Predictors of the Effectiveness of Insulin Pumps in Patients with Type 1 Diabetes Mellitus

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Research Article

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Abstract

Purpose

Insulin pump therapy has become the preferential treatment for type 1 diabetes (T1D) as it mimics the physiological secretion of insulin better than multiple daily injections. However, not all patients improve with insulin pump therapy. This study aims to determine the predictors of the effectiveness of insulin pumps in T1D.

Methods

We conducted a retrospective observational study of patients who started insulin pumps. Data from four timepoints (before, at 6, 12 and 36 months) were evaluated for outcomes of glycemic control and safety. The association of baseline predictors with outcomes was analyzed using linear and logistic regression models.

Results

We evaluated 136 patients (57.4% females, age 36 ± 12 years, duration of T1D 14 ± 9 years). During the follow-up, there was a mean decrease of HbA1c of 0.9 ± 1.2%. The improvement in HbA1c was independent of sex, age and duration of T1D. Higher baseline HbA1c, family history of diabetes and not being treated with statins were predictors of improvement in HbA1c. Not being treated with statins and higher baseline HbA1c predicted improvement in HbA1c without worsening hypoglycemia. History of hypoglycemia was a predictor of severe hypoglycemia. Family history, higher baseline HbA1c and psychological/psychiatric disorders were predictors of ketoacidosis.

Conclusion

Benefits of insulin pump were independent of sex, age, and duration of T1D. Baseline HbA1c, family history of diabetes, treatment with statins, history of hypoglycemia and psychological/psychiatric disorders were predictors of outcomes and may allow the identification of patients who benefit most from insulin pump therapy or who are at increased risk of complications.

Introduction

Type 1 Diabetes (T1D) represents 10–15% of all diabetes cases [1]. It is a chronic autoimmune disease that results from the interaction of genetic, environmental and immunological factors [2]. T1D is characterized by destruction of pancreatic beta cells, which causes an absolute or almost absolute deficiency in endogenous insulin production [3, 2].
Patients with T1D are at risk of acute (diabetic ketoacidosis and severe hypoglycemia) and chronic complications of diabetes (macrovascular, microvascular and other complications). Proper management of hyperglycemia is essential to decrease the risk of acute and long-term complications [4–6]. Intensive glucose treatment decreases the risk of microvascular complications [7] and may decrease the risk of macrovascular complications on the long-term follow-up. [8] However, most patients with T1D have poor glycemic control [9], and acute and chronic complications are still frequent in patients with T1D [10, 11].

The objective of treatment in T1D is to mimic the physiological secretion of insulin. The insulin dose to be administered must be adjusted considering glycemia, diet and physical activity [12, 13]. Intensive treatment of T1D can be divided in two main strategies: multiple daily injections and insulin pump therapy. The latter is frequently considered the preferred strategy for glycemic control, since it is the one that most accurately can mimic the physiological action of the pancreas [14, 15]. Insulin pump therapy is more expensive but allows more flexible adjustments on basal insulin rates and on the types of insulin bolus [15]. Over the past 20 years, there have been several improvements in insulin pumps, ensuring greater reliability of the technology resulting in an increasing use of insulin pump therapy [16]. However, the evidence showing the superiority of one form of treatment over the other is still limited [17].

Several studies have shown improvements in glycemic control with transition from multiple daily injections to insulin pump therapy [18, 17, 19]. However, this improvement is not observed in all patients [10], and some may worsen or have more acute complications after transitioning to insulin pump therapy [11]. The reason why some patients improve glycemic control with this treatment while others do not improve is not yet fully established. The aim of this study was to determine which predictors are related to the effectiveness of insulin pumps in patients with T1D previously treated with multiple daily injections.

Materials And Methods

Study Design and Participants

We conducted a retrospective longitudinal observational study, at the Department of Endocrinology, Diabetes and Metabolism of the Centro Hospitalar Universitário de São João (CHUSJ) in Porto, Portugal, to determine which predictors influence the effectiveness of insulin pump therapy in patients with T1D. The presented investigation was approved by the Ethics Committee of CHUSJ/Faculty of Medicine of the University of Porto.

Data was retrospectively collected from clinical records at four different timepoints: before transitioning to insulin pump therapy, and at 6 months, 12 months and 36 months after starting therapy with insulin pump.

We included patients with T1D that started therapy with insulin pump between 2005 and 2020, that were followed for at least 6 months after starting insulin pump and were 18 years-old or older in the last time point assessed. No patient was using sensor-augmented pumps during the evaluation period. Patients
with missing data on baseline demographics, baseline HbA1c or all follow-up HbA1c levels were excluded from our analysis. Data were collected until the end of February 2021.

In February 2021, 300 patients were being treated with insulin pump at CHUSJ. Fifteen additional patients had started this therapy between 2005 and 2020 at CHUSJ and were no longer followed at CHUSJ. From the 315 identified patients, 149 were excluded as they had less than 18 years-old during the entire follow-up period, 18 due to insufficient information on the clinical records and 12 because they were treated with insulin pump for less than 6 months. As a result, a total of 136 patients were included in the present analysis.

Assessment of Predictors

The following clinical parameters were collected from clinical records at baseline (less than one year before starting insulin pump therapy) and assessed as predictors of outcomes: sex, age, duration of diabetes, education (less than 12th grade, 12th grade, or higher education), start of insulin pump therapy in pediatric or adult setting, family history of diabetes, exercise practice (any intensity), current smoking, alcohol consumption (any consumption); diagnosis of diabetic retinopathy (by ophthalmologic evaluation), diabetic nephropathy [defined as urine albumin to creatinine ratio (ACR) greater than 30mg/g creatinine or eGFR < 60 ml/min/1.73m² (CKD-EPI formula)], diabetic neuropathy (defined as diagnosis of any form of diabetic neuropathy reported in clinical record), history of coronary artery disease, cerebrovascular disease, peripheral vascular disease; diagnosis of hypertension, autoimmune thyroiditis, history of psychological or psychiatric disorder (including anxiety, depression, eating behavior disorder, obsessive-compulsive disorder and attention-deficit/hyperactivity syndrome); treatment with statins; body mass index (BMI); HbA1c, lipid profile (total cholesterol, HDL, LDL, triglycerides), TSH level, estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI equation), urine albumin to creatinine ratio (ACR); occurrence of hypoglycemia (defined as episodes of glucose < 70 mg/dL reported in clinical record), history of severe hypoglycemia (defined as hypoglycemia requiring external assistance for recovery), and history of diabetic ketoacidosis.

Study Outcomes

The main outcomes of the present study were: variation of HbA1c (difference between mean HbA1c at follow-up evaluations and HbA1c at baseline), improvement of HbA1c (defined as mean HbA1c at follow-up evaluations lower than baseline HbA1c), improvement of HbA1c without worsening hypoglycemia (worsening hypoglycemia was defined as occurrence of hypoglycemia at any follow-up time in participants without hypoglycemia at baseline), improvement of hypoglycemia (defined as absence of hypoglycemia at all follow-up times in participants with hypoglycemia at baseline), and improvement of hypoglycemia without worsening of HbA1c (worsening of HbA1c defined as mean HbA1c at follow-up evaluations higher than baseline HbA1c).

Additionally, we considered as safety outcomes: occurrence of hypoglycemia after starting insulin pump therapy (episodes of glucose < 70 mg/dL), severe hypoglycemia after starting insulin pump therapy (any
hypoglycemia requiring external assistance for recovery after starting insulin pump therapy) and diabetic ketoacidosis after starting insulin pump therapy.

**Statistical Analysis**

The association of predictors with study outcomes was evaluated using linear regression (for continuous outcomes) and logistic regression (for dichotomic outcomes). We also performed adjusted analysis including in the linear and logistic regression models all predictors that were statistically significant for each outcome. Due to non-normal distribution, triglycerides and ACR were log-transformed for inclusion in regression models. Adjusted models were not evaluated for severe hypoglycemia and ketoacidosis after starting insulin pump therapy due to low number of events (< 10 events). For graphical representation, we divided into three categories the variables age (< 18 years, 18–40 years and > 40 years) and duration of T1D (< 10 years, 10–20 years and > 20 years).

Continuous variables are described as mean ± standard deviation or median (25th-75th percentiles) and categorical variables as proportions (percentages).

A two-sided p-value of < 0.05 was considered statistically significant. Analyses were performed with Stata (version 14.2).

**Results**

Baseline characteristics of the 136 patients included in the analysis are shown in Table 1. The mean (± standard deviation) age was 36 ± 12 years and 57.4% were women. Fifty-nine percent had 12th grade and 29.6% had higher education. The mean duration of the disease was 14 ± 9 years. Thirty-seven percent had a positive family history of diabetes. Regarding microvascular complications, 28.6% had diabetic retinopathy, 18.8% diabetic nephropathy and 9.8% diabetic neuropathy. Fourteen percent had a history of severe hypoglycemia and 6.1% had history of diabetic ketoacidosis.
Table 1
Baseline characteristics (n = 136)

| Male sex, n (%) | 58 (42.6%) |
|----------------|------------|
| Age, years     | 36.0 ± 12.2|
| Duration of diabetes, years | 14.1 ± 9.3 |
| Educational level, n (%) | |
| Less than 12th grade | 8 (11.3%) |
| 12 years       | 42 (59.2%) |
| Higher education | 21 (29.6%) |
| Pediatric age at onset of insulin pump, n (%) | 25 (18.4%) |
| Family history of diabetes, n (%) | 46 (37.1%) |
| Hypertension, n (%) | 20 (15.3%) |
| Treatment with statins, n (%) | 34 (25.6%) |
| Autoimmune thyroiditis, n (%) | 30 (22.6%) |
| Current smoking, n (%) | 27 (20.3%) |
| Alcohol consumption, n (%) | 15 (11.4%) |
| Psychological / psychiatric disorders, n (%) | 36 (27.1%) |
| Hypoglycemia, n (%) | 126 (97.7%) |
| History of severe hypoglycemia, n (%) | 18 (13.5%) |
| History of diabetic ketoacidosis, n (%) | 8 (6.1%) |
| Diabetic neuropathy, n (%) | 13 (9.8%) |
| Diabetic retinopathy, n (%) | 38 (28.6%) |
| Diabetic nephropathy, n (%) | 25 (18.8%) |
| Coronary artery disease, n (%) | 0 (0%) |
| Cerebrovascular disease, n (%) | 0 (0%) |
| Peripheral vascular disease, n (%) | 1 (0.8%) |
| Exercise practice, n (%) | 56 (60.2%) |
| BMI\(^a\) kg/m\(^2\) | 24.2 ± 3.6 |
| HbA1C, % | 8.3 ± 1.5 |
Baseline characteristics of study population before starting insulin pump therapy. 

| Male sex, n (%) | 58 (42.6%) |
|----------------|-----------|
| Total cholesterol, mg/dL | 179.4 ± 32.4 |
| LDL<sup>b</sup> cholesterol, mg/dL | 104.4 ± 26.4 |
| HDL<sup>c</sup> cholesterol, mg/dL | 57.6 ± 13.3 |
| Triglycerides, mg/dL | 76.0 (58.0, 112.0) |
| eGFR<sup>d</sup>, mL/min/1.73m² | 109.6 ± 26.4 |
| Albuminuria, mg/L | 6.3 (3.5, 13.3) |
| TSH, mU/L | 2.1 ± 1.2 |

During the follow-up, there was a mean HbA1c variation of -0.9 ± 1.2% (HbA1c of 8.3% ± 1.5 at baseline, 7.3% ± 0.9 at 6 months and 12 months, and 7.4% ± 1.0 at 36 months, p < 0.001) (Fig. 1), 80.0% had improvement of HbA1c, 75.4% had improvement of HbA1c without worsening of hypoglycemia, 23.5% had improvement of hypoglycemia and 18.4% had improvement of hypoglycemia without the worsening HbA1c. Regarding safety outcomes, 72.4% had hypoglycemia after starting insulin pump therapy, 4.5% had severe hypoglycemia after starting insulin pump therapy and 4.5% had diabetic ketoacidosis after starting insulin pump therapy (Table 2).
### Table 2
Study outcomes

| Main outcomes                                      |           |
|---------------------------------------------------|-----------|
| HbA1c variation, %                                 | -0.9 ± 1.2|
| Improvement of HbA1c, n (%)                        | 104 (80.0%)|
| Improvement of HbA1c without worsening of hypoglycemia, n (%) | 98 (75.4%)|
| Improvement of hypoglycemia, n (%)                 | 31 (23.5%)|
| Improvement of hypoglycemia without worsening of HbA1c, n (%) | 23 (18.4%)|

| Safety outcomes                                    |           |
|---------------------------------------------------|-----------|
| Hypoglycemia after starting insulin pump therapy, n (%) | 84 (72.4%)|
| Severe hypoglycemia after starting insulin pump therapy, n (%) | 6 (4.5 %) |
| Ketoacidosis after starting insulin pump therapy, n (%) | 6 (4.5 %) |

Study outcomes: main outcomes and safety outcomes.
| Predictor                                                                 | β (95% CI)      | P Value | Adjusted P value* |
|--------------------------------------------------------------------------|-----------------|---------|------------------|
| Male sex, n (%)                                                          | 0.37 (-0.04 to 0.78) | 0.076   |                  |
| Age, years                                                               | 0.01 (-0.01 to 0.03) | 0.20    |                  |
| Duration of diabetes, years                                             | 0.01 (-0.01 to 0.04) | 0.25    |                  |
| Educational level                                                        | -0.24 (-0.74 to 0.26) | 0.35    |                  |
| Less than 12th grade, n (%) (reference)                                  |                 |         |                  |
| 12 years, n (%)                                                          | -0.08 (-1.09 to 0.93) | 0.87    |                  |
| Higher education, n (%)                                                  | -0.41 (-1.48 to 0.67) | 0.45    |                  |
| Pediatric age at onset of insulin pump, n (%)                            | -0.05 (-0.59 to 0.49) | 0.85    |                  |
| Family history of diabetes, n (%)                                        | -0.72 (-1.14 to -0.29) | 0.001   | 0.004            |
| Hypertension, n (%)                                                       | 0.44 (-0.14 to 1.02) | 0.14    |                  |
| Treatment with statins, n (%)                                            | 0.26 (-0.21 to 0.73) | 0.27    |                  |
| Autoimmune thyroiditis, n (%)                                            | 0.09 (-0.40 to 0.57) | 0.73    |                  |
| Current smoking, n (%)                                                   | 0.06 (-0.44 to 0.57) | 0.81    |                  |
| Alcohol consumption, n (%)                                               | 0.24 (-0.40 to 0.87) | 0.47    |                  |
| Psychological /psychiatric disorders, n (%)                             | -0.27 (-0.74 to 0.19) | 0.25    |                  |
| Hypoglycemia, n (%)                                                      | -0.31 (-1.69 to 1.08) | 0.66    |                  |
| Severe hypoglycemia, n (%)                                               | -0.03 (-0.64 to 0.58) | 0.95    |                  |
| Diabetic ketoacidosis, n (%)                                             | -1.24 (-2.13 to -0.35) | 0.006   | 0.35             |
| Diabetic neuropathy, n (%)                                               | -0.04 (-0.75 to 0.67) | 0.92    |                  |
| Diabetic retinopathy, n (%)                                              | -0.06 (-0.51 to 0.40) | 0.80    |                  |
| Diabetic nephropathy, n (%)                                              | -0.63 (-1.15 to -0.10) | 0.020   | 0.062            |
| Exercise practice, n (%)                                                 | 0.03 (-0.44 to 0.51) | 0.89    |                  |
| BMI a, kg/m²                                                              | 0.03 (-0.04 to 0.09) | 0.41    |                  |
| HbA1C, %                                                                 | -0.64 (-0.72 to -0.56) | <0.001  | <0.001           |
| Total cholesterol, mg/dL                                                 | -0.00 (-0.01 to 0.00) | 0.25    |                  |
| LDL b cholesterol, mg/dL                                                 | -0.00 (-0.01 to 0.01) | 0.69    |                  |
|                                                                             | 0.00 (-0.01 to 0.02) | 0.60    |                  |
Predictors of HbA1c Variation (%), using the mean of HbA1c over the follow-up period after starting insulin pump therapy.  

- Body Mass Index.  
- Low Density Lipoprotein.  
- High Density lipoprotein.  
- Estimated glomerular filtration rate calculated using the CKD-EPI equation. * Adjusted for variables with P value <0.05 in the unadjusted analysis.

The improvement of HbA1c was independent of sex, age and duration of the disease (Fig. 2). Patients with higher HbA1c before insulin pump therapy had greater reductions of HbA1c (Fig. 3). The presence of family history of diabetes, higher baseline HbA1c, diabetic nephropathy, albuminuria and history of diabetic ketoacidosis were predictors of greater reductions of HbA1c. In the adjusted analysis for HbA1c, only family history of diabetes and baseline HbA1c were predictors of reductions of HbA1c (Table 3).
Table 4
Improvement of HbA1c without worsening hypoglycemia

|                                      | No improvement of HbA1c without worsening hypoglycemia | Improvement of HbA1c without worsening hypoglycemia | P value | Adjusted P value* |
|--------------------------------------|--------------------------------------------------------|-----------------------------------------------------|---------|-------------------|
| n = 32                               | n = 98                                                  |                                                     |         |                   |
| Male sex, n (%)                      | 21 (65.6%)                                              | 36 (36.7%)                                          | 0.004   | 0.30              |
| Age, years                           | 37.3 ± 14.9                                             | 35.5 ± 11.3                                         | 0.47    |                   |
| Duration of diabetes, years          | 16.1 ± 11.8                                             | 13.4 ± 8.3                                          | 0.15    |                   |
| Educational level                    |                                                         |                                                     | 0.59    |                   |
| Less than 12th grade, n (%)          | 2 (13.3%)                                               | 6 (11.3%)                                           |         |                   |
| 12 years, n (%)                      | 10 (66.7%)                                              | 29 (54.7%)                                          |         |                   |
| Higher education, n (%)              | 3 (20.0%)                                               | 18 (34.0%)                                          |         |                   |
| Pediatric age at onset of insulin pump therapy, n (%) | 7 (21.9%)                                              | 16 (16.3%)                                          | 0.48    |                   |
| Family history of diabetes, n (%)    | 8 (28.6%)                                               | 38 (41.8%)                                          | 0.21    |                   |
| Hypertension, n (%)                  | 5 (15.6%)                                               | 14 (14.6%)                                          | 0.89    |                   |
| Treatment with statins, n (%)        | 14 (43.8%)                                              | 19 (19.4%)                                          | 0.006   | 0.008             |
| Autoimmune thyroiditis, n (%)        | 6 (18.8%)                                               | 24 (24.5%)                                          | 0.5     |                   |
| Current smoking, n (%)               | 7 (21.9%)                                               | 20 (20.4%)                                          | 0.86    |                   |
| Alcohol consumption, n (%)           | 5 (15.6%)                                               | 10 (10.3%)                                          | 0.42    |                   |
| Psychological /psychiatric disorders, n (%) | 9 (28.1%)                                              | 25 (25.5%)                                          | 0.77    |                   |
| Hypoglycemia before insulin pump, n (%) | 28 (90.3%)                                              | 95 (100.0%)                                         | 0.020   | 0.36              |
| History of severe hypoglycemia, n (%)| 1 (3.1 %)                                               | 16 (16.3%)                                          | 0.054   |                   |
| Diabetic ketoacidosis, n (%)         | 1 (3.2 %)                                               | 6 (6.2 %)                                           | 0.53    |                   |
|                                      | Study Population | Control Population | P-value |
|--------------------------------------|------------------|--------------------|---------|
| Diabetic neuropathy, n (%)           | 3 (9.4 %)        | 9 (9.2 %)          | 0.97    |
| Diabetic retinopathy, n (%)          | 11 (34.4%)       | 27 (27.6%)         | 0.46    |
| Diabetic nephropathy, n (%)          | 7 (21.9%)        | 16 (16.3%)         | 0.48    |
| Exercise practice, n (%)             | 12 (57.1%)       | 40 (59.7%)         | 0.84    |
| BMI\(^a\), kg/m\(^2\)                | 24.9 ± 3.1       | 24.1 ± 3.7         | 0.29    |
| HbA1C, %                            | 7.7 ± 1.0        | 8.5 ± 1.6          | 0.007   |
| Total cholesterol, mg/dL             | 179.6 ± 39.2     | 179.3 ± 30.4       | 0.96    |
| LDL\(^b\) cholesterol, mg/dL        | 105.8 ± 34.5     | 103.8 ± 23.6       | 0.73    |
| HDL\(^c\) cholesterol, mg/dL        | 58.6 ± 14.0      | 57.3 ± 13.1        | 0.67    |
| Triglycerides, mg/dL                 | 67.5 (55.0, 136.0) | 80.0 (59.0, 110.0) | 0.67 |
| eGFR\(^d\), mL/min/1.73m\(^2\)     | 107.9 ± 26.1     | 110.0 ± 26.9       | 0.71    |
| Albuminuria, mg/L                    | 7.2 (4.4, 18.4)  | 5.6 (3.4, 10.7)    | 0.39    |
| TSH, mU/L                            | 2.0 ± 1.5        | 2.2 ± 1.2          | 0.46    |

\(^a\)- Body Mass Index. \(^b\)- Low Density Lipoprotein. \(^c\)- High Density lipoprotein. \(^d\)- Estimated glomerular filtration rate calculated using the CKD-EPI equation. * Adjusted for variables with P value <0.05 in the unadjusted analysis.

The outcome improvement in HbA1c without the worsening of hypoglycemia was more common among women, in those with higher HbA1c at baseline, in patients not treated with statins, and in patients with history of hypoglycemia. After adjustment only higher HbA1c at baseline and not being treated with statins were significant predictors of decrease in HbA1c without worsening hypoglycemia (Table 4).

In the adjusted analysis, it was found that higher HbA1c at baseline, family history of diabetes and not being treated with statins as independent predictors of improvement in HbA1c (with or without worsening of hypoglycemia) (Supplementary Table 1). There were no statistically significant predictors of improvement in hypoglycemia or improvement of hypoglycemia without worsening HbA1c (Supplementary Tables 2 and 3).

Regarding the safety outcomes, there were no predictors of hypoglycemia after starting insulin pump therapy (Supplementary Table 4), and hypoglycemia at baseline was a predictor of severe hypoglycemia.
after starting insulin pump therapy (Supplementary Table 5). The incidence of diabetic ketoacidosis was higher in those with higher HbA1c at baseline, in those with family history of diabetes and in those with history of psychological or psychiatric disorder (Supplementary Table 6).

**Discussion**

In this analysis of patients with T1D transitioning from multiple daily injections to insulin pump therapy, higher HbA1c and not being treated with statins were independent predictors of improvement of HbA1c without worsening hypoglycemia. Higher baseline HbA1c and family history of diabetes were independent predictors of reduction of HbA1c. And higher baseline HbA1c, family history of diabetes and not being treated with statins were independent predictors of improvement in HbA1c. Having hypoglycemia before insulin pump therapy was a predictor of severe hypoglycemia after starting this treatment, and family history of diabetes, higher HbA1c and psychological/psychiatric disorders were predictors of diabetic ketoacidosis after therapy with insulin pump.

Insulin pump therapy has several advantages over multiple daily injections that have been already highlighted in previous studies [20, 17, 21]. This therapy allows more flexible, programmable and customizable basal insulin rates, with downloadable records and easy adjustment of insulin doses with physical activity. The possibility of using different types of boluses adjusted to the type of meal is also an advantage of insulin pump therapy. In addition, the increased flexibility improves the feeling of well-being and motivation of patients, improving their adherence to therapy [22, 23, 15]. Although more expensive, previous studies have shown that insulin pump therapy is more cost-effective than multiple daily injections [24]. Insulin pump therapy also have disadvantages that may justify why some patients have poorer glycemic control with this therapy. The disadvantages include the risk of potential infection of the site, occlusion of the catheter, or the cosmetic impact of the device, which can be discouraging for patients [22, 23, 25].

Our results are in agreement with previous reports evidencing an improvement in HbA1c levels after start therapy with insulin pump [18, 21, 19]. The association of higher baseline HbA1c values with greater reduction of HbA1c is also in agreement with other studies [26]. This association is probably explained by the greater margin to improve that patients with higher HbA1c have in comparison with patients with HbA1c closer to the target.

In our study, family history of diabetes was a predictor of reduction and improvement of HbA1c after insulin pump therapy. Other studies suggested that having a family history of diabetes may be associated with worse glycemic control and higher HbA1c levels [27–29]. As higher levels of HbA1c are associated with a greater improvement in HbA1c, this may partially explain this finding. However, in the adjusted analysis, family history of diabetes was an independent predictor of reduction of HbA1c, suggesting that additional mechanisms are involved. Having a family history of diabetes is associated with a greater awareness of the disease [30]. Family members with diabetes may be more prepared to help managing the insulin pump system, which may contribute to the improvement of HbA1c [31, 32].
The presence of a family history was also a predictor of diabetic ketoacidosis after insulin pump therapy. This may be justified by the higher levels of HbA1c found in these patients. This finding is in agreement with the study by Vakharia J et al. that found an association between family history of diabetes and a higher risk for diabetic ketoacidosis recurrence in youth with T1D [33, 29].

Patients not treated with statins were more likely to improve HbA1c levels after transitioning to therapy with insulin pump. While several studies have shown an association of treatment with statins and increased HbA1c levels and risk of diabetes in the general population and in type 2 diabetes, [34–36] few studies assessed this association in T1D. In the Thousand & 1 Study, use of statins was independently associated with increased HbA1c in patients T1D. It is uncertain whether the association of statins with HbA1c is causal or simply a marker for another mechanism such a dietary or lifestyle factor.

The improvement in HbA1c was independent of several factors including sex, age, duration of the disease and education level. Most previous studies also reported similar benefits for men and women [37, 38]. Concerning age, previous studies found discordant results. While some studies also found no difference according to age, [39, 38] other studies showed that an younger age at insulin pump initiation was associated with better glycemic controls [40, 37, 41]. Although the education level was not associated with improvement in HbA1c in our study, it should be noted that the population included in our study had higher education levels that the general Portuguese population. This suggests that people with higher education are being more frequently treated with insulin pumps, which was also reported in previous studies [42].

Regarding the safety outcomes, we found that hypoglycemia before therapy with insulin pump was a predictor for severe hypoglycemia after starting this therapy. Previous studies have shown that the main predictor of future severe hypoglycemia is previous occurrence of severe hypoglycemia or the occurrence of frequent hypoglycemia. Our results highlight that preventive measures to avoid severe hypoglycemia with insulin pump therapy are particularly relevant among patients that had hypoglycemia before starting this therapy [43, 33, 18, 44]. Due to the low number of severe hypoglycemias, our study may have been underpowered to identify other predictors. Previous reports have also identified long-standing type 1 diabetes, peripheral neuropathy and smoking as predictors of severe hypoglycemia [45, 46].

One of the most dreaded complications of T1D is diabetic ketoacidosis. As insulin pump therapy uses only fast acting insulins, failure of the device may lead to diabetic ketoacidosis in a few hours if no appropriate intervention is performed [47]. In our study, 4.5% of the population had ketoacidosis during the 3 years of follow-up. Higher baseline HbA1c levels and the presence of psychological/psychiatric disorders was a predictor of having diabetic ketoacidosis after insulin pump therapy, which is in agreement with other studies [48, 49]. This relationship can be attributed to the negative impact of psychopathology on diabetes, since it may influence blood glucose levels indirectly through lower adherence to therapy and directly increasing by promoting the release of catecholamines and corticosteroids [48].
Other studies found other predictors of improvements in HbA1c that were not assessed in our study including increased frequency of blood glucose monitoring [40] and using the bolus calculator feature [41].

Our study has limitations, including the retrospective design which limited our analysis to predictors that are routinely assessed during clinical practice. Furthermore, the study was carried out in a single center and only included adult participants, which may decrease the generalizability of our findings. Our analysis did not include patients with sensor-augmented pump therapy and, as such, our conclusions may not be applicable to this type of pump.

The strengths of our study include the specific questions that we addressed. Although several studies evaluated factors associated with outcomes during treatment with insulin pumps, few studies assessed which baseline predictors were associated with glycemic control and acute complications after transitioning to insulin pump. The identification of predictors of HbA1c improvement and predictors of severe hypoglycemia and ketoacidosis after starting insulin pump therapy is of clinical relevance as it will help to guide clinical practice. This allows a better selection of patients that most benefit from insulin pump therapy and those that are at increased risk of complications during treatment with insulin pumps.

In conclusion, insulin pump therapy was associated with improvement of glycemic control in most patients and a low risk of acute complications of diabetes. Higher baseline HbA1c, family history of diabetes and not being treated with statins were predictors of improvement of HbA1c, while hypoglycemia before insulin pump therapy was a predictor of severe hypoglycemia after starting this therapy. Family history of diabetes, higher HbA1c and psychological/psychiatric disorders were predictors of diabetic ketoacidosis after starting therapy with insulin pump. Future studies evaluating strategies to improve results in patients at risk of worse results after transitioning to insulin pump therapy are warranted.

Declarations

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Availability of data and material: The datasets analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Code availability: Not applicable.
**Ethics approval:** The authors declare that the procedures followed were in accordance with the regulations of Ethics Committee of the Centro Hospitalar Universitário de São João/ Faculty of Medicine of University of Porto and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Author contributions:** All authors contributed to the study conception. Joana Camões Neves: study design, manuscript design and conception, acquisition and interpretation of data, work draft and critical review, final approval of the manuscript; João Sérgio Neves: study design, manuscript design and conception, analysis and interpretation of data, work draft and critical review, final approval of the manuscript; Celestino Neves: work draft and critical review, final approval of the manuscript; Davide Carvalho: work draft and critical review, final approval of the manuscript.

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Figures
Figure 1

Variation of HbA1c (mean and standard deviation) over the follow-up period.

Figure 2

Variation of HbA1c (mean values) during follow-up according to Sex (A), Age category (B) and Years of T1D. SD not shown for illustrative clarity.
Figure 3

Mean reduction of HbA1c during the follow-up period, according to baseline HbA1c.

Supplementary Files

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