA between January 1996 and December 2015 was then retrospectively identified using the HILMO hospitalization and ICD-10 codes as detailed above. This inclusion strategy effectively excluded events that occurred in patients with potentially less than two years duration of diabetes. The study has permissions from the Finnish National Institute for Health and Welfare (THL/786/6.02.00/2016) and Statistics Finland (TK53-26-16).

Statistical methods

Crude DKA rates and DKA mortality rates were calculated per 100 person-years with 95% Poisson confidence intervals. We used linear regression to model the age-standardized prevalence curves. In order to model the prognostic variables related to DKA, Cox regression analyses were conducted on prospective data obtained from the time of baseline visit. Time-to event was estimated by

Kaplan-Meier survival analyses and the log rank test was used to test for between-group differences. Poisson regression was used to model predictors of all DKA events including recurrent events. Statistical analyses were performed using SAS 9.4 version (SAS Institute Inc, Cary, NC, USA).

Results

Baseline characteristics of the FinnDiane cohort

The baseline characteristics of individuals experiencing hospitalization for DKA during the prospective follow-up phase are shown in Table 1, compared to those not experiencing DKA during follow-up. Those with at least one DKA hospitalization had more frequently prior DKA, insulin pump therapy, higher HbA1c, mean and variability of serial HbA1c, dose of weekly alcohol consumption, insulin dose, total cholesterol and triglycerides, but lower age at onset of diabetes, BMI and estimated glucose disposal rate compared with patients without DKA. In addition, they had more likely smoking history, hypertension, kidney disease, severe diabetic retinopathy. Patients with two or more DKAs had further more likely history of excess alcohol usage.

The incidence of hospitalization for DKA for participants in the FinnDiane cohort

Between 1996 and 2015, there were 1206 hospitalizations for DKA and 22 fatal DKA events in the FinnDiane participants resulted in an overall rate of 1.4 per 100 person-years. The proportion individuals managed as inpatients was similar in those with eGFR<60 (62.4%) and with eGFR≥60 (63.0%) (p=0.81). The annualized frequency of DKA events is shown in Figure 1A. There was a modest but significant increase in the frequency of DKAs over this time period (~2.4% per year (95% CI 0.3-4.5%, p<0.03). The modelled mean incidence was 1.1 per 100 person-years in 1996 while in 2015 it had risen to 1.6 per 100 person-years. These DKA events occurred in 617 participants (13.0%), meaning the majority of individuals experiencing hospitalization for DKA, only experienced DKA on

a single occasion in this time period (65%). Notably the frequency of these "one off" DKAs remained constant in this cohort (Figure 1A).

Predictors of the incidence of hospitalization for DKA in the FinnDiane cohort

From the time of their enrollment in the FinnDiane cohort, there were 969 non-fatal or fatal DKAs that occurred in 461 individuals over a median follow-up of 14.4 (10.6-16.6) years from baseline visit, equating to an overall event rate of 1.5 per 100 person-years only over the prospective follow-up period. This number is slightly higher than the total hospitalizations detailed above, in the same individuals that occurred between 1996 and 2015.

The majority of these DKAs (n=709, 73%) occurred in individuals that did not have a prior recorded DKA hospitalizations as an adult (aged >18) in the HILMO database, beyond the first two years of their diabetes. Only 92 individuals (20%) experiencing a DKA hospitalization after enrollment had been hospitalized for DKA previously as an adult. 369 participants that had a DKA hospitalization event prior to enrollment, did not have a subsequent event after baseline during prospective follow-up.

After adjusting for a prior history of hospitalization for DKA, incident DKA in this population was independently associated with smoking and alcohol consumption at baseline, raised HDL cholesterol and plasma triglycerides concentrations, insulin pump therapy, and poor glucose control (HbA1c) at baseline (Table 2). In particular, HbA1c levels over the course of follow-up and HbA1c variability trait were also independently associated with the incidence of hospitalization for DKA in adults with type 1 diabetes (Figure 2, Table 2) – such that those individuals with the best glycemic control and the least variability in their HbA1c also had the lowest incidence of DKA, while those individuals with the highest rates of DKA also had worse glucose control and more variability in their control. The

predictors of time to first event on Cox regression analysis were the same as those for all DKA events determined using Poisson regression (data not shown).

Most importantly, diabetic nephropathy was associated with increased risk of DKA. After adjustment for these other risk factors patients with ESRD, macro- and microalbuminuria the risk was 2.09-fold (95% CI 1.40-3.12; p<0.0001), 1.65 (1.23-2.19; p=0.0007) and 0.87-fold (0.61-1.24; p=0.43) compared with patients with normal albumin excretion rate (Figure 3A). After excluding participants with ESRD, and adjusting for other risk factors, the presence of moderate to severe impairment in kidney function (eGFR <60 ml/min/1.73m^2) remained associated with the incidence of hospitalization for DKA in adults with T1D, such that those individuals with eGFR<60 ml/min/1.73m^2 were twice as likely to be hospitalized for DKA (HR 1.71, [1.26-2.67]; p<0.0001) when compared to those with an eGFR>60 ml/min/1.73m^2 (Table 2, Figure 3B). Hyperfiltration at baseline (eGFR >130 ml/min/1.73m^2) was also associated with an increased risk of incident DKA (HR 2.35; 95% CI 1.50-3.66; p=0.0002). However, after adjusting for glycemic control and glycemic variability during the study this association also became non-significant (p=0.07). Notably, the duration of T1D or the age at diagnosis were not associated with incidence of DKA in adults with type 1 diabetes. In addition, there was no association between incident DKA and sex, socioeconomic status, the control of LDL cholesterol or blood pressure or the presence of retinal complications at baseline (defined by the need for laser therapy).

The frequency of hospitalization for DKA in the Finnish retrospective cohort

In 15,149 adults with type 1 diabetes from the general population, over the same time period of 20 years (1996-2015), there were 4771 hospitalizations for DKA and 143 fatal DKA events affecting 2376 (15.7%) individuals, equating to an event rate of 1.8 per 100 person-years over this time period. This retrospective cohort did not show significant increase in annual incidence (p=0.09,

Figure 1B). The modelled incidence of hospitalization for DKA was 1.5 in 1996 per 100 person-years and 2.1 in 2015. Again, as in the FinnDiane cohort, most of the individuals experiencing DKA events in the retrospective cohort only had one event during this time period and the frequency of "one off" DKA events remained constant in this cohort (Figure 1B). Mortality from DKA though rare, did not appear to decline with time (Figure 1B), though more patients were hospitalized with DKA over the same time period, meaning that DKA deaths as percentage of DKA events declined slightly, consistent with recent registry data (5, 6).

Discussion

DKA is an important and surprisingly common acute complication of T1D that results in increased healthcare costs (1-3), hospitalization (3, 4), and premature mortality (6, 12). In this contemporary prospective cohort of Finnish adults with T1D, one in tenth were hospitalised or died from DKA over a 14-year period, 36% of whom were hospitalised on more than one occasion. The rate of DKA was similar in adults with T1D from the Finnish general population than in participants in the FinnDiane study. Importantly, we report in both cohorts, the annual incidence rate in the same individuals did not decline over time and actually increased over the follow-up time period. Tragically, between 1.8-3.0% of all DKA events leading to hospitalisation were associated with patient death.

It is widely regarded that DKA is only a problem of early diabetes management, and becomes less likely in patients with established and ongoing insulin use and dedicated diabetes care. This assumption is supported by outcomes in the DCCT/EDIC cohort that showed a reduction in DKAs over the follow-up, with an incidence rate of approximately two cases per 100 person-years at baseline falling to no events at the 12-year follow-up, even in the standard treatment arm (13). Similarly, in a prospective follow-up of the Pittsburgh Epidemiology of Diabetes Complications (EDC) study cohort, the incidence of DKA fell to less than one case per 100 person-years at the 18-year

follow-up (13). However, it is possible that the trials settings and close attention to diabetes control both during and after these studies may have progressively reduced the risk of DKA in these studies. In real-world data from adults with T1D in the FinnDiane study and adults with T1D in the Finnish general T1D population, DKA clearly did not decline, even as 'one-off' events. These data suggest that regardless of the duration of diabetes, the risk of DKA remains a constant companion.

Previous cross-sectional registry-based studies exploring the predictors of DKA in populations have been inevitably dominated by new cases of T1D and the inclusion of children and young adults that have the highest risks of DKA. The clinical characteristics of these individuals therefore largely determine the reported risk factors for DKA in these reports. Such risks may be less relevant to the adult with established T1D, in whom longitudinal risks for DKA have not been well studied. The FinnDiane study is a large prospective cohort study designed specifically to look at complications in adults. Taking this prospective approach, and excluding all events in the first two years after diagnosis, we have been able to follow the incidence for hospitalization for DKA over 14 years within individual adults with T1D. We anticipate that this approach may be more useful in determining individuals who may be ketosis prone, or risk factors at baseline that may be usefully associated with subsequent DKA in the long term.

Consistent with previous studies, in participants within FinnDiane cohort, poor glucose control was associated with an increased risk of hospitalization for DKA, which was clearly associated with both HbA1c at baseline, mean HbA1c during the follow-up and intra-individual HbA1c variability. It is likely that each of these markers capture some of the risk for DKA associated with recurrent hyperglycaemia, inadequate insulin therapy and/or non-adherence. The presence of elevated serum triglycerides may also capture some of this risk. However, even in those with good ongoing

glucose control during the study, and the least variability in HbA1c, hospitalization for DKA still occurred.

In a recent metanalysis of trials, use of continuous insulin subcutaneous infusions (CSII) has also been associated with a higher incidence of reported diabetic ketoacidosis compared with conventional insulin therapy (14). The small percentage of participants in the FinnDiane cohort using insulin pumps at baseline (6.6%) also had a higher incidence of hospitalisation for DKA (HR = 2.44, 95% CI 1.60-3.72, p<0.001) compared to those receiving standard insulin therapy. Beyond malfunction of insulin pump and/or catheter occlusion, the reasons behind this association are unclear but may include a failure to up-titrate insulin during acute illness. Notably, the association between DKA hospitalization and CSII was independent to poor baseline or achieved glucose control, which is often an indicator for pump initiation.

Smoking and alcohol consumption were also independently associated with DKA in the FinnDiane cohort. While these may both be markers of risk-taking behaviours on non-adherent adults with T1D, the association remained significant after adjusting for ongoing glucose control and HbA1c variability. Ethanol is metabolised by the liver to generate acetic acid, and subsequently acetyl-CoA, which is both a substrate for ketogenesis and inhibitor of peripheral lipolysis. Oxidation of alcohol also increases generation of NADH, which inhibits gluconeogenesis and further drives the generation of beta-hydroxybutyrate. These pathways are augmented in the absence of insulin, making excess alcohol intake and T1D a potentially dangerous combination. It is possible that increasing alcohol consumption in Finland following a reduction of 33% in alcohol taxes in 2005–2007, partly contributed to the increasing prevalence of DKA observed in this study, as well as increased alcohol-related mortality in the general population (15).

Previous studies have identified socioeconomic status and educational attainment as key risk factors for DKA (16). The nature of society and the cost-of care support for individuals with T1D (without requiring medical insurance) may substantially attenuate the impact of their impact in Finland and no association was observed between socioeconomic status and DKA in our cohort, after adjusting for alcohol use and glycaemic attainment. Some cross-sectional studies have also suggested that female gender is associated with an increased risk of hospitalization for DKA, despite similar overall indices of glucose control. By contrast, recent US data reported higher incidence of DKA hospitalization in males, possible as male patients with T1D present at a younger age. By comparison, in our prospective and retrospective cohorts we saw no association between gender and DKA in Finnish adults with T1D. We have previously documented higher risk-taking behaviour (e.g. smoking and drinking excessively) in males with T1D and a higher risk of chronic complications of their diabetes (6, 17). However, after adjusting for confounding effects, gender appeared to play no role in incident DKA in our cohort.

In this study, we report for the first time a strong independent association between diabetic nephropathy, kidney function and DKA hospitalisation. In particular, a reduced eGFR (<60ml/min/1.73m^2) was associated with a higher risk of hospitalization for DKA. This association was independent of markers of glycaemic control which may also be disturbed in individuals with complications. It is also possible to speculate that the increasing incidence of DKA in Finnish adults with T1D over this time period was partly determined by the progressive decline in kidney function that occurred over the same time period. It is known that the kidney plays a key role in mitigating the effects of hyperglycaemia and ketonaemia, such that in individuals with renal impairment reduced renal excretion of excess ketones and glucose alongside impaired anion exchange, may facilitate progression to DKA. This is a particularly important observation, as many studies of the potential vasculoprotective effects of SGLT2 inhibitors in patients with T1D are now in planning

stages, and individuals with severely increased albumin excretion rates and/or reduced eGFR are the recruitment targets because of their high rate of renal and cardiovascular complications. It is now clear that this population also has an increased risk of hospitalization for DKA, making the use of SGLT2 inhibitors in this setting problematic. For example, there was a higher incidence of DKA (HR =1.6, p=0.01) in individuals with established CVD at baseline (i.e. the setting where SGLT2 inhibition has benefits for atherothrombotic MACE in type 2 diabetes (18)). This was entirely explained by increased prevalence of renal impairment in this setting.

The reason why elevated HDL cholesterol should be associated with DKA is unclear. It may be that HDL cholesterol is a marker of excessive alcohol intake. However, increased HDL cholesterol is also common in T1D, especially in women. It is thought to result from peripheral hyperinsulinemia and hyperadiponectinemia, leading to increased lipoprotein lipase activity which then enriches HDL with cholesterol following the hydrolysis of triglyceride-rich lipoproteins (19). We have previously described that the high HDL cholesterols subtype may be associated with an increased risk of chronic complications (20). It may also be that HDL cholesterol is a marker of other unmeasured risk factors in the diet, including ketogenic substrates (21).

A number of previous registry publications describing prevalence and incidence of DKA have been based on patient self-report and short recall periods. The key strength of our study is the longitudinal nature of the prospective and retrospective surveys, made possible through the tracking of a large number of individuals with T1D using the HILMO database that captures all hospital admissions across Finland and records the primary diagnosis. The use of ICD-10 and ICD-9 codes which provide for a specific code for DKA compared to ICD-8 in which DKA was included with coma is also advantageous.

Several study limitations also need to be considered. First, the criteria to distinguish between type 1 and type 2 diabetes used in the literature have not been validated although widely used. We used a cut-off of <40 years for age at onset of diabetes in order to minimize inclusion of patients with type 2 diabetes, insulin therapy initiation within one year as well as a C-peptide value <0.30 nmol/l to ensure insulin dependence. Secondly, we only examine hospital visits (to emergency departments, outpatients or admission) associated with a diagnosis of DKA (or death). We do not include any DKA events managed out of hospital. There may be bias in which patients are sent to hospital and which are managed out of hospital, including disease severity, comorbidity, independence etc. This is conceptually similar to the endpoint of hospitalisation for heart failure which does not include all acute HF events (e.g. HF treated in primary care). Nonetheless, it appears a valid surrogate for significant DKA events that are important to predict and prevent. Thirdly, our predictor studies are limited by reliance on data obtained from baseline and these factors may be less consistent over time, including changes in therapy, such as the initiation of CSII. Although we have obtained serial HbA1c data during follow-up, ongoing lipid control, alcohol use and incident renal impairment have not been incorporated into our analysis. Fourthly, these data are essentially observational, and although observational studies have a number of potential advantages, it is also possible that associations demonstrated in this study may be due to confounding by unmeasured factors or ones that are difficult to quantify. For example, DKA may be associated with a range of differences in metabolism that may themselves impact on adverse outcomes in diabetic individuals.

Fiftly, we have no measures of compliance and mental health which may both influence glucose control and the risk for DKA (22-24). Finally, FinnDiane is an enriched cohort of adults with T1D who have volunteered to take part in this project. Such willing participants may have different risks to those in the general population, although the frequency of DKA and annualised trends were similar in both cohorts.

Most DKA events are sudden, associated with a significant inter-current illness or stressor that liberates stress hormones including glucocorticoids, leptin, and growth hormone, which oppose the actions of (inadequate) insulin. Such inter-current illnesses are an unavoidable part of life. Even in adults with long-standing established T1D, such events can sometimes sporadically trigger DKA, even if there is no history of DKA events, poor glucose control, insulin pump failure or risk-taking behaviour. It is now clear that the potential risks for DKA never go away in T1D, even in individuals with no prior history of DKA. They may actually increase with time, particularly as renal function declines. More needs to be done to understand and mitigate these risks, and avoid these sudden serious events in adults with T1D who are normally well. This understanding is particularly important given the ketogenic actions of SGLT2 inhibitors which are beginning to be studied in type 1 diabetes.

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Figure legends

Figure 1. The increasing frequency in incidence of hospitalization for DKA or death from DKA between 1996 and 2015 in adults with T1D (A) participating in the FinnDiane study (n=4758) and (B) in adults with T1D from the Finnish general population (n=16,219). Black circles show annualised rates for all DKA hospitalisations (upper line) white circles (middle line) show annualized rates for a DKA hospitalization that occurred in an individual who subsequently experienced no further admissions for DKA (i.e. one-off admissions) and triangles (lower line) shows annualised DKA mortality rates. Dashed line shown mean with 95% upper and lower confidence intervals.

Figure 2. The cumulative incidence of first hospitalization for DKA following enrolment of adults with T1D into the FinnDiane study, stratified according to mean and variability (coefficient of variation, CV) of serial HbA_{1c} above and below the median.

Figure 3. The cumulative incidence of first hospitalization for DKA following enrolment of adults with T1D into the FinnDiane study, stratified according to diabetic nephropathy status at baseline (A) and to the presence of an eGFR<60 ml/min/1.73m^2 at baseline (B).

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Table 1. Baseline characteristics of adults with T1D from the Finn Diane study cohort, stratified according to incident DKA during follow-up after enrolment.

	No DKA events during the baseline visit until 2015, n=4,297	**At least 1 DKA event during the baseline visit until 2015 n=461**	**1 DKA event during the baseline visit until 2015 n=273**	**≥ 2 DKA events during the baseline visit until 2015 n=188**
Prior DKA (%) (1987-baseline) §	8.1	20.0*	19.2*	22.7*
Insulin pump therapy (%)	4.1	8.2 *	9.0*	7.1‡
Sex (female %)	47.4	48.4	51.4	49.2
Age (years)	37.9 (29.0-47.4)	38.2 (28.5-46.4)	38.7 (28.5-45.9)	36.3 (27.2-45.0)
Age at diabetes diagnosis (years)	14.3 (9.3-23.0)	13.5 (8.9-20.9) ‡	13.4 (9.0-20.9)	13.2 (7.8-20.8) ‡
Age at diagnosis of diabetes				
0-4	9.5	11.3	9.4	15.5
5-9	19.0	19.7	20.0	21.0
10-14	24.1	26.3	29.0	21.0
>=15	47.4	42.7	41.6	42.5 ‡
Duration of diabetes	21.4 (12.2-31.0)	23.1 (13.0-31.4)	22.9 (11.5-31.3)	22.8 (13.3-31.0)
HbA_{1c} (%)	8.3±1.4	9.1±1.7 *	8.9±1.6 *	9.5±1.9 *
Intra-individual mean of HbA_{1c} (%)	8.3 (7.6-9.1)	8.9 (8.1-9.9) *	8.8 (8.0-9.7) *	9.1 (8.4-10.3) *
Coefficient of variability in HbA_{1c}	0.09 (0.07-0.12)	0.11 (0.08-0.14) *	0.11 (0.08-0.14) *	0.11 (0.08-0.15) *
Smoking history (%) ||	45.8	58.8 *	61.2 *	53.2
Alcohol consumption (yes %)	72.1	72.5	75.8	66.4
Alcohol excess (yes %)	16.4	20.2	16.9	24.0 ‡
Alcohol consumption (g/week) ¶	48 (24-90)	60 (24-120) *	48 (24-120)	72 (36-144) *
Blue collar workers	50.0	55.1 ‡	54.7	53.6
without education	16.5	21.3	21.6	18.8
with education	33.5	33.8	33.1	34.8
White collar workers	24.5	21.3	21.2	23.8
lower	20.7	15.7	14.3	18.8
upper	8.3	5.6	6.9	5.0
Other or not known	25.5	23.6	24.1	22.6
Body Mass Index (kg/m^2)	25.1±3.7	24.4±3.6 *	24.5±3.5 ‡	24.0±3.4 *
Waist-to-hip ratio	0.87±0.09	0.87±0.08	0.87±0.08	0.87±0.08
Systolic blood pressure (mmHg)	134±19	136.±21	136±22	136±20

Diastolic blood pressure (mmHg)	79±10	80±11	79±10	82±11 †
Blood pressure lowering therapy (%)	42.4	52.7 *	50.2 ‡	53.6 †
Hypertension (%) #	56.0	62.5 †	59.6	64.1 ‡
Insulin dose/kg body weight (IU)	0.69±0.27	0.72±0.27 ‡	0.70±0.28	0.75±0.27 †
Estimated glucose disposal rate	6.3±2.5	5.6±2.4 *	5.8±2.4 †	5.3±2.3 *
Total cholesterol (mmol/l)	4.89±0.98	5.18±1.07 *	5.15±1.10 *	5.21±1.04 *
HDL cholesterol (mmol/l)	1.34±0.39	1.36±0.44	1.36±0.44	1.36±0.46
Triglycerides (mmol/l)	1.02 (0.77-1.46)	1.21 (0.85-1.80) *	1.21 (0.84-1.84) *	1.25 (0.82-1.79) *
Detectable C-peptide level (%)	21.9	18.3	22.2	13.4‡
Lipid lowering therapy (%) at baseline	15.8	16.5	16.3	16.0
Normoalbuminuria	61.9	48.4 *	51.2 *	45.9 *
Microalbuminuria	12.1	12.2	11.4	13.3
Macroalbuminuria	13.2	21.0	20.4	21.6
Albuminuria not known	5.1	7.1	6.4	7.6
ESRD	7.7	11.3	10.6	11.6
eGFR (ml/min/1.73m^2) ‡‡	95 (78-110)	94 (73-112)	95 (74-112)	93 (66-112)
eGFR< 60 ml/min/1.73m^2 (%) ‡‡	10.8	17.9 *	18.7	18.1 †
SDR, laser treatment (%)	33.7	43.5 *	39.5	47.2 *
CVD (%) #	6.3	7.6	6.6	9.0
hs-CRP (mg/L)	4.42±8.98	5.40±11.01	5.55±12.43	5.42±9.66

Abbreviations: DKA – diabetic ketoacidosis; ESRD – end-stage renal disease; eGFR – estimated glomerular filtration rate using CKD-EPI formula; SDR – severe diabetic retinopathy; hs-CRP – high sensitive CRP. *P <0.001, †P <0.01, ‡P <0.05 for comparison with no DKA; § Prior hospitalization for DKA as an adult (aged >18 years) and after the first two years of diabetes; || Smoking history was defined as smoking at least 1 cigarette per day for at least 1 year; ¶ among those who consume any alcohol; # Hypertension defined as either systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90, based on the average of 2 measurements, or any use of antihypertensive medication;‡‡ Patients with ESRD excluded; # includes coronary artery disease and stroke

Table 2. Independent predictors of incident DKA in adults with T1D during the FinnDiane study cohort prospective follow-up period identified using Cox-regression analysis. Patients with ESRD at baseline were excluded for this analysis.

	Hazard ratio	**95% CI**	**p-value**
Prior history of DKA (yes)	2.05	1.58-2.67	<0.0001
Insulin pump therapy (yes)	2.44	1.60-3.72	<0.0001
Smoking history (yes)	1.31	1.04-1.66	0.02
Weekly alcohol consumption (per 10g)	1.02	1.01-1.03	0.002
Serial HbA1c (%)	1.48	1.35-1.62	<0.0001
HbA1c variability (per 10 percentage points)	1.31	1.07-1.61	0.01
HDL cholesterol (mmol/L)	1.82	1.36-2.45	<0.0001
Triglycerides (mmol/L)	1.15	1.03-1.29	0.01
eGFR<60 ml/min/1.73m^2 (yes)	1.71	1.26-2.67	<0.0001