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Original Research

Risk Factors for Recurrent Diabetic Ketoacidosis in Adults With Type 1 Diabetes



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Key Messages

- Some risk factors for recurrent diabetic ketoacidosis have been reported, but no study has addressed this question in the adult Canadian population.
- Nonadherence to insulin therapy and, possibly, also psychiatric comorbidities were identified as independent risk factors for recurrent diabetic ketoacidosis in our cohort.
- These are potential targets for the prevention of this complication.

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ABSTRACT

Objectives: Identification of risk factors for recurrent diabetic ketoacidosis (DKA) in patients with type 1 diabetes could help target those at high risk so as to implement preventive measures. The main objective of this study was to identify factors associated with recurrent DKA in adult Canadian patients with type 1 diabetes.

Methods: This is a retrospective cohort study of adult patients who had a diagnosis of type 1 diabetes for at least 1 year and who were hospitalized for an isolated or recurrent DKA episode between January 2007 and January 2017 in 5 Québec City tertiary care hospitals. Factors associated with recurrent DKA in bivariate logistic regression with a p value <0.1 were included in a multivariate analysis. Results are reported as odds ratios (OR) and 95% confidence intervals (CI).

Results: We included 212 patients who met the inclusion criteria. Of these, 141 and 71 had an isolated episode or recurrent DKA episodes, respectively. Problems of alcohol or illicit drug abuse (OR 2.81; 95% CI 1.55 to 5.07; $p<0.01$) and higher glycated hemoglobin levels (OR 1.26; 95% CI 1.08 to 1.47; $p<0.01$) were associated with recurrent DKA in bivariate analysis. However, only nonadherence to insulin therapy (OR 26.29; 95% CI 1.78 to 388.5; $p=0.02$) was significantly associated with recurrent DKA in the multivariate analysis, although a diagnosis of psychiatric illness was possibly another risk factor (OR 2.72; 95% CI 0.94 to 7.89; $p=0.06$).

Conclusions: Interventions targeting adherence to insulin therapy, and possibly also psychiatric illness, could help reduce recurrent DKA in patients with type 1 diabetes.

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R É S U M É

Objectifs : L'identification des facteurs de risque d'acidocétose diabétique (ACD) récidivante chez les patients atteints de diabète de type 1 pourrait contribuer à cibler les patients exposés à un risque élevé de façon à mettre en œuvre des mesures préventives. L'objectif principal de la présente étude était d'identifier les facteurs associés à l'ACD récidivante chez les patients adultes canadiens atteints de diabète de type 1.

Mots clés :

acidocétose diabétique

facteurs de risque

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Méthodes : Il s'agit d'une étude rétrospective d'une cohorte de patients adultes qui avaient un diagnostic de diabète de type 1 depuis au moins 1 an et qui étaient hospitalisés en raison d'un épisode isolé d'ACD ou d'épisodes récidivants d'ACD entre janvier 2007 et janvier 2017 dans 5 hôpitaux de soins tertiaires de la ville de Québec. Les facteurs associés à l'ACD récidivante dans le modèle bivarié de régression logistique dont la valeur p était $< 0,1$ étaient inclus dans une analyse multivariée. Les résultats sont rapportés en ratios d'incidence approchés (RIA) et en intervalles de confiance (IC) à 95 %.

Résultats : Nous avons sélectionné 212 patients qui répondaient aux critères d'inclusion. Parmi ces derniers, 141 et 71 avaient respectivement eu soit un épisode isolé d'ACD soit des épisodes récidivants d'ACD. Dans l'analyse bivariée, les problèmes d'alcool ou l'abus de drogues illicites (RIA 2,81; IC à 95 % de 1,55 à 5,07; $p < 0,01$) et les concentrations plus élevées d'hémoglobine glyquée (RIA 1,26; IC à 95 % de 1,08 à 1,47; $p < 0,01$) étaient associés à l'ACD récidivante. Toutefois, dans l'analyse multivariée, seule la non-observance à l'insulinothérapie (RIA 26,29; IC à 95 % de 1,78 à 388,5; $p = 0,02$) était associée de manière significative à l'ACD récidivante, quoiqu'un diagnostic de maladie psychiatrique était possiblement un autre facteur de risque (RIA 2,72; IC à 95 % de 0,94 à 7,89; $p = 0,06$).

Conclusions : Les interventions qui visent l'observance à l'insulinothérapie, et possiblement la maladie psychiatrique, pourraient aider à réduire l'ACD récidivante chez les patients atteints de diabète de type 1.

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Introduction

Diabetic ketoacidosis (DKA) is a dramatic, acute metabolic complication of type 1 diabetes. The reported incidence rate of DKA varies between 4.6 and 8.0 cases per 1,000 person-years, representing 5,000 to 10,000 hospital admissions annually in Canada (1). Despite prevention efforts made by health-care professionals, notably through education, a large number of patients with type 1 diabetes suffer from repeated (>1) episodes of DKA. This condition is not only potentially fatal, with an estimated mortality rate between 4% and 10% (1,2), but it also consumes important health-care resources, with an estimated yearly cost of \$2.4 billion for DKA-related hospital admissions in the United States (2).

Apart from missed or inadequate insulin dosing, classically recognized precipitating factors for DKA are newly diagnosed diabetes, infection and other acute medical conditions, such as stroke, pancreatitis and acute coronary syndrome (1). Previous studies that examined risk factors for recurrent DKA in patients with type 1 diabetes found that nonadherence to insulin therapy was, unsurprisingly, the most important (3–8). Young age (8,9), history of depression or psychological problems (4,8,9) as well as alcohol and illicit drug use (4,7,9) have also been identified. Finally, low socioeconomic status (2,6,8,9), ethnic minority status (2,6,7) and lack of private insurance coverage (2,9) were identified as additional risk factors. Identification of factors contributing to recurrent DKA in patients with type 1 diabetes is essential to implement preventive measures that target patients at high risk for recurrence. To our knowledge, no study has addressed this question in the Canadian context, which is relevant because risk factors for recurrent DKA may be specific to our population of patients with type 1 diabetes who have universal access to a public health-care system. Therefore, the main objective of this study was to identify risk factors for recurrent DKA in Canadian adults with type 1 diabetes. Exploratory aims were to assess whether duration of hospital stay, presence of psychological support or education provided by a nurse specializing in diabetes care, all-cause mortality and age at the time of death differed between patients with isolated vs. recurrent DKA episodes.

Methods

Study design and patient selection

We conducted a retrospective cohort study comparing patients who experienced an isolated episode vs. recurrent episodes of DKA. We reviewed the electronic files of all patients who were hospitalized for a DKA episode between January 1, 2007, and January 1,

2017, at the Centre Hospitalier Universitaire de Québec-Université Laval, a network of 5 tertiary care hospitals in Québec City, Québec. Inclusion criteria were a hospital admission for DKA, being at least 18 years of age and having a diagnosis of type 1 diabetes for at least 1 year. Exclusion criteria were a diagnosis of any other type of diabetes, DKA being the initial presentation of a new diabetes diagnosis, and nonautonomy in the management of diabetes (e.g. residing in a long-term care facility). There are no official diagnostic criteria for DKA (10). The main elements are high anion gap, metabolic acidosis, hyperglycemia and ketonemia. Hyperventilation in response to metabolic acidosis commonly decreases the partial pressure of carbon dioxide and, therefore, can result in metabolic acidosis with a normal pH (1).

The following biochemical criteria were, thus, used to confirm a diagnosis of DKA: plasma glucose superior or equal to 10 mmol/L, pH inferior or equal to 7.35 and bicarbonate inferior or equal to 15 mmol/L. If the pH and/or the bicarbonate were normal, but the anion gap was superior to 15 with an appropriate reduction of pCO_2 , testifying to the presence of a respiratory compensation, the episode was classified as DKA.

Data collection

The following information was collected from the electronic records of the patients who met the inclusion criteria: sex, age at the time of the DKA episode, presence of a diagnosis of psychiatric illness, eating disorder, alcohol abuse and/or illicit drug use, low socioeconomic status (defined as the absence of work-related income, which needed to be specifically noted in the medical file), ethnic minority status (non-Caucasian), nonadherence to the insulin treatment specified in the patient's medical record and the result of glycated hemoglobin (A1C) level on admission (or in the 3 months preceding the admission). Age at the time of diagnosis, duration of diabetes, presence of microvascular or macrovascular complications, daily insulin dose, insulin regimen (multiple injections or insulin pump), body mass index, presence of disease-related precipitating factors for DKA, neurocognitive disorder (including neurodegenerative disorders and intellectual disability), pregnancy and ongoing corticosteroid treatment during the DKA episode were also collected. Finally, data on duration of the hospital stay, psychosocial support offered during the hospitalization and education provided by a nurse specializing in diabetes care during the hospitalization or in the 6 following months were compiled. Death from any cause and at any point between the studied DKA episode and the time of the medical record review and age at the time of death were also retrieved.

Statistical analyses

We divided the patient cohort into 2 groups according to the presence of an isolated DKA episode or recurrent DKA episodes during the time of the study. For the group with recurrent DKA, only the second episode was considered. This choice was based on the consideration that patients with a first recurrence are probably newly exposed to the risk factors that predisposed them to another DKA episode. Baseline characteristics of the 2 groups, as well as duration of hospital stay and psychological support or nurse education provided during the hospitalization were compared using the Student *t* test for continuous variables, with correction for inequality of variances when appropriate, and the exact Pearson chi-squared test was used for categorical variables. A bivariate logistic regression was performed to evaluate the association between potential risk factors and recurrence of DKA. Variables that were found to be associated with recurrence of DKA in the bivariate model with a *p* value <0.1 were then entered simultaneously in a multivariate logistic regression model to identify independent factors associated with recurrence of DKA. Statistical significance was defined as a *p* value <0.05. Finally, the Wilcoxon Mann-Whitney test was used to determine whether there was a difference between the 2 groups regarding age at the time of death and the time elapsed between the last DKA episode and death.

Results

We reviewed 315 electronic medical records between August 2017 and April 2018. Of these, 212 patients met the inclusion criteria and were included in the statistical analyses (Supplementary Figure 1). The main reasons for exclusion were DKA as the first manifestation of diabetes, conditions that did not meet the DKA biochemical criteria or a diagnosis of type 2 diabetes or pancreatogenic diabetes.

Comparison of patients' characteristics according to the presence of isolated or recurrent DKA

Of the 212 included patients, 141 had isolated episodes of DKA (iDKA), and 71 had recurrent episodes (rDKA). Several characteristics were similar between the iDKA and the rDKA groups, including age, prevalence of low socioeconomic status and ethnicity, prevalence of eating disorders and duration of diabetes (Table 1). However, several differences were observed between the groups. Indeed, insulin pumps were used less commonly in the rDKA group. Moreover, psychiatric illness and alcohol abuse and/or illicit drug use were more prevalent, whereas acute illness held responsible for the DKA episode was found less commonly in patients in the rDKA group. Gastroenteritis, pneumonia and material dysfunction were the acute conditions most frequently encountered. In addition, poor adherence to insulin therapy was more common, and A1C levels were higher in the rDKA group. Finally, there was a nonsignificant trend toward a predominance of men in the rDKA group.

Risk factors associated with recurrent DKA in bivariate and multivariate analyses

In the bivariate logistic regression, poor adherence to insulin therapy (OR 6.10, 95% CI 2.60 to 14.27; *p*<0.01); higher mean A1C levels (OR 1.26, 95% CI 1.08 to 1.47; *p*<0.01); the presence of psychiatric illness (OR 2.84, 95% CI 1.56 to 5.16; *p*<0.01) or alcohol abuse and/or illicit drug use (OR 2.81, 95% CI 1.55 to 5.07; *p*<0.01), lower use of an insulin pump (OR 0.12, 95% CI 0.02 to 0.92; *p*=0.04); and a disease-related precipitating factor for the DKA episode (OR 0.44; 95% CI 0.24 to 0.79; *p*<0.01) were identified as risk factors for

Table 1

Comparison of patients' characteristics according to the presence of isolated or recurrent DKA

	Recurrent DKA (n=71)	Isolated DKA (n=141)	<i>p</i> value*
Age at DKA episode, years	36.0±12.2	37.7±15.2	0.41
Men, %	60.6	47.5	0.08
Non-Caucasian, %	2.8	2.8	1.0
Body mass index, kg/m ²	23.3±3.4	24.4±4.7	0.19
Low socioeconomic status, %	40.0	29.2	0.25
Age at diabetes diagnosis, years	17.9±11.7	18.3±11.2	0.79
Duration of diabetes, years	17.8±12.6	19.2±13.6	0.48
Microvascular complications, %	47.9	42.6	0.47
Macrovascular complications, %	12.7	23.4	0.07
Insulin regimen, %			
Multiple injections	98.6	89.3	0.02
Insulin pump	1.4	10.7	
Total daily insulin dose, units/day	58.1±20.5	56.3±24.8	0.62
A1C, %	11.1±2.0	10.0±2.1	<0.01
Precipitating factor for DKA episode, %	35.2	55.3	<0.01
Poor adherence to insulin therapy, %	90.1	60.0	<0.01
Corticosteroid use during DKA episode, %	2.8	5.0	0.51
Pregnancy during DKA episode, %	3.6	4.1	1.0
Psychiatric illness, %	49.3	25.5	<0.01
Eating disorder, %	1.4	2.1	1.0
Neurocognitive disorder, %	1.4	7.8	0.06
Alcohol abuse and/or illicit drug use, %	53.5	29.1	<0.01

A1C, glycated hemoglobin; DKA, diabetic ketoacidosis.

Note: Data are mean ± SD or %.

* Based on the Student *t* test or the chi-squared test, as appropriate.

rDKA (Table 2). However, only poor adherence to insulin therapy remained statistically significant in the multivariate regression analysis (OR 26.29; 95% CI 1.78 to 388.5; *p*=0.02), although a trend was observed for psychiatric illness (OR 2.72; 95% CI 0.94 to 7.89; *p*=0.06).

Length of hospitalization and psychological support or diabetes education received

Characteristics related to the hospitalization were similar between groups, with a mean stay of 96.7 h in the rDKA group and 119.0 h in the iDKA group. Psychosocial support was offered to 26% of patients, and 50% received education from a nurse specializing in diabetes care, regardless of the group.

Mortality

Mortality from any cause and at any point between the studied DKA episode and the time of the medical record review was not statistically different between the rDKA and iDKA groups (19.7% vs. 14.2%; OR 1.49; 95% CI 0.70 to 3.15; *p*=0.302). However, patients in the rDKA group died approximately 10 years younger than those in the iDKA group (43.7 vs. 53.1 years old; *p*=0.08), although this difference was not statistically significant. They also died more closely to their last episode of DKA (17 months vs. 28 months; *p*=0.31). The causes of death were unknown in half of the patients, but among those with known causes, cardiovascular disease was the leading cause, accounting for 23.5% of the total deaths. That was followed by infection and cancer, with a prevalence of 8.8% each (Supplementary Table 1).

Discussion

In our adult population with type 1 diabetes, patients with rDKA were more likely to be nonadherent to insulin therapy and to have a psychiatric illness, a problem of alcohol or illicit drug abuse and

Table 2
Bivariate and multivariate analyses of risk factors for recurrent DKA

	Bivariate analysis*		Multivariate analysis [†]	
	OR (95% CI)	p value	OR (95% CI)	p value
Sex (men)	1.70 (0.95–3.03)	0.07	0.91 (0.29–2.82)	0.87
Macrovascular complications	0.48 (0.21–1.06)	0.07	0.98 (0.20–4.82)	0.98
Insulin regimen (pump)	0.12 (0.02–0.92)	0.04	0.21 (0.01–9.17)	0.42
Precipitating factor for DKA episode	0.44 (0.24–0.79)	<0.01	0.97 (0.35–2.68)	0.95
Poor adherence to insulin therapy	6.10 (2.60–14.27)	<0.01	26.29 (1.78–388.5)	0.02
A1C	1.26 (1.08–1.47)	<0.01	1.20 (0.93–1.55)	0.16
Psychiatric illness	2.84 (1.56–5.16)	<0.01	2.72 (0.94–7.89)	0.06
Neurocognitive disorder	0.17 (0.02–1.33)	0.09	0.14 (0.01–3.53)	0.23
Alcohol abuse and/or illicit drug use	2.81 (1.55–5.07)	<0.01	1.63 (0.56–4.69)	0.37

A1C, glycated hemoglobin; CI, confidence interval; DKA, diabetic ketoacidosis; OR, odds ratio.

* Bivariate logistic regression with Wald confidence interval (only the factors with p values <0.1 are presented).

[†] Multivariate logistic regression with FIRTH correction, including all factors with p values <0.1 in the bivariate logistic regression.

higher A1C levels prior to the DKA episode. On the other hand, they were less likely to have an identified disease-related precipitating factor for DKA and to use insulin pump therapy compared with those with iDKA. Moreover, poor adherence to insulin treatment was the strongest and only risk factor identified in the multivariate analysis. Regarding our exploratory aims, we found the 2 groups to be similar with regard to the durations of hospital stay, the presence of psychological support and the education provided by a nurse specializing in diabetes care. Patients with recurrent DKA were more likely to die younger than those with isolated episodes, although the numbers were not statistically significant.

As identified by previous studies, poor adherence to insulin treatment was the predominant risk factor for rDKA in our study (4–9). Higher mean A1C levels in the rDKA group, usually a reflection of poor adherence, support this association. Similarly, the fact that the prevalence of patients using insulin pumps was higher in the iDKA group is probably related to their better adherence, which is usually required to access this technology in our local population. Education may also play a role; patients using insulin pumps are generally well educated about diabetes and how to prevent DKA. The lower prevalence of disease-related precipitating factors in the rDKA group is probably linked to the fact that poor adherence to insulin treatment is the main precipitating factor leading to DKA in the rDKA group. It is noteworthy that in children with type 1 diabetes, being female and having poor family functioning were associated with increased DKA risk (11). However, in our adult population, sex was not identified as a risk factor for recurrent DKA and, unfortunately, information about family functioning was not collected.

Despite ongoing efforts to improve patients' education, a study by Randall et al still showed that many patients do not know how to adjust their diabetes treatment during sick days, even if most of them had received education about diabetes (4). Furthermore, the mean Patient Health Questionnaire-9 score, a depression scale, was suggestive of mild to moderate depression in patients who had at least 1 DKA episode (4). In line with this observation, the prevalence of depression was reported to be higher in patients with type 1 diabetes compared to individuals without diabetes (12,13). In addition, a diagnosis of mental illness was associated with poorer adherence to treatment for diabetes (14), which can result in

increased rates of complications, including DKA. It is, thus, essential to address this psychological dimension during the follow-up of patients with type 1 diabetes while reassessing the need for further education in the management of their disease. In this regard, a study by Simmons et al concludes that the cost of hospitalization for acute glycemic events could be reduced by a multidisciplinary approach involving both diabetes and mental health specialists (3). Moreover, it has been shown that even with the high cost associated with multidisciplinary approaches, long-term reductions in expenses for the health-care system were possible (4).

In our study, even if as much as 49% of the rDKA patients had histories of psychiatric illness, and 54% were involved with alcohol abuse and/or illicit drug use, psychosocial support was offered to only 26% of them. This low percentage of psychosocial support offered may be the result of a lack of resources in our health-care facilities, but lack of awareness of the negative impacts of these comorbidities on DKA risk may have played a more important role. Unfortunately, we could not find in the literature a study providing such data in a similar population so we could compare our low rate of psychological and educational interventions.

As in preceding studies, our results point toward an association between these comorbidities and risk for recurrent DKA (4,7–9). Our results are also in line with previous findings showing an association between diagnosis of mental illness and poor adherence to the treatment of diabetes (14) that could lead to recurrent DKA. We can presume that reducing the impact of these risk factors by offering more psychosocial support to patients could enhance diabetes control and lower the risk for DKA.

Our analysis has not been able to demonstrate a statistically different incidence of mortality between the rDKA and the iDKA groups. However, it showed a surprisingly high incidence of death in both groups (20% and 14%) during the study period, with a young age at the time of death (43.7 vs. 53.1 years of age). Even considering that death was not necessarily related to diabetes, this seems to indicate that patients with type 1 diabetes and at least 1 episode of DKA over a 10-year period may have reduced life expectancies. Moreover, patients with recurrent DKA died, on average, 10 years younger than patients with isolated episodes and closer to their last episode, even though that finding was not statistically significant. This highlights that DKA is a severe condition and suggests that better control of diabetes and prevention of DKA might reduce mortality and, possibly, also address psychological distress.

The principal strengths of our study include the long observation period and the methodical review of the medical records, with confirmation that each DKA episode fulfilled the pre-established inclusion and exclusion criteria. Also, it is the first observational study done in the adult population of the province of Quebec for DKA risk factors, and the inclusion of 5 different hospitals in the same living area minimized the risk of selection bias.

The main limitation of our study, except for its retrospective design, is a possible classification bias attributable to the pre-determined period of observation for events; some patients may have presented with DKA episodes before 2007 or after 2017 and were not considered. The impact of this limitation was minimized by our prolonged period of observation of 10 years. Some patients could also have been hospitalized in other health centres, but the risk of missing such episodes was reduced by the data collection from 5 different hospitals that offer care to most of the Quebec City population. Also, there may be an ascertainment bias for insulin nonadherence because physicians are more likely to ask whether there was insulin nonadherence when a patient presents with a DKA episode. However, this bias was the same in both groups, and nonadherence was checked in the files, regardless of whether the episode was unique or isolated.

Furthermore, the low prevalence of some risk factors in our population (e.g. ethnic minority status and eating disorders) did

not allow us to draw any conclusions with regard to their impacts on the risk for recurrent DKA. Insulin omission related to weight control that does not meet the Diagnostic and Statistical Manual of Mental Disorders criteria for eating disorders is a frequently reported condition in young women with type 1 diabetes (15). Data concerning this condition were not specifically collected in our study. Nonetheless, disordered eating behaviour was associated with higher A1C levels and more microvascular complications in female adolescents with type 1 diabetes in Rydall's prospective study (16) and could be an interesting potential risk factor for DKA in future research. Missing data were minimal, except for socioeconomic status since the patient's work-related income was not often reported. A prospective study over a longer period of time, in which the data would be systematically collected, would help to reduce missing data, thus improving the statistical power of the results. Finally, because we did not study our overall population with type 1 diabetes, including those who never had DKA episodes, we cannot conclude whether these risk factors bring higher DKA risks in all adults with type 1 diabetes in the Quebec City area.

Conclusions

DKA is a dramatic complication of type 1 diabetes that is responsible for an important human and socioeconomic burden. Current evidence regarding effective prevention initiatives is scarce. Identifying risk factors for recurrent DKA in our population was the first step toward the development of targeted actions for the prevention of this complication. In light of our results, we believe that nonadherence to insulin therapy and psychiatric comorbidities are important risk factors to address in preventive interventions. Future prospective studies measuring the impact of such interventions on the risk for recurrent DKA are needed to help prevent this complication and reduce its associated negative outcomes.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at <https://www.canadianjournalofdiabetes.com>.

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Author Disclosures

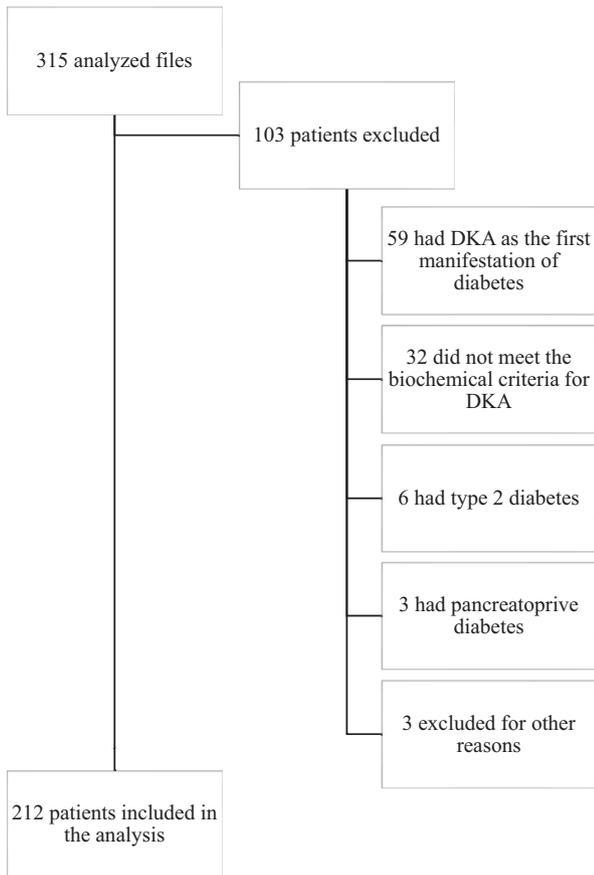
GB has received speaker honoraria from Johnson & Johnson, Abbott, Medtronic and AstraZeneca; CG has received speaker honoraria from Eli Lilly and Janssen; all other authors report no conflicts of interest.

Author Contributions

GB initiated the idea and contributed to the literature review and the conception and design of the study; SDD contributed to the literature review, the conception and design of the study, the acquisition of data and the writing of the manuscript; FD contributed to the acquisition of data and the writing of the manuscript; all authors reviewed and edited the manuscript.

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Supplementary Figure 1. Flow chart.

Supplementary Table 1
Frequency of causes of death

Cause of death	n	%
Diabetic ketoacidosis	1	2.9
Cancer	3	8.8
Hypoglycemia	1	2.9
Unknown	17	50.0
Infection	3	8.8
Cardiovascular disease	8	23.5
Bleeding	1	2.9