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FMUP FACULDADE DE MEDICINA
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MESTRADO INTEGRADO EM MEDICINA

2020/2021

Joana de Camões Castro Neves

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

ABRIL, 2021

FMUP

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

Mestrado Integrado em Medicina

Área: Ciências Médicas e da Saúde; Medicina Clínica

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutor João Sérgio de Lima Soares Neves

E sob a Coorientação de:

Professor Doutor Davide Maurício Costa Carvalho

Doutor Manuel Celestino Silva Neves

Trabalho organizado de acordo com as normas da revista:

Endocrine - International Journal of Basic and Clinical Endocrinology

ABRIL, 2021

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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Ciências Médicas e da Saúde, Medicina Clínica

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

PREDICTORS OF THE EFFECTIVENESS OF INSULIN PUMPS IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Faculdade de Medicina da Universidade do Porto, 09/04/2021

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DEDICATÓRIA

Quero expressar os meus sinceros agradecimentos e dedicar esta dissertação a todos os que me apoiaram nesta etapa e contribuíram para a sua realização.

Ao Doutor João Sérgio Neves de quem tenho imensa admiração e do qual levo um modelo de orientação a seguir. Agradeço a imprescindível, colaboração, disponibilidade, empenho constante e os conselhos e ensinamentos científicos e metodológicos ao longo da realização desta dissertação.

Aos Coorientadores Doutor Celestino Neves e Professor Doutor Davide Carvalho pelo apoio e disponibilidade prestada ao longo da realização deste trabalho.

Aos meus pais e irmã, eternos merecedores do meu agradecimento, por todos os valores que me transmitiram e que fizeram de mim o que sou hoje, por estarem sempre presentes, acreditarem e me apoiarem incondicionalmente ao longo da minha vida.

À minha família, pela força que sempre me transmitiram e pela compreensão da minha ausência em alguns eventos familiares.

A todos os colegas e amigos que estiveram ao meu lado continuamente.

A todos os Professores e auxiliares que estiveram presentes na minha educação e me ajudaram ao longo do meu percurso académico.

PREDICTORS OF THE EFFECTIVENESS OF INSULIN PUMPS IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Short title: Predictors of The Effectiveness of Insulin Pumps

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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.

Keywords: Type 1 Diabetes Mellitus; Insulin Pumps; Glycemic Control; Diabetes Treatment; Continuous Subcutaneous Insulin Infusion

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/1.73m^2 (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.

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, $p<0.001$) (Figure 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).

The improvement of HbA1c was independent of sex, age and duration of the disease (Figure 2). Patients with higher HbA1c before insulin pump therapy had greater reductions of HbA1c (Figure 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).

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.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Department of Endocrinology, Diabetes and Metabolism of Centro Hospitalar Universitário São João for allowing this study to be carried out, providing technical and consultancy support.

DECLARATIONS

Funding: No funding was received for conducting this study.

Conflicts of interest: The authors declare that they have no conflict of interest.

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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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
Total cholesterol, mg/dL	179.4 ± 32.4
LDL[b] cholesterol, mg/dL	104.4 ± 26.4
HDL[c] cholesterol, mg/dL	57.6 ± 13.3
Triglycerides, mg/dL	76.0 (58.0, 112.0)
eGFR[d], mL/min/1.73m2	109.6 ± 26.4
Albuminuria, mg/L	6.3 (3.5, 13.3)
TSH, mU/L	2.1 ± 1.2

Table 1. Baseline characteristics of study population before starting insulin pump therapy. [a] - Body Mass Index. [b] - Low Density Lipoprotein. [c] – High Density lipoprotein. [d] - Estimated glomerular filtration rate calculated using the CKD-EPI equation.

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 %)

Table 2. Study outcomes: main outcomes and safety outcomes.

Table 3. Predictors of HbA1c Variation (%)

	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/m^2	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	
HDL[c] cholesterol, mg/dL	0.00 (-0.01 to 0.02)	0.60	
Triglycerides, mg/dL	-0.36 (-0.78 to 0.07)	0.097	
eGFR[d], mL/min/1.73m2	-0.00 (-0.01 to 0.01)	0.98	
Albuminuria, mg/L	-0.19 (-0.38 to -0.00)	0.046	0.63
TSH, mU/L	-0.04 (-0.21 to 0.14)	0.67	

Table 3. Predictors of HbA1c Variation (%), using the mean of HbA1c over the follow-up period after starting insulin pump therapy. [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.

Table 4. Improvement of HbA1c without worsening hypoglycemia

	No improvement of HbA1c without worsening hypoglycemia n=32	Improvement of HbA1c without worsening hypoglycemia n=98	P value	Adjusted P value*
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	
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	0.009
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/1.73m2	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	

Table 4. Improvement of HbA1c without worsening hypoglycemia. [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.

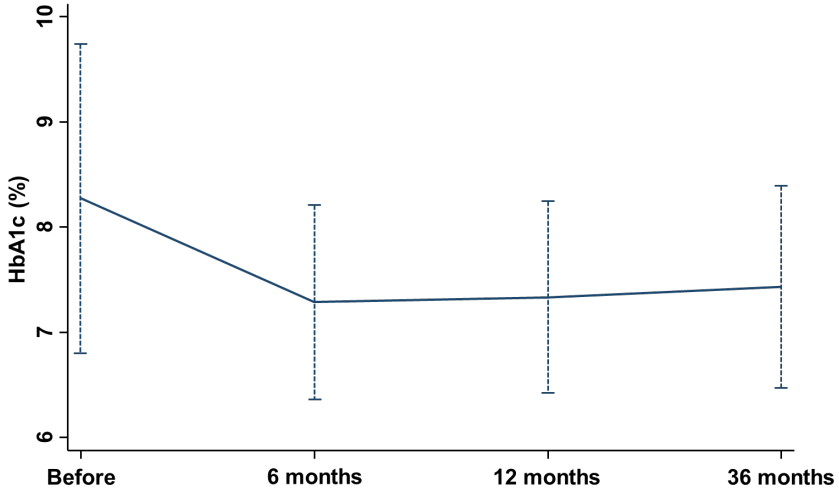


Fig 1. Variation of HbA1c (mean and standard deviation) over the follow-up period.

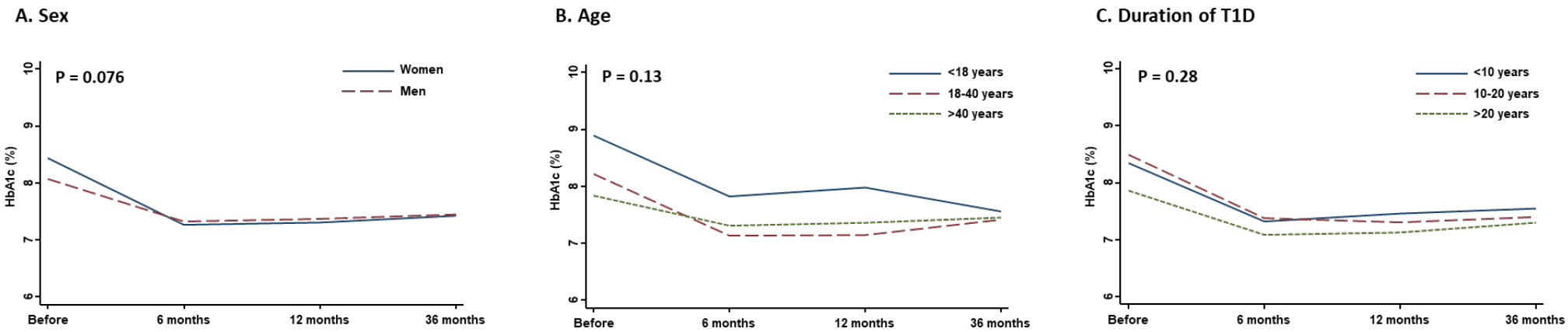


Fig 2. Variation of HbA1c (mean values) during follow-up according to Sex (A), Age category (B) and Years of T1D. SD not shown for illustrative clarity.

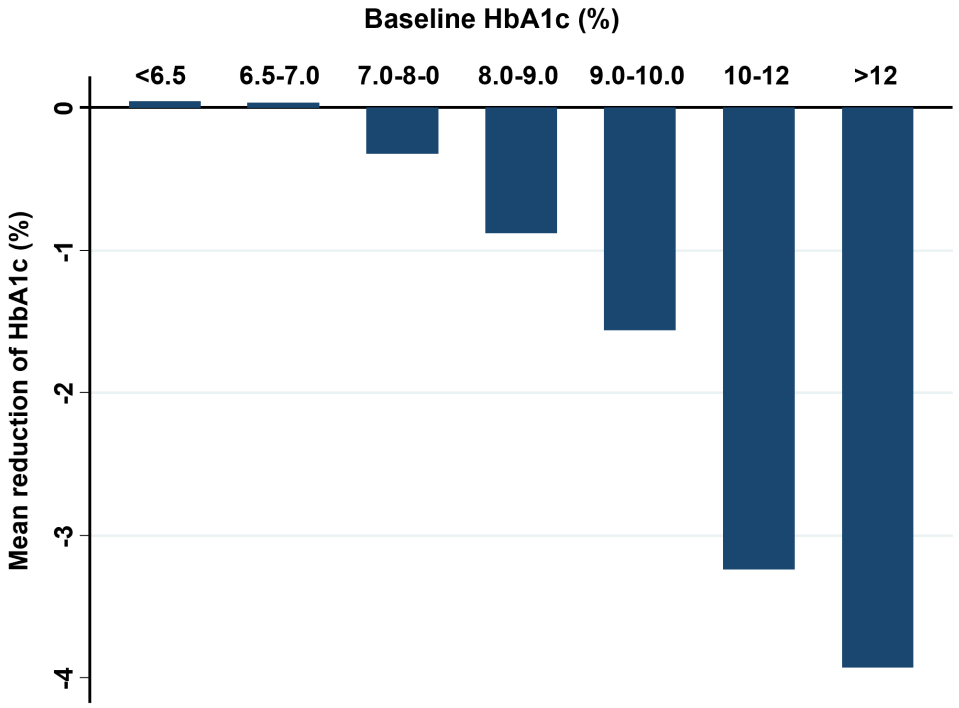


Fig 3. Mean reduction of HbA1c during the follow-up period, according to baseline HbA1c.

Supplementary table 1. Improvement of HbA1c

	No improvement of HbA1c n=26	Improvement of HbA1c n=104	P value	Adjusted P value
Male sex, n (%)	17 (65.4%)	40 (38.5%)	0.013	0.30
Age, years	37.8 ± 15.4	35.5 ± 11.3	0.38	
Duration of diabetes, years	16.9 ± 12.4	13.4 ± 8.3	0.09	
Educational level			0.76	
Less than 12th grade, n (%)	2 (15.4%)	6 (10.9%)		
12 years, n (%)	8 (61.5%)	31 (56.4%)		
Higher education, n (%)	3 (23.1%)	18 (32.7%)		
Pediatric age at onset of insulin pump therapy, n (%)	6 (23.1%)	17 (16.3%)	0.42	
Family history of diabetes, n (%)	4 (18.2%)	42 (43.3%)	0.029	0.022
Hypertension, n (%)	5 (19.2%)	14 (13.7%)	0.48	
Treatment with statins, n (%)	12 (46.2%)	21 (20.2%)	0.007	0.015
Autoimmune thyroiditis, n (%)	4 (15.4%)	26 (25.0%)	0.3	
Current smoking, n (%)	6 (23.1%)	21 (20.2%)	0.75	
Alcohol consumption, n (%)	4 (15.4%)	11 (10.7%)	0.5	
Psychological /psychiatric disorders, n (%)	8 (30.8%)	26 (25.0%)	0.55	
Hypoglycemia before insulin pump, n (%)	24 (96.0%)	99 (98.0%)	0.55	0.78
History of severe hypoglycemia, n (%)	1 (3.8 %)	16 (15.4%)	0.12	
History of diabetic ketoacidosis, n (%)	1 (4.0 %)	6 (5.8 %)	0.72	
Diabetic neuropathy, n (%)	2 (7.7 %)	10 (9.6 %)	0.76	
Diabetic retinopathy, n (%)	8 (30.8%)	30 (28.8%)	0.85	
Diabetic nephropathy, n (%)	6 (23.1%)	17 (16.3%)	0.42	
Exercise practice, n (%)	8 (53.3%)	44 (60.3%)	0.62	
BMI[a], kg/m^2	24.7 ± 3.1	24.2 ± 3.7	0.56	
HbA1C, %	7.5 ± 0.9	8.5 ± 1.5	0.004	0.003
Total cholesterol, mg/dL	179.2 ± 40.6	179.4 ± 30.6	0.98	
LDL[b] cholesterol, mg/dL	105.1 ± 35.6	104.1 ± 23.9	0.88	
HDL[c] cholesterol, mg/dL	58.7 ± 13.3	57.4 ± 13.4	0.68	
Triglycerides, mg/dL	68.0 (59.0, 133.0)	79.0 (58.0, 112.0)	0.77	
eGFR[d], mL/min/1.73m2	108.7 ± 27.1	109.6 ± 26.6	0.87	
Albuminuria, mg/L	7.3 (4.8 , 21.4)	5.6(3.2 , 10.7)	0.22	
TSH mU/L	2.1 ± 1.6	2.2 ± 1.2	0.86	

Supplementary table 1. Improvement of HbA1c. [a]- Body Mass Index. [b]- Low Density Lipoprotein. [c] – High Density lipoprotein. [d] - Estimated glomerular filtration rate calculated using the CKD-EPI equation.

Supplementary table 2. Improvement of hypoglycemia without worsening HbA1c

	No improvement of hypoglycemia without worsening HbA1c n=102	Improvement of hypoglycemia without worsening HbA1c n=23	P value
Male sex, n (%)	43 (42.2%)	10 (43.5%)	0.91
Age, years	35.8 ± 12.5	38.2 ± 12.2	0.4
Duration of diabetes, years	14.2 ± 9.4	15.0 ± 9.3	0.71
Educational level			0.57
Less than 12th grade, n (%)	6 (10.2%)	2 (20.0%)	
12 years, n (%)	34 (57.6%)	6 (60.0%)	
Higher education, n (%)	19 (32.2%)	2 (20.0%)	
Pediatric age at onset of insulin pump therapy, n (%)	19 (18.6%)	3 (13.0%)	0.53
Family history of diabetes, n (%)	33 (35.5%)	11 (50.0%)	0.21
Hypertension, n (%)	14 (14.0%)	4 (17.4%)	0.68
Treatment with statins, n (%)	27 (26.5%)	6 (26.1%)	0.97
Autoimmune thyroiditis, n (%)	22 (21.6%)	6 (26.1%)	0.64
Current smoking, n (%)	20 (19.6%)	6 (26.1%)	0.49
Alcohol consumption, n (%)	10 (9.9 %)	5 (21.7%)	0.12
Psychological /psychiatric disorders, n (%)	26 (25.5%)	9 (39.1%)	0.19
Hypoglycemia before insulin pump, n (%)	1.0 ± 0.0	1.0 ± 0.0	.
History of severe hypoglycemia, n (%)	12 (11.8%)	5 (21.7%)	0.21
History of diabetic ketoacidosis, n (%)	6 (5.9 %)	1 (4.3 %)	0.77
Diabetic neuropathy, n (%)	9 (8.8 %)	2 (8.7 %)	0.98
Diabetic retinopathy, n (%)	30 (29.4%)	8 (34.8%)	0.61
Diabetic nephropathy, n (%)	17 (16.7%)	6 (26.1%)	0.29
Exercise practice, n (%)	43 (60.6%)	7 (50.0%)	0.46
BMI[a], kg/m^2	24.2 ± 3.4	24.7 ± 4.4	0.56
HbA1C, %	8.3 ± 1.6	8.5 ± 1.1	0.63
Total cholesterol, mg/dL	179.4 ± 33.8	175.8 ± 26.3	0.64
LDL[b] cholesterol, mg/dL	103.5 ± 27.0	104.0 ± 23.8	0.94
HDL[c] cholesterol, mg/dL	58.0 ± 12.6	54.8 ± 16.8	0.34
Triglycerides, mg/dL	95.5 ± 58.3	81.5 ± 50.1	0.31
eGFR[d], mL/min/1.73m2	109.0 ± 26.4	109.6 ± 29.2	0.93
Albuminuria, mg/L	18.8 ± 35.2	8.8 ± 8.0	0.19
TSH, mU/L	2.2 ± 1.3	2.1 ± 1.0	0.72

Supplmentary table 2. Improvement of hypoglycemia without worsening HbA1c. [a]- Body Mass Index. [b]- Low Density Lipoprotein. [c] – High Density lipoprotein. [d] - Estimated glomerular filtration rate calculated using the CKD-EPI equation.

Supplementary table 3. Improvement of hypoglycemia

	No improvement of hypoglycemia n=101	Improvement of hypoglycemia n=31	P value
Male sex, n (%)	45 (44.6%)	13 (41.9%)	0.8
Age, years	35.5 ± 12.5	37.4 ± 11.7	0.44
Duration of diabetes, years	13.5 ± 8.6	16.1 ± 10.9	0.17
Educational level			0.51
Less than 12th grade, n (%)	5 (9.3 %)	3 (20.0%)	
12 years, n (%)	32 (59.3%)	8 (53.3%)	
Higher education, n (%)	17 (31.5%)	4 (26.7%)	
Pediatric age at onset of insulin pump therapy, n (%)	20 (19.8%)	4 (12.9%)	0.38
Family history of diabetes, n (%)	34 (37.4%)	12 (40.0%)	0.8
Hypertension, n (%)	15 (15.2%)	4 (12.9%)	0.76
Treatment with statins, n (%)	24 (23.8%)	9 (29.0%)	0.55
Autoimmune thyroiditis, n (%)	22 (21.8%)	8 (25.8%)	0.64
Current smoking, n (%)	21 (20.8%)	6 (19.4%)	0.86
Alcohol consumption, n (%)	9 (9.0 %)	6 (19.4%)	0.11
Psychological /psychiatric disorders, n (%)	24 (23.8%)	12 (38.7%)	0.1
Hypoglycemia before insulin pump, n (%)	94 (96.9%)	31 (100.0%)	0.32
History of severe hypoglycemia, n (%)	12 (11.9%)	5 (16.1%)	0.54
History of diabetic ketoacidosis, n (%)	6 (6.1 %)	1 (3.2 %)	0.54
Diabetic neuropathy, n (%)	10 (9.9 %)	2 (6.5 %)	0.56
Diabetic retinopathy, n (%)	27 (26.7%)	11 (35.5%)	0.35
Diabetic nephropathy, n (%)	17 (16.8%)	7 (22.6%)	0.47
Exercise practice, n (%)	43 (60.6%)	10 (52.6%)	0.53
BMI[a], kg/m^2	24.0 ± 3.4	25.0 ± 4.1	0.18
HbA1C, %	8.3 ± 1.6	8.1 ± 1.1	0.48
Total cholesterol, mg/dL	180.9 ± 33.9	174.5 ± 26.9	0.37
LDL[b] cholesterol, mg/dL	104.9 ± 27.2	102.6 ± 24.1	0.7
HDL[c] cholesterol, mg/dL	58.0 ± 12.5	56.4 ± 15.7	0.58
Triglycerides, mg/dL	83.0 (58.0, 119.0)	68.5 (58.5, 77.5)	0.07
eGFR[d], mL/min/1.73m2	109.8 ± 26.9	109.1 ± 25.8	0.91
Albuminuria, mg/L	6.4 (3.2, 17.6)	6.2 (3.7, 10.5)	0.78
TSH, mU/L	2.2 ± 1.3	2.0 ± 0.9	0.51

Supplementary table 3. Improvement of hipoglycemia. [a]- Body Mass Index. [b]- Low Density Lipoprotein. [c] – High Density lipoprotein. [d]- Estimated glomerular filtration rate calculated using the CKD-EPI equation.

Supplementary table 4. Hypoglycemia after starting insulin pump therapy

	No hypoglycemia after starting insulin pump therapy n=32	Hypoglycemia after starting insulin pump therapy n=84	P value
Male sex, n (%)	13 (40.6%)	40 (47.6%)	0.5
Age, years	36.2 ± 12.0	35.4 ± 13.2	0.77
Duration of diabetes, years	15.5 ± 11.1	13.7 ± 8.6	0.35
Educational level			0.43
Less than 12th grade, n (%)	3 (20.0%)	4 (8.2 %)	
12 years, n (%)	8 (53.3%)	29 (59.2%)	
Higher education, n (%)	4 (26.7%)	16 (32.7%)	
Pediatric age at onset of insulin pump therapy, n (%)	5 (15.6%)	19 (22.6%)	0.41
Family history of diabetes, n (%)	13 (41.9%)	30 (39.0%)	0.78
Hypertension, n (%)	3 (9.4 %)	14 (17.1%)	0.3
Treatment with statins, n (%)	9 (28.1%)	19 (22.6%)	0.54
Autoimmune thyroiditis, n (%)	7 (21.9%)	20 (23.8%)	0.83
Current smoking, n (%)	5 (15.6%)	17 (20.2%)	0.57
Alcohol consumption, n (%)	6 (18.8%)	9 (10.8%)	0.26
Psychological /psychiatric disorders, n (%)	11 (34.4%)	21 (25.0%)	0.31
Hypoglycemia before insulin pump, n (%)	31 (96.9%)	80 (97.6%)	0.84
History of severe hypoglycemia, n (%)	3 (9.4 %)	12 (14.3%)	0.48
History of diabetic ketoacidosis, n (%)	1 (3.1 %)	3 (3.7 %)	0.89
Diabetic neuropathy, n (%)	1 (3.1 %)	8 (9.5 %)	0.25
Diabetic retinopathy, n (%)	11 (34.4%)	23 (27.4%)	0.46
Diabetic nephropathy, n (%)	7 (21.9%)	15 (17.9%)	0.62
Exercise practice, n (%)	12 (54.5%)	37 (60.7%)	0.62
BMI[a], kg/m^2	25.2 ± 4.1	23.9 ± 3.4	0.08
HbA1C, %	8.2 ± 1.1	8.4 ± 1.7	0.56
Total cholesterol, mg/dL	173.6 ± 25.6	180.5 ± 33.2	0.31
LDL[b] cholesterol, mg/dL	100.7 ± 21.4	105.3 ± 27.6	0.42
HDL[c] cholesterol, mg/dL	57.9 ± 16.2	57.5 ± 11.9	0.89
Triglycerides, mg/dL	67.0 (57.0, 75.0)	86.0 (59.0, 119.0)	0.08
eGFR[d], mL/min/1.73m2	110.3 ± 25.7	110.0 ± 28.3	0.96
Albuminuria, mg/L	6.3 (3.6 , 10.5)	6.0 (3.2 , 17.6)	0.85
TSH, mU/L	2.0 ± 1.0	2.2 ± 1.4	0.55

Supplementary table 4. Hypoglycemia after starting insulin pump therapy. [a]- Body Mass Index. [b]- Low Density Lipoprotein. [c] – High Density lipoprotein. [d] - Estimated glomerular filtration rate calculated using the CKD-EPI equation.

Supplementary table 5. Severe hypoglycemia after starting insulin pump therapy

	No severe hypoglycemia after insulin pump n=126	Severe hypoglycemia after insulin pump n=6	P value
Male sex, n (%)	55 (43.7%)	3 (50.0%)	0.76
Age, years	36.1 ± 12.3	32.8 ± 12.6	0.53
Duration of diabetes, years	14.2 ± 9.3	12.9 ± 9.1	0.74
Educational level			0.81
Less than 12th grade, n (%)	8 (12.1%)	0 (0.0 %)	
12 years, n (%)	38 (57.6%)	2 (66.7%)	
Higher education, n (%)	20 (30.3%)	1 (33.3%)	
Pediatric age at onset of insulin pump therapy, n (%)	23 (18.3%)	1 (16.7%)	0.92
Family history of diabetes, n (%)	43 (37.4%)	3 (50.0%)	0.54
Hypertension, n (%)	19 (15.3%)	0 (0.0 %)	0.3
Treatment with statins, n (%)	30 (23.8%)	3 (50.0%)	0.15
Autoimmune thyroiditis, n (%)	28 (22.2%)	2 (33.3%)	0.53
Current smoking, n (%)	26 (20.6%)	1 (16.7%)	0.81
Alcohol consumption, n (%)	14 (11.2%)	1 (16.7%)	0.68
Psychological /psychiatric disorders, n (%)	35 (27.8%)	1 (16.7%)	0.55
Hypoglycemia before insulin pump, n (%)	120 (98.4%)	5 (83.3%)	0.018
History of severe hypoglycemia, n (%)	16 (12.7%)	1 (16.7%)	0.78
History of diabetic ketoacidosis, n (%)	7 (5.6 %)	0 (0.0 %)	0.55
Diabetic neuropathy, n (%)	11 (8.7 %)	1 (16.7%)	0.51
Diabetic retinopathy, n (%)	35 (27.8%)	3 (50.0%)	0.24
Diabetic nephropathy, n (%)	23 (18.3%)	1 (16.7%)	0.92
Exercise practice, n (%)	49 (58.3%)	4 (66.7%)	0.69
BMI[a], kg/m^2	24.1 ± 3.6	26.4 ± 2.9	0.13
HbA1C, %	8.3 ± 1.5	8.5 ± 0.6	0.66
Total cholesterol, mg/dL	180.1 ± 32.5	165.5 ± 30.5	0.28
LDL[b] cholesterol, mg/dL	105.1 ± 26.3	87.2 ± 25.2	0.14
HDL[c] cholesterol, mg/dL	57.6 ± 13.1	58.3 ± 17.9	0.89
Triglycerides, mg/dL	75.0 (59.0, 105.0)	115.0 (54.0, 182.0)	0.42
eGFR[d], mL/min/1.73m2	109.7 ± 26.8	108.8 ± 23.6	0.94
Albuminuria, mg/L	6.3 (3.7, 13.8)	3.0 (2.6, 9.9)	0.27
TSH, mU/L	2.2 ± 1.2	1.6 ± 1.2	0.28

Supplementary table 5. Severe hypoglycemia after starting insulin pump therapy. [a] - Body Mass Index. [b] - Low Density Lipoprotein. [c] – High Density lipoprotein. [d] - Estimated glomerular filtration rate calculated using the CKD-EPI equation.

Supplementary table 6. Diabetic ketoacidosis after starting insulin pump therapy

	No diabetic ketoacidosis after insulin pump n=126	Diabetic ketoacidosis after insulin pump n=6	P value
Male sex, n (%)	57 (45.2%)	1 (16.7%)	0.17
Age, years	36.1 ± 12.3	31.5 ± 11.2	0.37
Duration of diabetes, years	14.1 ± 9.3	14.1 ± 8.9	0.99
Educational level			0.36
Less than 12th grade, n (%)	8 (12.1%)	0 (0.0 %)	
12 years, n (%)	39 (59.1%)	1 (33.3%)	
Higher education, n (%)	19 (28.8%)	2 (66.7%)	
Pediatric age at onset of insulin pump therapy, n (%)	22 (17.5%)	2 (33.3%)	0.32
Family history of diabetes, n (%)	41 (35.7%)	5 (83.3%)	0.019
Hypertension, n (%)	19 (15.3%)	0 (0.0 %)	0.3
Treatment with statins, n (%)	32 (25.4%)	1 (16.7%)	0.63
Autoimmune thyroiditis, n (%)	29 (23.0%)	1 (16.7%)	0.72
Current smoking, n (%)	26 (20.6%)	1 (16.7%)	0.81
Alcohol consumption, n (%)	14 (11.2%)	1 (16.7%)	0.68
Psychological /psychiatric disorders, n (%)	32 (25.4%)	4 (66.7%)	0.027
Hypoglycemia before insulin pump, n (%)	120 (97.6%)	5 (100.0%)	0.72
History of severe hypoglycemia, n (%)	17 (13.5%)	0 (0.0 %)	0.34
History of diabetic ketoacidosis, n (%)	6 (4.8 %)	1 (25.0%)	0.08
Diabetic neuropathy, n (%)	11 (8.7 %)	1 (16.7%)	0.51
Diabetic retinopathy, n (%)	36 (28.6%)	2 (33.3%)	0.8
Diabetic nephropathy, n (%)	23 (18.3%)	1 (16.7%)	0.92
Exercise practice, n (%)	51 (59.3%)	2 (50.0%)	0.71
BMI[a], kg/m^2	24.2 ± 3.6	24.4 ± 2.8	0.89
HbA1C, %	8.2 ± 1.4	9.6 ± 2.1	0.021
Total cholesterol, mg/dL	178.8 ± 32.9	190.2 ± 22.1	0.41
LDL[b]cholesterol, mg/dL	104.2 ± 27.0	107.3 ± 14.0	0.78
HDL[c] cholesterol, mg/dL	57.6 ± 13.1	57.8 ± 18.0	0.97
Triglycerides, mg/dL	74.0 (58.0, 104.5)	140.0 (82.0, 182.0)	0.09
eGFR[d], mL/min/1.73m2	109.9 ± 24.8	103.6 ± 53.6	0.57
Albuminuria, mg/L	6.1 (3.4, 12.7)	9.2 (5.6, 24.4)	0.32
TSH, mU/L	2.1 ± 1.2	2.4 ± 1.6	0.7

Supplementary table 6. Diabetic ketoacidosis after starting insulin pump therapy. [a]- Body Mass Index. [b] - Low Density Lipoprotein. [c] – High Density lipoprotein. [d] - Estimated glomerular filtration rate calculated using the CKD-EPI equation.

Anexo 1

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1; 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3;4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5;6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed	5;7

		(*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5;8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

1 (a) – Página 2:"We conducted a retrospective observational study of patients who started insulin pump therapy."

1 (b) – Página 2: "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. (…)We evaluated 136 patients (…) Benefits of insulin pump therapy 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"

2 – Página 3 e 4: "there have been several improvements in insulin pumps, ensuring greater reliability of the technology resulting in an increasing use of insulin pumps therapy. [16] However, the evidence showing the superiority of one form of treatment over the other is still limited (…) The reason why some patients improve glycemic control with this treatment while others do not improve is not yet fully established."

3 – Página 4: "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."

4 – Página 5: 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 time points: before transitioning to insulin pump therapy, and at 6 months, 12 months and 36 months after starting therapy with insulin pump."

5 – Página 5: 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 (…) 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. (…) Data were collected until the end of February 2021."

6 (a) – Página 5: "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."

6 (b): Não aplicável uma vez que, neste estudo, não foram estabelecidos critérios de correspondência e os indivíduos não foram classificados como expostos e não expostos.

7 – Página 5 e 6: "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. (…) 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."

8 – Página 5: "Data was retrospectively collected from clinical records at four different time points: before transitioning to insulin pump therapy, and at 6 months, 12 months and 36 months after starting therapy with insulin pump."

9 – Página 7: We also performed adjusted analysis including in the linear and logistic regression models all predictors that were statistically significant for each outcome.

10 – Página 5: "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 in the present analysis."

11 – Página 7: “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).”

12 (a) e (b) – Página 7: “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).

12 (c) – “Patients with missing data on baseline demographics, baseline HbA1c or all follow-up HbA1c levels were excluded from our analysis.”

12 (d) – Não aplicável, porque não se registaram perdas de follow up.

12 (e) – ““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).”

13 (a) – Página 8: “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)”

13 (b) – Não aplicável. Os indivíduos não foram excluídos de cada estadio.

13 (c) – Não aplicável. O único motivo para os indíduos não participarem em determinado estadio do estudo seria não terem dados suficientes e, como explicado na secção “Materials and Methods”, esses não foram tidos em conta (“Patients with missing data on baseline demographics, baseline HbA1c or all follow-up HbA1c levels were excluded from our analysis”).

14 (a) – Página 8: “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% d. iabetic nephropathy and 9.8% diabetic neuropathy. Fourteen percent had a history of severe hypoglycemia and 6.1% had history of diabetic ketoacidosis.”

14 (b) – Não aplicável, porque não realizada feita esta avaliação na análise dos dados.

14 (c) – Página 5: “before transitioning to insulin pump therapy, and at 6 months, 12 months and 36 months after starting therapy with insulin pump” – referido nos “Materials and Methods”.

15 – Página 8: “During the follow-up, there was a mean HbA1c variation of -0.9 ± 1.2% (HbA1c of 8.3% ± 1.5, 7.3% ± 0.9 at 6 months and 12 months, and 7.4% ± 1.0 at 36 months, p<0.001), 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).”

16 – Página 8 e 9: “The improvement of HbA1c was independent of sex, age and duration of the disease (Figure 2). Patients with higher HbA1c before insulin pump therapy had greater reductions of HbA1c (Figure 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). 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).”

16 (b) – Página 7-9: A divisão feita foi especificada na secção “Materials and Methods” e mostrada nas figuras, indicadas na secção “Results” – “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).”

16 (c): Não aplicável, não foi considerado relevante para este estudo.

17 – Página: 7-9: Os diferentes outcomes e preditores foram analisados de acordo com as seguintes análises: “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.”

18 – Página 10: “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.”

19 – Página 12: “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.”

20 – Página 10-13: “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

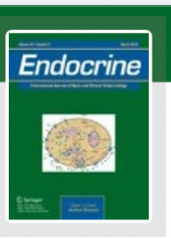
adjusted analysis, family history of diabetes was an independent predictor of reduction of HbA1c, suggesting that additional mechanisms are involved. Having a family history of diabetes is associated with a greater awareness of the disease [30]. Family members with diabetes may be more prepared to help 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].”

21 – Página 13: “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.”

22 – Não aplicável. Não foi recebido nenhum financiamento para a realização deste estudo.”

Anexo 2



Endocrine
International Journal of Basic and Clinical Endocrinology

Submission guidelines

Contents

Instructions for Authors

Here you can find the information you will need to prepare a manusript for Endocrine.

Types of papers

Manuscript categories

1. Original article

This contribution should contain original controlled experimental data of basic and clinical research. The manuscript should be organized in the following sections: Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figure Legends, Tables, Figures. Manuscripts should not exceed 4,000 words, 60 references, and 7 tables/figures

2. Review

This contribution is usually solicited by the Editors. If unsolicited, the authors are advised to contact the Editor-in-Chief (editor.endocrine@gmail.com) with an outline of the proposed review and CV of the authors.

This type of article does not have a strict limit in word and reference number although the editorial recommendation is that the article does not exceed 4000 words and 350 references.

3. Mini-Review

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This type of article has a word limit of 2000 and no more than 100 references.

4. New Horizons in

This contribution should be based on the outcomes of a scientific meeting and will be devoted to underline open issues as well as future basic and clinical research perspectives in an endocrine field. This type of article has a word limit of 2000 and no more than 50 references. Interested authors should contact directly the Editor-in-Chief (editor.endocrine@gmail.com) submitting the meeting scientific program and an outline of their work.

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This contribution should be solicited by the Editors and deal with a controversial topic in either basic or clinical endocrinology on which the author, a leading expert in the field, is invited to express his views and interpretation of current literature. This type of article has a word limit of 1500, 1 figure or table and no more than 30 references.

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This contribution should be solicited by the Editors and relates to the topic of one or more contributions published in the same issue of the journal. This type of article has a word limit of 1500 and no more than 20 references.

8. Research Letter

This contribution contains particularly original preliminary basic or clinical data presented in a very concise way (no abstract, word limit of 1250, 1 table of figure and maximum 20 references).

9. Endocrine Genetics/Epigenetics

This contribution contains novel insights in the genetics/epigenetics in endocrine physiology and diseases. Data should be presented in a concise way (word limit of 2000, 2 table or figure and maximum 30 references.

10. Book review

This contribution should be a short evaluation from an expert in the field on a relevant book in a certain area of endocrinology. This article should not exceed 750 words and no references are allowed.

11. Letter to the Editor

Text is limited to 750 words, with no abstract. There may be 1 figure, up to 3 references, and no more than 3 authors, with author affiliations only including main institution, place name and (state plus) country (i.e. no departments, etc).

12. Endocrine Imaging

Text is limited to 500 words, with no abstract, and illustrative of 1 Figure in which a particularly significant and original result of an imaging technique (e.g. MRI, CT, ultrasound) obtained during the diagnostic process of an endocrine disease should be included. No more than 3 references and 3 authors (with author affiliations only including main institution, place name and (state plus) country) are allowed.

13. Pros and Cons in Endocrine Practice

This contribution should deal with a controversial topic in endocrine practice in which pros and cons of an endocrine disease treatment or diagnostic process are examined and

reported in a balanced and constructive way. A proposed algorithm or indication for an integrated approach should be produced. This type of article has a word limit of 2000, 1 figure and 1 table, no more than 50 references and can be written by a single author reviewing the two sides of the topic or by two authors each dealing with one aspect of the topic.

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This contribution contains the description of a previously unreported research method or modification of an already known method particularly relevant to the endocrine field. New laboratory assays for hormone measurement as well as new diagnostic techniques or new applications of a diagnostic technique are also eligible for this manuscript category. Data should be presented in a concise way (word limit of 1500, 1 table or figure and maximum 25 references).

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This contribution is devoted to registered clinical trials in which treatments for an endocrine or metabolic disease are studied. Manuscripts can deal with the description of the protocol of a trial, can report data from interim analysis of an ongoing clinical trial, can report preliminary or final results of the trial as well as post-hoc analysis of the trial. The authors are invited not to exceed 2500 words and 75 references for reporting final results of a trial. Interim analysis or preliminary data of an ongoing clinical trial as well as post-hoc analysis of a trial should not exceed 1500 words and 50 references. The authors should not exceed 1000 words and 30 references for the description of the protocol of a new trial.

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Text is limited to 500 words, with no abstract and only one Figure if strictly necessary, with the description of a potential side effect not previously reported which occurred during the treatment with an endocrine drug or of an endocrine disease. No more than 3 references and 3 authors (with author affiliations only including main institution, place name and (state plus) country) are allowed.

17. Clinical Management of Endocrine Diseases

This contribution should discuss the practical aspects of the management of an endocrine or metabolic disease with particular reference to critical aspects of the clinical guidelines in the specific field if available. Resulting decisional diagnostic and therapeutic algorithms should be aimed at helping clinicians in their daily practice. This type of article is generally invited, has a word limit of 2000, no more than 2 figures and 75 references.

18. Position statements/Guidelines

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19. Endocrine Surgery

This contribution is devoted to report original manuscripts on innovative techniques in endocrine surgery as well as on results and side effects of surgical treatment of endocrine diseases. Manuscripts should not exceed 2500 words, 100 references and 4 Figures or Tables.

Manuscript Submission

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Title Page

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The title should be concise and informative.

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- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author

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If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

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Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusion

For life science journals only (when applicable)

Trial registration number and date of registration

Trial registration number, date of registration followed by “retrospectively registered”

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Please provide 4 to 6 keywords which can be used for indexing purposes.

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To be used for all articles, including articles with biological applications

Funding (information that explains whether and by whom the research was supported)

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Availability of data and material (data transparency)

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Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory)

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals
Ethics approval (include appropriate approvals or waivers)

Consent to participate (include appropriate statements)

Consent for publication (include appropriate statements)

Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs.

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Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

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Please use no more than three levels of displayed headings.

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Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist

solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

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Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

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If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

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Hamburger, C.: Quasimonotonicity, regularity and duality for nonlinear systems of partial differential equations. Ann. Mat. Pura Appl. 169, 321–354 (1995)

- Article by DOI

Sajti, C.L., Georgio, S., Khodorkovsky, V., Marine, W.: New nanohybrid materials for biophotonics. Appl. Phys. A (2007). https://doi.org/10.1007/s00339-007-4137-z

- Book

Geddes, K.O., Czapor, S.R., Labahn, G.: Algorithms for Computer Algebra. Kluwer, Boston (1992)

- Book chapter

Broy, M.: Software engineering — from auxiliary to key technologies. In: Broy, M., Denert, E. (eds.) Software Pioneers, pp. 10–13. Springer, Heidelberg (2002)

- Online document

Cartwright, J.: Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1 (2007). Accessed 26 June 2007

Always use the standard abbreviation of a journal’s name according to the ISSN List of Title Word Abbreviations, see

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- All tables are to be numbered using Arabic numerals.
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- For each table, please supply a table caption (title) explaining the components of the table.
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- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

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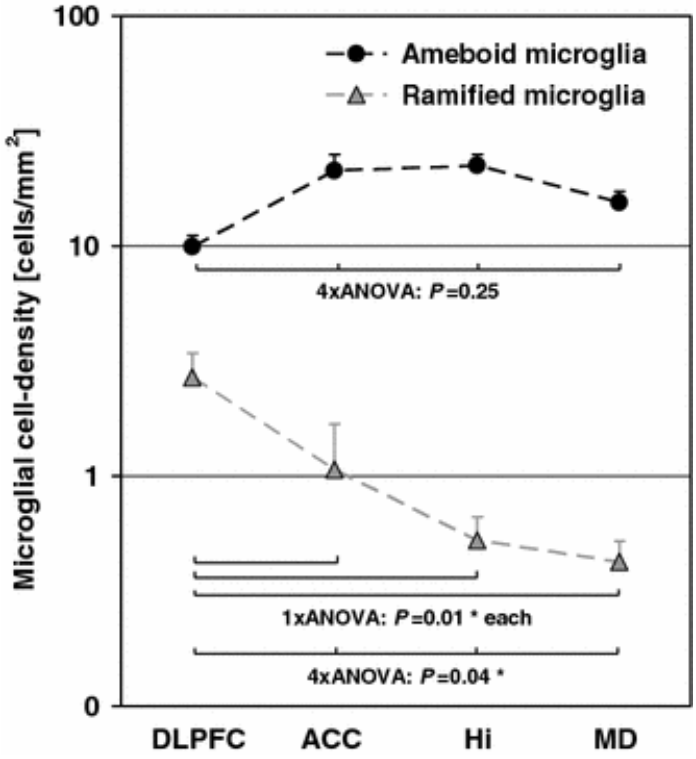

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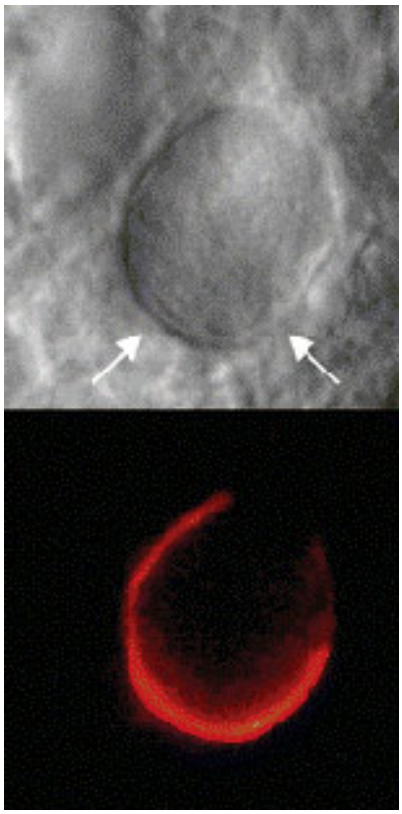

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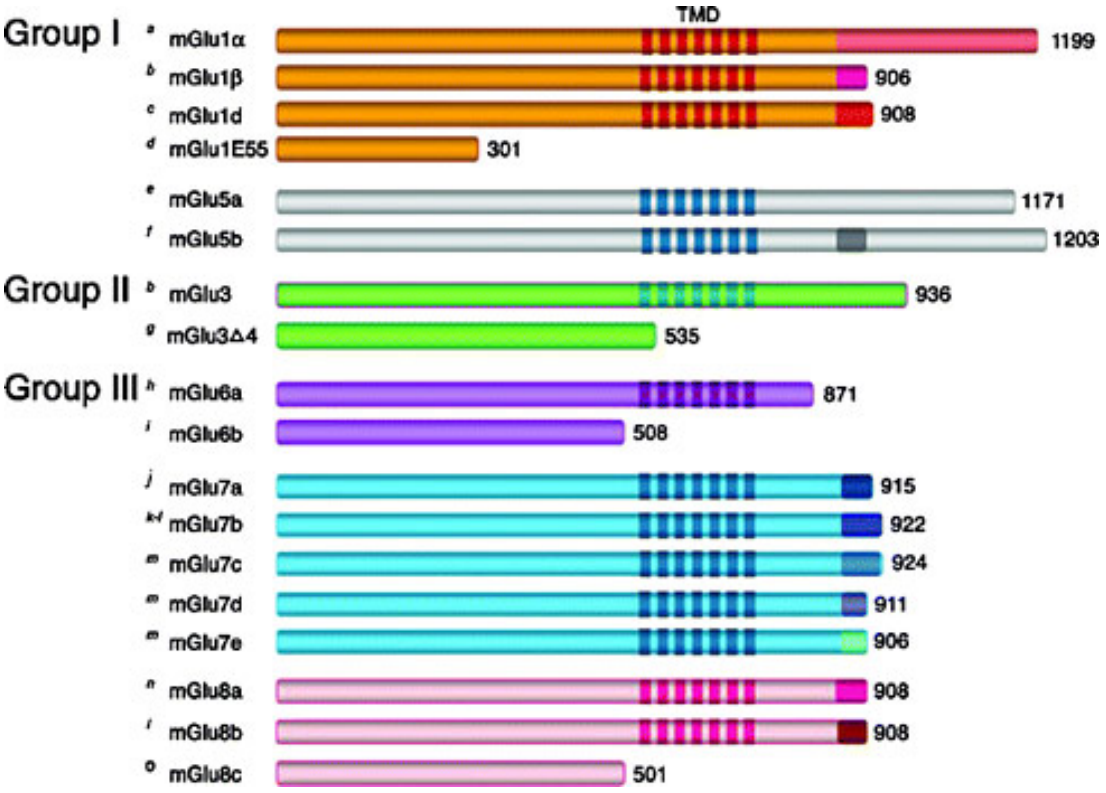

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Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is

a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

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Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered “informed”. However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

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For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

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Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Conflicts of interest/competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate":**

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish":**

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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