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Prevalence of autoimmune comorbidities and association with glycemic control by CGM-derived parameters in type 1 diabetes

Ana Margarida Rebelo Lopes

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Eu, Ana Margarida Rebelo Lopes, abaixo assinado, nº mecanográfico 201905359, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração do meu trabalho de Dissertação ou Monografia.

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TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Prevalence of autoimmune comorbidities and association with glycemic control by CGM-derived parameters in type 1 diabetes

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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Faculdade de Medicina da Universidade do Porto, 6 / 01 / 2025

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Ana Margarida Rebelo Lopes, abaixo assinado, nº mecanográfico 201905359, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 6/01/2025

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Ana Margarida Rebelo Lopes

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"É loucura odiar todas as rosas porque uma te espetou; abandonar todos os sonhos porque um deles não se realizou; perder a fé em todas as orações porque uma não foi atendida; desistir de todos os esforços porque um fracassou. (...) É loucura deitar fora todas as possibilidades de ser feliz porque uma tentativa não deu certo.
Recorda-te: há sempre outra oportunidade, outra amizade, outro amor, uma nova força. Para todo fim, um recomeço."

Estas palavras traduzem na perfeição o espírito com que encarei esta jornada e são a moldura ideal para os agradecimentos que aqui deixo.

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A conclusão desta etapa simboliza não apenas um fim, mas também o início de "novos recomeços", "há sempre outra oportunidade, outra amizade, outro amor, uma nova força.".

Trabalho de acordo com as normas da revista "Endocrine"

Prevalence of autoimmune comorbidities and association with glycemic control by CGM-derived parameters in type 1 diabetes

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Abstract

Purpose: Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease frequently associated with other autoimmune diseases. This study aims to evaluate the prevalence of additional autoimmunity in adults with T1D and its association with glycemic control, chronic complications, and other comorbidities.

Methods: We performed a cross-sectional study in adult patients with T1D, followed at the Endocrinology Department of a tertiary hospital, between May 2022 and May 2024. Clinical data collected included glycemic control (HbA1c and continuous glucose monitoring [CGM] parameters), diabetes complications, and other comorbidities. These parameters were compared according to the history of autoimmune diseases. Statistical analysis was performed using parametric and non-parametric tests, ANCOVA and logistic regression models, unadjusted and adjusted for age and sex.

Results: Of the 439 participants (48.8% female and mean age 36.8±14.1 years), 29.0% had at least one autoimmune disease, predominantly Hashimoto's thyroiditis (24.0%) and celiac disease (3.9%), with higher prevalence in women (p=0.001). HbA1c (7.8±1.3 vs. 7.7±1.3%, p=0.53) and CGM-derived parameters, such as glucose management indicator (7.4±0.8% vs. 7.4±0.9%, p=0.91) and time in range (56.7±16.2% vs. 58.6±19.7%, p=0.48), were similar in patients with and without autoimmune diseases.

Conclusions: Over one fourth of patients with T1D had a concomitant autoimmune disease. Our results suggest that the presence of other autoimmune diseases does not preclude the attainment of similar glycemic targets. Given the high risk of autoimmunity in T1D, systematic screening and personalized treatment should be considered. Prospective studies are warranted to explore the long-term implications on metabolic control and cardiovascular outcomes.

Keywords: Type 1 diabetes mellitus, autoimmune diseases, glycemic control, continuous glucose monitoring (CGM), hashimoto's thyroiditis, celiac disease

Introduction

Type 1 diabetes mellitus (T1D) is a complex autoimmune disease characterized by the destruction of pancreatic β-cells, leading to insulin deficiency and hyperglycemia. A recent meta-analysis (encompassing studies published from January 1980 to September 2019) reported a global incidence rate of T1D at 15 cases per 100,000 individuals and a prevalence rate of 9.5 cases per 10,000 individuals **[1].**

T1D is influenced by a combination of genetic, immunological, and environmental factors. **[2, 3]**. Autoimmune diseases encompass a spectrum group of chronic disorders characterized by dysregulated immune responses directed against self-antigens, culminating in tissue damage and functional impairment of affected organs. Due to shared genetic susceptibilies and overlapping immunopathogenic pathways, these conditions frequently co-occur in the same individual and within familial lineages **[4]**.

The interplay between T1D and other autoimmune diseases, along with their cumulative impact on glycemic control and chronic complications, remains an area of significant clinical interest and research **[5]**. A systematic review has shown that the prevalence of autoimmune hypothyroidism, celiac disease, adrenal insufficiency, vitiligo, and gastric autoimmunity is higher in individuals with T1D **[6]**.

The onset of T1D is most common during childhood and adolescence and frequently occurs before the development of other autoimmune conditions. By examining the presence of these coexisting conditions in adults with long-standing T1D, we can better understand the full burden of autoimmune diseases over a lifetime. This long-term perspective is vital, as the accumulation of autoimmune diseases may complicate diabetes management, impair glycemic control, and increase the risk of diabetes-related complications **[7]**. However, the evidence regarding the prevalence of concurrent autoimmune diseases and its impact on T1D is currently scarce.

Unlike previous research that primarily relied on mean HbA1c levels as the measure of control **[5, 8]**, our study assessed glycemic regulation using both CGM metrics and HbA1c levels, providing a more comprehensive analysis of glycemic patterns and control.

This cross-sectional study aims to evaluate and characterize patients with T1D concerning autoimmunity, and to investigate the relationship between the presence of other autoimmune diseases with detailed data on glycemic control, utilizing a range of CGM metrics.

Materials and methods

Study Design and Sample

We performed a cross-sectional study of adult patients (aged 18 years or older) with T1D who were followed in the Insulin Pump Clinic of the Endocrinology Department of São João Local Health Unit, in Porto, Portugal between May 2022 and May 2024. All patients with at least one clinic evaluation during this period were included in this analysis. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement **[9]**. The study protocol was reviewed and approved by the Ethical Committee of CHUSJ. For this type of study formal individual consent is not required.

Clinical Variables Collected and Comorbidities Definitions

Clinical characteristics were collected from the electronic health records. We collected demographic data, consisting of sex, age and educational level, physical activity, smoking habits, date of T1D diagnosis, duration of diabetes, family history of T1D, type of diabetes treatment (multiple daily injections or insulin pump), total daily dose of insulin (TDDI), the use of additional antidiabetic medications, vitamin D supplementation, micro- and macrovascular complications, and prevalent comorbidities.

Physical activity was graded as 0 (no activity or less than once a week) or 1 (twice or more a week). Smoking was defined as 0 (never smoked), 1 (current smoker) or 2 (former smoker).

Data on complications of T1D was also collected, including diabetic retinopathy, diabetic kidney disease and peripheral neuropathy. Diabetic kidney disease was diagnosed based on an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m² or the presence of albuminuria greater than 30 mg/day, for at least three months, attributed to diabetes.**[10]** Macrovascular complications such as coronary artery disease (CAD), cerebrovascular disease and peripheral arterial disease (PAD) were also recorded.

Concomitant comorbidities in the study population included hypertension and dyslipidemia. Hypertension was defined as the presence of an office systolic or diastolic blood pressure ≥140/90 mmHg in at least two separate consultations or the ongoing use of antihypertensive medications **[11]**. Dyslipidemia was identified based on total cholesterol levels >240 mg/dL, LDL cholesterol >130 mg/dL, HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, or triglyceride levels >150 mg/dL, or by the use of lipid-lowering medications **[12]**.

We collected anthropometric data, including height, weight, body mass index (calculated as weight/height^2), heart rate and office systolic and diastolic blood pressure, from the same clinical evaluation.

Autoimmune Disease Definition

This study assessed various autoimmune conditions based on established diagnostic criteria, through previous specific antibody screenings and clinical evaluations. Autoimmune thyroid disease was defined by the presence of positive anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies, with serum levels of thyroid-stimulating hormone (TSH) and thyroxine (T4) measured to assess thyroid function **[13]**. Celiac disease was diagnosed by the presence of anti-tissue transglutaminase IgA

(TTG-IgA) and anti-gliadin IgA antibodies, with confirmation through gastrointestinal biopsy **[14]**. Autoimmune gastritis was identified by detecting anti-parietal cell and anti-intrinsic factor antibodies, with diagnosis confirmed by gastric biopsy if positive **[15]**. For primary adrenal insufficiency, adrenal function was evaluated through measurements of adrenocorticotropic hormone (ACTH) and cortisol levels **[16]**. Systemic lupus erythematosus was assessed by investigating anti-nuclear antibodies (ANAs), anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), and anti-phospholipid antibodies, following standard diagnostic guidelines **[17]**.

Biochemical Variables

Analytical variables collected included glycated hemoglobin (HbA1c) and creatinine. Estimated glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula **[18]**.

Continuous Glucose Monitoring Parameters

In the timepoint of the clinical visit, the Continuous Glucose Monitoring (CGM) parameters of a 14-day report were extracted from the clinical records or LibreView® platform, if the active CGM time was ≥70%: time in range (TIR, 70–180 mg/dL), time below range (TBR, <70 mg/dL), time below 54 mg/dL (TB54), time above range (TAR, >180 mg/dL), time above 250 mg/dL (TA250), coefficient of variation (CV), glucose management indicator (GMI) and time in tight range (TITR, 70–140 mg/dL).

Statistical analysis

Results are presented as mean ± standard deviation for continuous normally distributed variables, or as median (25th – 75th percentiles) for non-normally distributed continuous variables. Categorical variables are presented as percentages and frequencies.

Clinical, analytical, and CGM-derived parameters were compared in T1D patients with and without the presence of other autoimmune diseases using t-student tests, for parametric variables, Mann-Whitney U tests, for non-parametric variables, and $\chi 2$ tests, for categorical variables. Logistic regression analysis and analysis of covariance (ANCOVA) adjusted for age and sex were also performed using the presence of autoimmune diseases as dependent variables and clinical, analytical and CGM-derived parameters as independent variables.

Unadjusted linear regression analysis was performed to evaluate the variation of clinical, analytical and CGM-derived parameters according to the absence or the presence of one or at least 2 autoimmune diseases (other than T1D).

Statistical analyses were performed with Stata® software, version 17.0 (StataCorp). A p value <0.05 was considered significant.

Results

Characteristics of the Sample and Prevalence of AID

This cross-sectional study comprised 439 individuals with T1D, with a mean age of 36.8 ± 14.1 years and 48.8% female. The average duration of diabetes was 18.0 years. Regarding lifestyle factors, 59.6% reported doing regular physical exercise and 77.2% abstained from alcohol consumption. Additionally, 12.6% were current smokers **(Table 1)**

Regarding comorbidities, hypertension was observed in 32.8% of individuals, while dyslipidemia was the most prevalent, affecting 55.1% of participants. Diabetic kidney disease was present in 12.1%, diabetic neuropathy in 5.7%, and diabetic retinopathy in 32.5%. Cardiovascular conditions were less common, with coronary artery disease (CAD) affecting 2.3%, cerebrovascular disease 1.6%, and peripheral artery disease (PAD) 2.1% of the study population.

Concurrent autoimmunity in T1D

Among the cohort, 127 (29.0%) were found to have at least one autoimmune disease. The most prevalent autoimmune disease identified was Hashimoto's thyroiditis, affecting 105 (24.0%) , followed by celiac disease (n=17, 3.9%), Graves' disease (n=9, 2.1%) and vitiligo (n=3, 0.7%). Notably, 2.1% of individuals had two or more autoimmune diseases. **(Table 1**)

Of the patients included, 387 had at least one determination of anti-thyroid antibodies, with 74 (19.1%) testing positive. A total of 337 patients had at least one determination of anti-celiac antibodies, with 23 (6.8%) testing positive. Of the 172 patients screened at least once for anti-gastritis antibodies, 25 (14.5%) had positive results. Finally, among the patients included in the study, 44 had at least one determination of anti-nuclear antibodies, with 17 (38.6%) showing positive results. **(Supplementary Table 1)**

Comparison between individuals according to the presence of other autoimmune disease

The presence of autoimmunity was associated with significant differences in gender distribution, with a lower proportion of males among those with autoimmune diseases (33.9% vs. 58.7%, $p<0.001$) **(Table 2)**. There was no significant difference in the mean age between the groups (37.8 ± 13.8 years for those with concurrent autoimmune diseases and 36.3 ± 14.2 years for those without, $p=0.33$), nor in educational level, physical activity, alcohol consumption, or smoking status. No significant difference between groups was observed for diabetes micro- or macrovascular complications or other comorbidities **(Table 2).**

In the analysis based on the number of autoimmune diseases (none, one, or two or more), the group with more autoimmune diseases had a lower proportion of males **(Supplementary Table 2)**.

Glycemic control in individuals according to the presence of other AID

Glycemic control, assessed via CGM metrics and HbA1c levels, showed no significant differences between the two groups. TIR did not differ significantly between those with autoimmune diseases and those without (58.6 ± 19.7% vs. 56.7 ± 16.2%, $p=0.48$). The coefficient of variation (CV) was also similar

between groups **(Table 3)**. GMI was comparable between the groups (7.4 ± 0.8 vs. 7.4 ± 0.9, p=0.82). Similar results were observed in the analysis by number of concurrent autoimmune diseases **(Supplementary Table 3)**.

When analyzing glycemic control by specific autoimmune disease, individuals with Hashimoto's thyroiditis (n=105) exhibited a mean HbA1c of 7.6 ± 1.2%, with a TIR of 60.3 ± 16.9% **(Table 4)**. Conversely, participants with celiac disease (n=17) had poorer glycemic metrics, with a mean HbA1c of 8.4 ± 2.1% and a lower TIR of 46.3 ± 34.1% **(Table 4)**.

Discussion

This cross-sectional study provides valuable insights into the prevalence and impact of autoimmune diseases among individuals with T1D. The findings demonstrate that autoimmunity is common in T1D and that approximately one in four patients with T1D had a concomitant autoimmune disease, most commonly Hashimoto's thyroiditis and celiac disease. A key strength of this study is that, to the best of our knowledge, this is the first to investigate the impact of autoimmune diseases on glycemic control using CGM parameters. Furthermore, it is also the first to explore the correlation between T1D and autoimmunity in a Portuguese cohort. Although this study underscores a high prevalence of autoimmune diseases in individuals with T1D, no significant association was identified between autoimmune comorbidity and impaired glycemic control.

The prevalence of additional autoimmune diseases among participants with T1D in our study was 29.0%, which markedly exceeds the estimated 3%–8% prevalence in the general population **[19, 20]** and some previously reported autoimmunity frequencies in T1D populations **[5, 7, 21]** .

Autoimmune thyroid disease is well recognized as the most common autoimmune disease in T1D **[8, 21]**, with an incidence 2-4 times higher than in the general population **[22]**. In our cohort, autoimmune thyroid disease was found in 26.1% of T1D participants, aligning with previous reports (15%–30%) **[8]**.

The diagnosis of thyroid disease was based on the presence of positive anti-thyroid antibodies, which are known to increase in frequency with age, disease duration, and long-term persistence of anti-glutamic acid decarboxylase (anti-GAD) antibodies in patients with T1D **[22]**. Among thyroid autoimmune diseases, Hashimoto's thyroiditis was the most prevalent in our study at 24%, while Graves' disease was identified in 2.1% of participants. These findings are comparable to previous studies, which reported prevalence ranges of 14%–28% for Hashimoto's thyroiditis and 0.5%–7% for Graves' disease **[8]**. This significant prevalence highlights the importance of regular screening for this disease from the onset of T1D, ideally on an annual basis or every two years, as recommended by the guidelines of the International Society for Paediatric and Adolescent Diabetes (ISPAD). **[5, 23]**

Celiac disease was diagnosed in 3.9% of the patients in our study, a figure consistent with the reported prevalence in other populations (4%–9%) **[8]**. This prevalence was slightly lower than the reported range in other studies, potentially due to the mean age of our cohort being 36.8 ± 14.1 years, whereas previous studies have typically focused on younger age groups. Furthermore, the prevalence of celiac disease varies significantly across different regions, influenced in part by the diagnostic criteria and the intensity of screening employed **[7]**. A recent meta-analysis reported a global prevalence of 1.4% when diagnosed using antitissue transglutaminase or antiendomysial antibody tests, but only 0.7% when confirmed by duodenal biopsy **[24]**. In our study, celiac disease was diagnosed through the assessment of specific antibodies, followed by confirmation via small intestine biopsy. Prior research **[5]** has demonstrated that the majority of celiac disease cases are identified within the first 5 years following the onset of T1D. However, diagnoses occurring up to 15 years post-T1D onset have also been reported, underscoring the importance of extending the screening period beyond 5 years **[23].**

Vitiligo was diagnosed in less than 1% of our cohort, consistent with the prevalence reported in a previous study (0.7%) **[5]**. It is well-established that vitiligo in patients with T1D elevates the risk of developing other conditions, particularly autoimmune thyroid disease and gastritis **[8, 25, 26]**.

No cases of primary adrenal insufficiency, systemic lupus erythematosus (SLE), rheumatoid arthritis, or premature ovarian failure were identified in our cohort, likely due to the limited sample size of this study. Nevertheless, previous research has established an association between these autoimmune disorders and type 1 diabetes (T1D), with higher prevalence rates reported in this patient population **[22].** The prevalence of Addison's disease in adult patients with T1D has been estimated at 0.8–1.9% **[27, 28]**; while the prevalence of SLE and rheumatoid arthritis in this population has been reported as 1.15% and 1.2%, respectively **[29]**.

These differences in prevalence between studies may be attributed to the geographical origin of our study population, which suggests potential variations in genetic predispositions and environmental exposures. Additionally, differences in screening policies and, most notably, age distribution among study cohorts could further account for the observed discrepancies **[7].**

The presence of concomitant autoimmune diseases was associated with significant differences in gender distribution, with a higher proportion of female among those with AIDs (66.1% vs. 41.3%, $p<0.001$). This female predominance is consistent with findings from similar studies **[5, 7, 21, 30]** and aligns with the established female preponderance in autoimmune disease literature **[31]**. This disparity is thought to be the result of several factors, such as the stronger immune response and the role of estrogen in enhancing the immune activity; also, genetic factors, such as X-chromosome-linked predispositions, physiological differences in organ vulnerability, environmental exposures and microchimerism may influence this increases risk **[31].**

Despite the high prevalence of autoimmune diseases, their presence did not significantly affect overall glycemic control, as assessed by HbA1c and CGM metrics. This suggests that additional autoimmune conditions do not preclude the attainment of similar glycemic targets in patients with only T1D. Interestingly, a trend towards improved glycemic metrics was observed in individuals with two or more autoimmune diseases. Although this observed trend did not reach statistical significance, it raises important questions about the potential factors contributing to enhanced glycemic regulation in this group. One plausible explanation could be the stricter clinical management typically offered to patients with multiple autoimmune conditions. This contrasts with findings that suggest that the presence of concurrent autoimmune diseases in individuals with T1D complicates glycemic control and induces varied symptomatology, affecting quality of life **[6, 8].**

Our results also suggest a different impact on glycemic control of different autoimmune diseases. For instance, participants with celiac disease had poorer glycemic outcomes compared to those with Hashimoto's thyroiditis, suggesting that specific autoimmune conditions may exert distinct influences on glucose regulation. This variability in the effects of autoimmune diseases on glycemic control has been suggested in prior studies, where hypothyroidism, celiac disease, and Addison’s disease were associated with hypoglycemia **[8]**, while hyperthyroidism increased the risk of hyperglycemia **[7]**.

This study distinguishes itself from other studies, such as the Finnish **[7]** and Swedish cohorts **[5]**, that reported results exclusively using HbA1c as a marker for glycemic control, by using Continuous

Glucose Monitoring (CGM) parameters to estimate the impact of autoimmune diseases on glycemic variability in individuals with Type 1 Diabetes. Although HbA1c is a well-established marker that reflects mean glucose levels over the past 2-3 months, it does not account for acute glycemic fluctuations or glucose variability, which can be important for understanding day-to-day glucose changes. Also, there are some studies that have highlighted the limitations of HbA1c, such as its inability to reflect interday or intraday glycemic variability and its susceptibility to being confounded by conditions like anemia and hemoglobinopathies, which may lead to misinterpretations of glycemic control **[32, 33]**. In contrast to this, CGM provides real-time data on glucose variations, allowing for a more detailed understanding of glycemic patterns **[34]**. This study takes a more comprehensive approach to evaluating the relationship between autoimmune diseases and glycemic control in T1D by utilizing a range of CGM metrics, including time-in-range (TIR), coefficient of variation (CV), and glucose management indicator (GMI). These metrics offer insights beyond what is provided by HbA1c alone, enhancing the understanding of glucose variability and control in T1D patients.

Given the challenges in managing both T1D and additional autoimmune diseases, these results underscore the need for personalized treatment strategies that address the unique clinical profiles of each patient. For instance, the poorer glycemic control observed in individuals with celiac disease suggests that these patients may require more intensive management and monitoring. Research has shown that a gluten-free diet could improve glycemic control, reduce hypoglycemic episodes in T1D, and prevent long-term bowel mucosal damage in celiac disease, as gluten is a well-known trigger for these autoimmune responses **[35]**.

It is important to highlight the limitations of this work. In a registry-based study, the accuracy and reliability of the findings are directly influenced by the quality of the recorded data, and any inaccuracies in registration can impose limitations on the findings. Moreover, linking the data to the electronic health records relies on the accuracy with which clinicians have documented patient diagnoses in the medical records. Additionally, we had no control regarding the specific tests and assessments conducted to support the diagnostic information. Furthermore, screening of autoimmune diseases was a clinician decision, thus lack of screening may underestimate the true prevalence of autoimmune diseases.

The main strength of this study is that it is the first to assess glycemic control using CGM parameters to estimate the impact of autoimmune diseases on glycemic control in individuals with T1D. Furthermore, despite the limited cohort size, it is also the first to correlate the prevalence of autoimmune comorbidities with glycemic control in a Portuguese cohort of individuals with type 1 diabetes.

To conclude, our study revealed that 29.0% of the 439 participants were diagnosed with at least one autoimmune disease, with Hashimoto's thyroiditis being the most prevalent, followed by celiac disease. It also showed that the occurrence of autoimmune diseases was significantly higher in women. Notably, glycemic control metrics, including GMI and TIR, measured through CGM, did not differ significantly between patients with and without autoimmune diseases. These findings suggest that the presence of autoimmune diseases does not appear to substantially impact glycemic control in this cohort. Given the

high risk of additional autoimmunity in T1D, systematic screening for other autoimmune diseases, particularly Hashimoto's thyroiditis and celiac disease, and personalized treatment strategies should be considered. Prospective studies are warranted to investigate the long-term implications of autoimmune diseases on glycemic control and cardiovascular outcomes in patients with T1D.

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Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Authors Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ML, ARL, PF, IM, JM, ML, JL, BV, MJB, SSM, JSN. The first draft of the manuscript was written by AML, ARL and JSN and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the ethical standards of the institutional and/or national research committee (Ethics Committee of the Centro Hospitalar São João - Porto, Portugal) (Date 20/10/2023/No 362/2023) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

This was a retrospective study based on data previously collected during medical consultations and recorded in the Sclinic system. No risks or constraints to the included or excluded patients are anticipated. Patients were not notified, as their identities were safeguarded through data coding. Crucial identifying information, such as names, was removed and replaced with unique codes. Therefore, informed consent to participate was not required.

Consent to publish

This study does not contain any identifiable personal data, images, or videos. All data were anonymized by replacing identifying information with codes. As such, consent for publication was not applicable.

Table 1. Characteristics of the study sample (n=439)

	n=439
Age, years (n=439)	36.8 ± 14.1
Duration of T1D, years (n= 432)	18.0 [12.0; 27.0]
Male sex (n=439), n (%)	226 (51.2%)
Education (n=302)	
Less than 9th grade, n (%)	6 (2.0 %)
Grade 9th to 12th grade, n (%)	134 (44.4 %)
Higher Education, n (%)	162 (53.6%)
Familiar history of DM1 (n= 230), n (%)	43 (18.7%)
Lifestyle Factors	
Physical exercise (n=225), n (%)	134 (59.6 %)
Alcohol consumption (n=228), n (%)	
No	176 (77.2%)
Mild consumption	33 (14.5%)
Moderate consumption	9 (3.9%)
Severe consumption	10 (4.4%)
Current smoker (n=341), n (%)	43 (12.6%)
Number of concurrent autoimmune diseases (n= 437), n (%)	
0	312 (71.1%)
1	118 (26.9%)

≥2	9 (2.1%)
Concurrent autoimmune diseases, n (%)	
Hashimoto thyroiditis (n=438)	105 (24.0%)
Graves' disease (n=439)	9 (2.1%)
Celiac disease (n=439)	17 (3.9%)
Primary adrenal insufficiency (n=439)	0 (0%)
Systemic Lupus Erythematosus (n=439)	0 (0%)
Rheumatoid arthritis (n=439)	0 (0%)
Vitiligo (n=439)	3 (0.7%)
Premature ovarian failure (n=439)	0 (0%)
Other comorbidities, n (%)	
Hypertension (n= 439)	144 (32.8%)
Dyslipidemia (n= 439)	242 (55.1%)
Diabetic kidney disease (n= 438)	53 (12.1%)
Diabetic neuropathy (n= 423)	24 (5.7 %)
Diabetic retinopathy (n= 421)	137 (32.5%)
CAD (n= 439)	10 (2.3%)
Cerebrovascular disease (n= 439)	7 (1.6%)
PAD (n= 436)	9 (2.1%)
Physical Exam	
BMI, kg/m^2 (n= 393)	25.2 ± 4.1
Heart rate, bpm (n= 321)	82.2 ± 15.3

Systolic BP, mmHg (n= 390)	127.4 ± 13.6
Diastolic BP, mmHg (n= 390)	77.4 ± 8.8
Clinical Laboratory Data	
HbA1c, % (n= 369)	7.8 ± 1.3
eGFR, ml/min/1.73m^2 (n=367)	101.6 ± 21.7
Medications	
Total daily dose of insulin (n= 262)	48.2 [38.0; 63.2]
Use of insulin pump (n= 439), n (%)	231 (52.6%)
Oral antidiabetic drugs (n=439), n (%)	
Metformin	21 (4.8%)
GLP-1 analogue	9 (2.1%)
SGLT2 inhibitors	20 (4.6%)
Vitamin D supplementation (n=439), n (%)	89 (20.3 %)
CGM-derived parameters	
TIR, % (n= 201)	57.3 ± 17.3
Time in hypoglycemia, % (n=182)	3.0 [1.0; 7.0]
Time in hyperglycemia, % (n=168)	36.0 [24.5; 50.0]
CV, % (n=189)	38.7 ± 6.8
GMI (n=188)	7.4 ± 0.8
TTIR (n=156)	36.0 [26.0; 45.5]

Legend: Data are mean (standard deviation), median (percentile25-75) or number (%). No corrections for multiple testing were applied. CAD, coronary artery disease; PAD, peripheral artery disease; BMI, body mass index; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate;GLP-1 analogue, glucagon-like

peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitors; TIR, time in range; CV, coefficient of variation; GMI, glucose management indicator; TTIR, total time in range.

Table 2. Characteristics of the study sample (n=439)

	No Autoimmune Disease	**Autoimmune Disease**	**P-value**	**P- value adjusted for age and sex**
	n=312	n=127		
Demographic Variables				
Age, years (n=439)	36.3 ± 14.2	37.8 ± 13.8	0.33	0.32
Male sex (n=439), n(%)	**183 (58.7)**	**43 (33.9)**	**<0.001**	**<0.001***
Education (n=302) , n(%)			0.22	0.91
Less than 9th grade	3 (1.4)	3 (3.4)		
Grade 9th to 12th grade	101 (47.0)	33 (37.6)		
Higher Education	111 (51.6)	51 (58.6)		
Lifestyle Factors				
Physical exercise (n=225), n(%)	99 (60.4)	35 (57.4)	0.68	0.79
Alcohol consumption (n=228), n(%)			0.54	0.81
No	126 (77.3)	50 (76.9)		
Social consumption	22 (13.5)	11 (16.9)		
Moderate consumption	6 (3.7)	3 (4.6)		
Severe consumption	9 (5.5)	1 (1.5)		
Smoking (n=341) , n(%)			0.77	0.35
Current smoker	31 (12.8)	12 (12.1)		
Former smoker	17 (7.0)	5 (5.1)		

Never smoked	194 (80.2)	82 (82.8)		
Medical History				
Age at DM1 diagnosis (n=341)	15.6 ± 10.9	16.5 ± 11.8	0.41	0.99
Diabetes duration, years (n=432), n(%)	18.0 [12.0; 25.0]	20.0 [13.0; 30.0]	0.25	0.95
Familiar history of DM1 (n=230), n(%)	33 (20.0)	10 (15.2)	0.38	0.77
Hypertension (n=439), n(%)	103 (32.7)	42 (33.1)	0.94	0.92
Dyslipidemia (n=439), n(%)	172 (55.1)	70 (55.1)	1.00	0.37
Microvascular complication, n(%)				
Diabetic kidney disease (n=438)	41 (13.1)	12 (9.5)	0.29	0.29
Diabetic neuropathy (n=423)	16 (5.3)	8 (6.7)	0.58	0.62
Diabetic retinopathy (n=421)	96 (31.9)	41 (34.2)	0.65	0.88
Macrovascular complication, n(%)				
CAD (n=439)	**10 (3.2)**	**0 (0.0)**	**0.041**	= .
Cerebral vascular disease (n=439)	4 (1.3)	3 (2.4)	0.41	0.86
PAD (n=436)	7 (2.3)	2 (1.6)	0.67	0.58
Physical Exam				
BMI, kg/m^2 (n=493)	25.1 ± 4.0	25.3 ± 4.3	0.75	0.97
Heart rate, bpm (n=321)	81.9 ± 15.5	83.1 ± 14.8	0.51	0.85
Systolic BP, mmHg (n=390)	127.6 ± 13.2	127.0 ± 14.7	0.71	0.85
Diastolic BP, mmHg (n=390)	77.8 ± 8.9	76.5 ± 8.4	0.18	0.50
Clinical Laboratory Data				

eGFR, ml/min/1.73m^2 (n=367)	103.0 ± 21.8	98.4 ± 21.2	0.07	0.52
Vitamin D (n=331)	**24.0 [18.0; 36.0]**	**29.0 [21.0; 37.0]**	**0.048**	0.25
Medications				
Total daily dose of insulin (n=262), IU	50.1 [38.0; 64.3]	44.2 [36.5; 55.2]	0.06	0.54
Use of Insulin pump (n=439), n(%)	167 (53.5)	64 (50.4)	0.55	0.29
Oral antidiabetic drugs (n=439), n(%)				
Metformin	17 (5.4)	4 (3.1)	0.31	0.26
GLP-1 receptor agonist	**9 (2.9)**	**0 (0.0)**	**0.05**	-
SGLT2 inhibitors	17 (5.4)	2 (2.4)	0.16	0.15

Legend: Data are mean (standard deviation), median (percentile25-75) or number (%). No corrections for multiple testing were applied. P- value adjusted for age and sex. * adjusted only for age. CAD, coronary artery disease; PAD, peripheral artery disease; BMI, body mass index; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate;GLP-1 analogue, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

Table 3. Glycemic control according to the presence of autoimmune disease (n=439)

	No Autoimmune Disease n=312	Autoimmune Disease n=127	P-value	P- value adjusted for age and sex
HbA1c, %	7.8 ± 1.3	7.7 ± 1.3	0.53	0.57
CGM-derived data				
TIR (n= 201)	56.7 ± 16.2	58.6 ± 19.7	0.48	0.71
CV (n=189)	39.1 ± 6.8	37.6 ± 6.8	0.18	0.17
GMI (n=156)	7.4 ± 0.8	7.4 ± 0.9	0.91	0.44
TITR (n=156)	35.0 [26.0; 45.0]	41.0 [25.0; 49.0]	0.34	0.31
Time in hypoglycemia (n=182)	3.0 [1.0; 7.0]	2.5 [1.0; 5.0]	0.12	0.08
Time in hyperglycemia (n=168)	37.0 [27.0; 50.0]	32.0 [23.0; 51.0]	0.32	0.95

Legend: Data are mean (standard deviation), median (percentile25-75) or number (%). No corrections for multiple testing were applied. TIR, time in range; CV, coefficient of variation; GMI, glucose management indicator; TTIR, time in tight range.

Table 4. Glycaemic control in T1D patient with specific AIDsc

	Hashimoto Thyroiditis n=105
Hb A1c (n= 94)	7.6 ± 1.2
CGM-derived data	
TIR (n=49)	60.3 ± 16.9
CV (n=46)	38.5 ± 6.2
GMI (n=46)	7.3 ± 0.7
TTIR (n=37)	41.0 [30.0; 49.0]
Time in hypoglycemia (total) (n=44)	2.5 [1.0; 4.5]
Time in hyperglycemia (total) (n=39)	32.0 [23.0; 47.0]

	Celiac Disease n=17
Hb A1c (n= 15)	8.4 ± 2.1
CGM-derived data	
TIR (n=7)	46.3 ± 34.1
CV (n=7)	29.7 ± 5.5
GMI (n=7)	8.1 ± 1.6
TTIR (n=6)	19.5 [2.0; 59.0]

Time in hypoglycemia (total) (n=6)	0.0 [0.0; 2.0]
Time in hyperglycemia (total) (n=6)	61.0 [12.0; 88.0]

Legend: Data are mean (standard deviation), median (percentile25-75) or number (%). No corrections for multiple testing were applied. TIR, time in range; CV, coefficient of variation; GMI, glucose management indicator; TITR, time in tight range.

Supplementary Material

Supplementary Table 1: Positive autoantibody screening results

	Positive screening result n=439
Anti-thyroid antibodies (n= 387)	74 (19.1%)
Anti-celiac antibodies (n= 337)	23 (6.8%)
Anti-gastritis antibodies (n=172)	25 (14.5%)
Anti-nuclear antibodies (n=44)	17 (38.6%)

The total number of participants screened for each antibody type is indicated in parentheses. Data is presented as absolute frequencies (percentages).

Supplementary Table 2: Clinical and analytical characteristics according to the number of autoimmune diseases (0,1 or 2 or more)

	Autoimmune Disease=0	**Autoimmune Disease=1**	**Autoimmune Disease=2 or more**	**P value**
	n=312	n=118	n=9	
Demographic Variables				
Age, years (n=439)	36.3 ± 14.2	37.5 ± 13.9	41.1± 14.0	0.25
Male sex (n=439), n (%)	**183 (58.7)**	**40 (33.9)**	**3 (33.3)**	**<0.001**
Education (n=302), n (%)				0.38
Less than 9th grade	3 (1.4)	3 (3.8)	0 (0.0)	
Grade 9th to 12th grade	101 (47.0)	30 (37.5)	3 (42.9)	
Higher Education	111 (51.6)	47 (58.8)	4 (57.1)	
Lifestyle Factors				
Physical exercise (n=225), n(%)	99 (60.4)	34 (58.6)	1 (33.3)	0.55
Alcohol consumption (n=228), n(%)				0.79
No	126(77.3)	46 (79.3)	4 (57.1)	
Social consumption	22 (13.5)	8 (13.8	3 (42.9)	
Moderate consumption	6 (3.7)	3 (5.2)	0 (0.0)	
Severe consumption	9 (5.5)	1 (1.7)	0 (0.0)	
Smoking (n=341), n(%)				0.84
Current smoker	31 (12.8)	9 (9.9)	3 (37.5)	
Former smoker	17 (7.0)	5 (5.5)	0 (0.0)	

Never smoked	194 (80.2)	77 (84.6)	5 (62.5)	
Medical History, n(%)				
Age at DM1 diagnosis (n=431)	15.6 ± 10.9	16.5 ± 11.7	16.9 ± 13.4	0.41
Diabetes duration, years (n= 432)	18.0 [12.0; 25.0]	20.0 [14.9; 29.0]	18.0 [11.0; 37.0]	0.24
Familiar history of DM1 (n= 230)	33 (20.1)	10 (15.9)	0 (0.0)	0.31
Hypertension (n= 439)	102 (32.7)	37 (31.4)	5 (55.6)	0.63
Dyslipidemia (n= 439)	172 (55.1)	65 (55.1)	5 (55.6)	1.00
Microvascular complication				
Diabetic kidney disease (n= 438)	41 (13.1)	12 (10.3)	0 (0.0)	0.21
Diabetic neuropathy (n=423)	16 (5.3)	7 (6.1)	1 (16.7)	0.43
Diabetic retinopathy (n= 421)	96 (31.9)	39 (34.2)	2 (33.3)	0.67
Macrovascular complications				
CAD (n= 439)	10 (3.2)	0 (0.0)	0 (0.0)	0.050
Cerebral vascular disease (n= 439)	4 (1.3)	3 (2.5)	0 (0.0)	0.53
PAD (n= 436)	7 (2.3)	1 (0.9)	1 (12.5)	0.86
Physical Exam				
BMI, kg/m^2 (n= 393)	25.1 ± 4.0	25.1 ± 4.2	28.7 ± 4.5	0.38
Heart rate, bpm (n= 321)	81.9 ± 15.5	83.0 ± 14.9	84.8 ± 14.1	0.48
Systolic BP, mmHg (n= 390)	127.6 ± 13.2	126.8 ± 15.0	130.4 ± 9.4	0.86
Diastolic BP, mmHg (n= 390)	77.8 ± 8.9	76.1 ± 8.2	81.9 ± 9.7	0.39
Clinical Laboratory Data				
HbA1c, % (n=369)	7.8 ±1.3	7.7 ±1.3	7.8 ±1.4	0.62

eGFR, ml/min/1.73m^2 (n= 367)	103.0 ± 21.8	98.0 ± 21.5	102.7 ± 17.6	0.11
Vitamin D, ng/mL (n=331)	**24.0 [18.0; 36.0]**	**28.0 [21.0; 37.0]**	**31.5 [29.5; 38.0]**	**0.034**
Medications				
Total daily dose of insulin (n= 260), UI	50.1 [38.0, 64.3]	44.2 [37.2, 52.5]	58.6 [36.0, 92.0]	0.16
Use of insulin pump (n= 439), n(%)	167 (53.5)	59 (50.0)	5 (55.6)	0.63
Oral antidiabetic drugs (n=439), n(%)				
Metformin	17 (5.9)	3 (2.5)	1 (11.1)	0.51
GLP-1 receptor agonist	9 (2.9)	0 (0.0)	0 (0.0)	0.06
SGLT2 inhibitors	17 (5.4)	2 (1.7)	1 (11.1)	0.32
Vitamin D supplement (n=439)	64 (20.5)	22 (18.6)	3 (33.3)	0.92

Legend: Data are mean (standard deviation), median (percentile25-75) or number (%). No corrections for multiple testing were applied. CAD, coronary artery disease; PAD, peripheral artery disease; BMI, body mass index; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate;GLP-1 analogue, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

Supplementary Table 3: Glycaemic Control by Continuous Glucose Monitoring according to the number of autoimmune diseases (0,1 or 2 or more)

	Autoimmune Disease=0 (n=312)	**Autoimmune Disease=1 (n=118)**	**Autoimmune Disease=2 or more (n= 9)**	**P value**
TIR (n=201)	56.7 ± 16.2	58.1 ± 19.7	72.5 ± 19.1	0.36
CV (n=189)	39.1 ± 6.8	37.8 ± 6.8	33.0 ± 2.6	0.13
GMI (n=188)	7.4 ± 0.8	7.4 ± 0.9	7.0 ± 0.7	0.97
TITR (n=156)	35.0 [26.0; 45.0]	41.0 [25.0; 49.0]	46.0 [30.0; 62.0]	0.29

Time in hypoglycemia (total) (n=182)	3.0 [1.0; 7.0]	3.0 [1.0; 7.0]	1.0 [0.0; 2.0]	0.08
Time in hyperglycemia (total) (n= 168)	37.0 [27.0; 50.0]	32.0 [23.0; 51.0]	26.5 [12.0; 41.0]	0.26

Legend: Data are mean (standard deviation), median (percentile25-75) or number (%). No corrections for multiple testing were applied. Data from continuous glucose monitoring was extracted from 14-days reports. TIR, time in range; CV, coefficient of variation; GMI, glucose management indicator; TITR, time in tight range.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional 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	Page 1: "We performed a cross-sectional study"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 1: "This study aims to evaluate the prevalence of additional autoimmunity in adults with T1D and its association with glycemic control, chronic complications, and other comorbidities. "; "We performed a cross-sectional study in adult patients with T1D, followed at the Endocrinology Department of a tertiary hospital, between May 2022 and May 2024."; "Over one fourth of patients with T1D had a concomitant autoimmune disease. Our results suggest that the presence of other autoimmune diseases does not preclude the attainment of similar glycemic targets."
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2: "Type 1 diabetes mellitus (T1D) is a complex autoimmune disease characterized by the destruction of pancreatic β-cells, leading to insulin deficiency and hyperglycemia."; "The interplay between T1D and other autoimmune diseases, along with their cumulative impact on glycemic control and chronic complications, remains an area of significant clinical interest and research."; "Unlike previous research that primarily relied on mean HbA1c levels as the measure of control, our study assessed glycemic regulation using both CGM metrics and HbA1c levels, providing a more comprehensive analysis of glycemic patterns and control."
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2: "This cross-sectional study aims to evaluate and characterize patients with T1D concerning autoimmunity, and to investigate the relationship between the presence of other autoimmune diseases with detailed data on glycemic control, utilizing a range of CGM metrics."

Methods

Study design	4	Present key elements of study design early in the paper	Page 3: “We performed a cross-sectional study of adult patients (aged 18 years or older) with T1D”
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3: “adult patients (aged 18 years or older) with T1D who were followed in the Insulin Pump Clinic of the Endocrinology Department of São João Local Health Unit, in Porto, Portugal between May 2022 and May 2024. All patients with at least one clinic evaluation during this period were included in this analysis.”
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 3: “All patients with at least one clinic evaluation during this period were included in this analysis.”
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 3 and 4: "We collected demographic data, consisting of sex, age, and educational level, physical activity, smoking habits, date of T1D diagnosis, duration of diabetes, family history of T1D, type of diabetes treatment (multiple daily injections or insulin pump), total daily dose of insulin (TDDI), the use of additional antidiabetic medications, vitamin D supplementation, micro- and macrovascular complications, and prevalent comorbidities."; "Autoimmune thyroid disease was defined by the presence of positive anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies."; "Analytical variables collected included glycated hemoglobin (HbA1c) and creatinine."; "Time in range (TIR, 70–180 mg/dL), time below range (TBR, <70 mg/dL), time below 54 mg/dL (TB54), time above range (TAR, >180 mg/dL), time above 250 mg/dL (TA250), coefficient of variation (CV), and glucose management indicator (GMI)."
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment	Page 3 and 4: "Clinical characteristics were collected from the electronic health records." "The Continuous Glucose Monitoring (CGM) parameters of a 14-day report were extracted from the clinical records or LibreView® platform, if the active CGM time was ≥70%."

		methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	Page 4: "Analysis of covariance (ANCOVA) adjusted for age and sex was also performed using the presence of autoimmune diseases as dependent variables and clinical, analytical and CGM-derived parameters as independent variables."
Study size	10	Explain how the study size was arrived at	Page 3: "All patients with at least one clinic evaluation during this period were included in this analysis."
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 4: "Results are presented as mean ± standard deviation for continuous normally distributed variables or as median (25th–75th percentiles) for non-normally distributed continuous variables."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 4: "Clinical, analytical, and CGM-derived parameters were compared in T1D patients with and without the presence of other autoimmune diseases using t-student tests, for parametric variables, Mann-Whitney U tests, for non-parametric variables, and χ^2 tests, for categorical variables."; "Logistic regression analysis and analysis of covariance (ANCOVA) adjusted for age and sex were also performed using the presence of autoimmune diseases as dependent variables and clinical, analytical and CGM-derived parameters as independent variables. Unadjusted linear regression analysis was performed to evaluate the variation of clinical, analytical and CGM-derived parameters according to the absence or the presence of one or at least 2 AIDs (other than T1D). Statistical analyses were performed with Stata® software, version 17.0 (StataCorp)."
		(*b*) Describe any methods used to examine subgroups and interactions	Page 4: "Logistic regression analysis and analysis of covariance (ANCOVA) adjusted for age and sex were also performed using the presence of autoimmune diseases as dependent variables and clinical, analytical, and CGM-derived parameters as independent variables.";

			"Unadjusted linear regression analysis was performed to evaluate the variation of clinical, analytical, and CGM-derived parameters according to the absence or the presence of one or at least 2 AIDs (other than T1D).".
		(*c*) Explain how missing data were addressed	“Screening of autoimmune diseases was a clinician decision, thus lack of screening may underestimate the true prevalence of autoimmune diseases.”
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 3: "We performed a cross-sectional study of adult patients (aged 18 years or older) with T1D who were followed in the Insulin Pump Clinic of the Endocrinology Department of São João Local Health Unit, in Porto, Portugal between May 2022 and May 2024."
		(*e*) Describe any sensitivity analyses	The study did not report any formal 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	Page 5: "This cross-sectional study comprised 439 individuals with T1D."
		(b) Give reasons for non-participation at each stage	Our study had no exclusion criteria.
		(c) Consider use of a flow diagram	As we do not have exclusion criteria, it does not apply
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 5 and 6: "This cross-sectional study comprised 439 individuals with T1D, with a mean age of 36.8 ± 14.1 years and 48.8% female. The average duration of diabetes was 18.0 years. Regarding lifestyle factors, 59.6% reported doing regular physical exercise and 77.2% abstained from alcohol consumption. Additionally, 12.6% were current smokers." "Hypertension was observed in 32.8% of individuals, while dyslipidemia was the most prevalent, affecting 55.1% of participants.

			Diabetic kidney disease was present in 12.1%, diabetic neuropathy in 5.7%, and diabetic retinopathy in 32.5%." "Among the cohort, 126 (28.9%) were found to have at least one autoimmune disease. The most prevalent autoimmune disease identified was Hashimoto's thyroiditis, affecting 105 (24.0%)..."
		(b) Indicate number of participants with missing data for each variable of interest	In each table of the article, the number of patients with available data is presented.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 5 and 6: "The presence of autoimmunity was associated with significant differences in gender distribution, with a lower proportion of males among those with autoimmune diseases (32.8% vs. 58.9%, p<0.001)."; "Glycemic control, assessed via CGM metrics and HbA1c levels, showed no significant differences between the two groups."; "When analyzing glycemic control by specific autoimmune disease, individuals with Hashimoto's thyroiditis exhibited a mean HbA1c of 7.6 ± 1.2%, with a TIR of 60.3 ± 16.9%. Conversely, participants with celiac disease had poorer glycemic metrics, with a mean HbA1c of 8.4 ± 2.1% and a lower TIR of 46.3 ± 34.1%."
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	Page 4: "Logistic regression analysis and analysis of covariance (ANCOVA) adjusted for age and sex were also performed using the presence of autoimmune diseases as dependent variables and clinical, analytical, and CGM-derived parameters as independent variables." And in the tables of the article.
		(*b*) Report category boundaries when continuous variables were categorized	No continuous variable were categorized.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Estimates of relative risk were not translated into absolute risk.

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 4 to 6: "Unadjusted linear regression analysis was performed to evaluate the variation of clinical, analytical, and CGM-derived parameters according to the absence or the presence of one or at least 2 AIDs (other than T1D)." "The presence of autoimmunity was associated with significant differences in gender distribution, with a lower proportion of males among those with autoimmune diseases (32.8% vs. 58.9%, p<0.001)." "When analyzing glycemic control by specific autoimmune disease, individuals with Hashimoto's thyroiditis exhibited a mean HbA1c of 7.6 ± 1.2%, with a TIR of 60.3 ± 16.9%. Conversely, participants with celiac disease had poorer glycemic metrics, with a mean HbA1c of 8.4 ± 2.1% and a lower TIR of 46.3 ± 34.1%."
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 7: "This cross-sectional study provides valuable insights into the prevalence and impact of autoimmune diseases among individuals with T1D. The findings demonstrate that autoimmunity is common in T1D and that approximately one in four patients with T1D had a concomitant autoimmune disease, most commonly Hashimoto's thyroiditis and celiac disease. [...] Although this study underscores a high prevalence of autoimmune diseases in individuals with T1D, no significant association was identified between autoimmune comorbidity and impaired glycemic control."
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	Page 9: "It is important to highlight the limitations of this work. In a registry-based study, the accuracy and reliability of the findings are directly influenced by the quality of the recorded data, and any inaccuracies in registration can impose limitations on the findings. Moreover, linking the data to the electronic health records relies on the accuracy

			with which clinicians have documented patient diagnoses in the medical records. Additionally, we had no control regarding the specific tests and assessments conducted to support the diagnostic information. Furthermore, screening of autoimmune diseases was a clinician decision, thus lack of screening may underestimate the true prevalence of autoimmune diseases."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 8 and 9: “Despite the high prevalence of autoimmune diseases, their presence did not significantly affect overall glycemic control, as assessed by HbA1c and CGM metrics. This suggests that additional autoimmune conditions do not preclude the attainment of similar glycemic targets in patients with only T1D. Interestingly, a trend towards improved glycemic metrics was observed in individuals with two or more autoimmune diseases. Although this observed trend did not reach statistical significance, it raises important questions about the potential factors contributing to enhanced glycemic regulation in this group. One plausible explanation could be the stricter clinical management typically offered to patients with multiple autoimmune conditions.”; “Our results also suggest a different impact on glycemic control of different autoimmune diseases. For instance, participants with celiac disease had poorer glycemic outcomes compared to those with Hashimoto's thyroiditis, suggesting that specific autoimmune conditions may exert distinct influences on glucose regulation."; "This study distinguishes itself from other studies, such as the Finnish and Swedish cohorts, that reported results exclusively using HbA1c as a marker for glycemic control, by using Continuous Glucose Monitoring (CGM) parameters to estimate the impact of autoimmune diseases on glycemic variability in individuals with Type 1 Diabetes. [...] These metrics offer insights beyond what is provided by HbA1c alone, enhancing the understanding of glucose

			variability and control in T1D patients."; "Given the challenges in managing both T1D and additional autoimmune diseases, these results underscore the need for personalized treatment strategies that address the unique clinical profiles of each patient. For instance, the poorer glycemic control observed in individuals with celiac disease suggests that these patients may require more intensive management and monitoring."
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 7 to 9: "This prevalence was slightly lower than the reported range in other studies, potentially due to the mean age of our cohort being 36.8 ± 14.1 years, whereas previous studies have typically focused on younger age groups." "These differences in prevalence between studies may be attributed to the geographical origin of our study population, which suggests potential variations in genetic predispositions and environmental exposures. Additionally, differences in screening policies and, most notably, age distribution among study cohorts could further account for the observed discrepancies." "Given the challenges in managing both T1D and additional autoimmune diseases, these results underscore the need for personalized treatment strategies that address the unique clinical profiles of each patient."
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	Page 14: "The authors declare that no funds, grants, or other support were received during preparation of this manuscript."

*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 www.strobe-statement.org.

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Manuscript Submission

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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

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- Trial registration number and date of registration for prospectively registered trials
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References

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

1. Negotiation research spans many disciplines [3].

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- Book chapter

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- Authors should avoid untrue statements about an entity (who can be an individual person or a company) or descriptions of their behavior or actions that could potentially be seen as personal attacks or allegations about that person.
- Research that may be misapplied to pose a threat to public health or national security should be clearly identified in the manuscript (e.g. dual use of research). Examples include creation of harmful consequences of biological agents or toxins, disruption of immunity of vaccines, unusual hazards in the use of chemicals, weaponization of research/technology (amongst others).
- Authors are strongly advised to ensure the author group, the Corresponding Author, and the order of authors are all correct at submission. Adding and/or deleting authors during the revision stages is generally not permitted, but in some cases may be warranted. Reasons for changes in authorship should be explained in detail. Please note that changes to authorship cannot be made after acceptance of a manuscript.

*All of the above are guidelines and authors need to make sure to respect third parties rights such as copyright and/or moral rights.

Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results presented. This could be in the form of raw data, samples, records, etc. Sensitive information in the form of confidential or proprietary data is excluded.

If there is suspicion of misbehavior or alleged fraud the Journal and/or Publisher will carry out an investigation following COPE guidelines. If, after investigation, there are valid concerns, the author(s) concerned will be contacted under their given e-mail address and given an opportunity to address the issue. Depending on the situation, this may result in the Journal's and/or Publisher's implementation of the following measures, including, but not limited to:

- If the manuscript is still under consideration, it may be rejected and returned to the author.
- If the article has already been published online, depending on the nature and severity of the infraction:

  - an erratum/correction may be placed with the article

  - an expression of concern may be placed with the article

- or in severe cases retraction of the article may occur.

The reason will be given in the published erratum/correction, expression of concern or retraction note. Please note that retraction means that the article is **maintained on the platform**, watermarked "retracted" and the explanation for the retraction is provided in a note linked to the watermarked article.

- The author's institution may be informed
- A notice of suspected transgression of ethical standards in the peer review system may be included as part of the author's and article's bibliographic record.

Fundamental errors

Authors have an obligation to correct mistakes once they discover a significant error or inaccuracy in their published article. The author(s) is/are requested to contact the journal and explain in what sense the error is impacting the article. A decision on how to correct the literature will depend on the nature of the error. This may be a correction or retraction. The retraction note should provide transparency which parts of the article are impacted by the error.

Suggesting / excluding reviewers

Authors are welcome to suggest suitable reviewers and/or request the exclusion of certain individuals when they submit their manuscripts. When suggesting reviewers, authors should make sure they are totally independent and not connected to the work in any way. It is strongly recommended to suggest a mix of reviewers from different countries and different institutions. When suggesting reviewers, the Corresponding Author must provide an institutional email address for each suggested reviewer, or, if this is not possible to include other means of verifying the identity such as a link to a personal homepage, a link to the publication record or a researcher or author ID in the submission letter. Please note that the Journal may not use the suggestions, but suggestions are appreciated and may help facilitate the peer review process.

Authorship principles

These guidelines describe authorship principles and good authorship practices to which prospective authors should adhere to.

Authorship clarified

The Journal and Publisher assume all authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out, **before** the work is submitted.

The Publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In absence of specific guidelines it is recommended to adhere to the following guidelines*:

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

Disclosures and declarations

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

Data transparency

All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on (sharing) research data in concordance with disciplinary norms and expectations.

Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee(ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

Cell Line: RST307 cell line **RRID:CVCL_C321**

Antibody: Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered’ should be included as the last line of the manuscript abstract.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal’s Instructions for Authors.

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 ‘Ethics approval’.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

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.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

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.

Consent to Participate

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.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies.

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SÃO JOÃO

CUIDADOS DE SAÚDE PRIMÁRIOS

REPÚBLICA PORTUGUESA SAÚDE | SNS SERVIÇO NACIONAL DE SAÚDE | UNIDADE LOCAL DE SAÚDE SÃO JOÃO

DELIBERAÇÃO DO CONSELHO DE ADMINISTRAÇÃO

Após apreciação e pareceres favoráveis da Comissão de Ética e do Centro de Epidemiologia Hospitalar, considerando que se encontram reunidos os requisitos e demais trâmites previstos no circuito para submissão de projetos de investigação na ULS de São João e em conformidade com as disposições legais em vigor, o Conselho de Administração – ao abrigo das competências previstas no Artigo 71.º dos Estatutos dos hospitais, centros hospitalares, institutos portugueses de oncologia e unidades locais de saúde, aprovados pelo Decreto-Lei n.º 52/2022, de 4 de agosto – delibera:

1. Aprovar a realização do projeto de investigação:
   - "Avaliação e caraterização de doentes com Diabetes Mellitus tipo 1 no Hospital de São João do Porto".
   - Serviço(s) onde decorrerá o projeto de investigação: Endocrinologia.
   - Investigador(a) principal: João Sérgio Neves
2. Remeta-se à Comissão de Ética para os procedimentos adequados e demais trâmites convenientes.

CONSELHO DE ADMINISTRAÇÃO DA ULS DE SÃO JOÃO, EPE • REUNIÃO DE 15 DE FEVEREIRO DE 2024

Presidente do Conselho de Administração			
Prof.ª Doutora Maria João Baptista			
Diretor Clínico	Enfermeiro Diretor	Vogal Executiva	Vogal Executiva
--- AUSENTE ---		--- AUSENTE ---	
Prof.º Doutor Roberto Roncon	Enfermeiro Paulo Emílio Mota	Dra. Sofia Leal	Dra. Fernanda Oliveira

› Comissão de Ética
› Centro de Epidemiologia Hospitalar
› Direção Clínica

CE 362/2023

Centro de Epidemiologia Hospitalar

Tomei conhecimento. Nada a opor. À DC.

09 de Fevereiro de 2024

A Diretora do Centro de Epidemiologia Hospitalar

(Prof.ª Doutora Ana Azevedo)

n.º 362 / 2023

SÃO JOÃO

DIRECÇÃO CLÍNICA
12 FEV. 2024

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar Universitário de São João

Nome do Investigador Principal:
João Sérgio Neves

Título da Investigação:
Avaliação e caracterização de doentes com Diabetes Mellitus tipo 1 no Hospital de São João do Porto

Centro Hospitalar São João
Centro de Epidemiologia Hospitalar
01/02/2024

Pretendendo realizar no(s) Serviço(s) de:
Endocrinologia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar Universitário de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 08 *de* Outubro *de* 2023 .

Assinado por: **João Sérgio de Lima Soares Neves**
Num. de Identificação: 13590757
Data: 2023.10.08 22:58:19 +01'00'

CHAVE MÓVEL

SÃO JOÃO

Encarregado de Proteção de Dados
Data Protection Officer

Entrada 23/11/2023

CES-IM005-1

Parecer da Comissão de Ética do Centro Hospitalar Universitário de São João

Título do Projeto: Avaliação e caracterização de doentes com Diabetes Mellitus tipo 1 no Hospital de São João do Porto

Nome do Investigador Principal: Dr. João Sérgio de Lima Soares Neves (Assistente Hospitalar de Endocrinologia, no CHUSJ e Docente da FMUP), que dispõe da competência científica para a realização do estudo. Serão co-investigadoras as estudantes da FMUP Joana Maria Gomes Afonso Lagoa e Ana Margarida Rebelo Lopes.

Onde decorre o Estudo: No Serviço de Endocrinologia do CHUSJ. Apresentou a declaração da Dra. Joana Queiroz, Diretora do Serviço de Endocrinologia. O Serviço dispõe das condições para a realização do estudo

Objetivos do Estudo:

Trata-se de um estudo retrospetivo, observacional e sem intervenção que tem como objetivos: caracterizar, avaliar e relacionar a obesidade e patologias autoimunes em doentes com Diabetes Mellitus tipo 1 em estudo.

Conceção e Pertinência do estudo:

O estudo é pertinente e adequado porquanto consta no protocolo submetido à CES: "A conexão entre o Diabetes Mellitus tipo 1 e a autoimunidade é amplamente reconhecida; contudo, ainda é necessária uma análise abrangente e quantitativa que englobe todas as doenças autoimunes correlacionadas e sua incidência dentro desta condição clínica. Com esta investigação, pretende-se estudar a co-ocorrência de doenças autoimunes isoladas ou no contexto de síndromes autoimunes poliglandulares (APS) e autoimunidade familiar em doentes com DM1, com o intuito de se implementar a realização de rastreios adequados, visando um correto diagnóstico, a melhoria do controlo glicémico e da sintomatologia clínica."

Como já mencionado, este é um estudo observacional retrospetivo com doentes com Diabetes Mellitus tipo 1 do CHUSJ (tamanho da amostra: 1000 doentes).

Os dados a recolher de forma anonimizada e pertinente e adequada aos objetivos do estudo, são os seguintes: data e idade de diagnóstico, história familiar de Diabetes Mellitus tipo 1 e 2, anticorpos presentes na Diabetes, hemoglobina glicada, doenças autoimunes (doença tiroideia, doença celíaca, insuficiência suprarrenal primária, lúpus, insuficiência ovárica primária e vitiligo) e seus anticorpos respetivos; dados do estilo de vida, dados antropométricos, perfil lipídico, avaliação das tensões arteriais; complicações macrovasculares e microvasculares; fármacos anti-dislipidémicos, anti-diabéticos, anti-hipertensores e fármacos para a obesidade.; dados da bomba de insulina e da monitorização contínua de glicose.

Benefício/risco: Não aplicável (estudo retrospetivo).

Confidencialidade dos dados:

De modo a garantir a confidencialidade e segurança dos dados, estes serão colhidos, armazenados e tratados anonimamente através da codificação dos números do processo. Apenas o investigador principal terá acesso à chave.

Apresentou um pedido de reutilização de registos clínicos para Investigação e Desenvolvimento ao RAI, e uma 'avaliação sobre o impacto da proteção de dados' para o EPD.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável.

***Curriculum* do investigador**: Adequado à investigação.

Data previsível da conclusão do estudo: junho de 2024. Este estudo não tem encargos financeiros para o CHUSJ.

Conclusão: Proponho um parecer favorável à realização do estudo.

Porto, 20 de outubro de 2023

O Relator da CE, Prof. Doutor Manuel Vaz da Silva

Questionário eletrónico

n.º 362 / 2023

SÃO JOÃO

SUBMISSÃO DE PROJETO DE INVESTIGAÇÃO PARA PARECER E AUTORIZAÇÃO

Preenchimento em formato digital obrigatório

Caro/a Investigador/a

Este questionário vai ser objeto de apreciação pela Comissão de Ética (CE), que emitirá o competente parecer; pelo Responsável de Acesso à Informação (RAI), que emitirá um despacho de autorização ou indeferimento, relativamente à reutilização da informação a que pretende ter acesso; pelo Encarregado de Proteção de Dados (EPD), que emitirá um parecer, mediante a 'avaliação do impacto sobre a proteção de dados' (que deve anexar a este pedido); pelo Centro de Epidemiologia Hospitalar; sendo enviado, num último momento, para decisão institucional do Conselho de Administração do CHUSJ. Os respetivos despachos de parecer e autorização serão exarados no final deste documento, e enviados posteriormente, de modo a poder iniciar, nesse momento, a investigação a que se propõe.

IDENTIFICAÇÃO DO ESTUDO

Título do projeto:

Avaliação e caracterização de doentes com Diabetes Mellitus tipo 1 no Hospital de São João do Porto

Data prevista para início: 20 /11 /2023 Data prevista para o término: 30 /06 /2024

EQUIPA DE INVESTIGAÇÃO

1. Investigador principal

Nome: João Sérgio Neves

Afiliação institucional: ☒ CHUSJ ☒ FMUP Outro:

Serviço/ Departamento: Endocrinologia

Grupo profissional: Médico, Assistente Hospitalar Cédula Profissional n.º: 57073

Contacto telefónico: 914837245 Endereço eletrónico institucional: joao.sergio.neves@chsj.min-saude.pt

Formação em Boas Práticas Clínicas (GCP): ☐ Não ☒ Sim

2. Co-investigadores

Nome: Joana Maria Gomes Afonso Lagoa

Afiliação institucional: FMUP

Grupo profissional: Estudante Cédula Profissional n.º:

Contacto telefónico: 915006106 Endereço eletrónico institucional: up201907400@edu.med.up.pt

Nome: Ana Margarida Rebelo Lopes

Afiliação institucional: FMUP

Grupo profissional: Estudante Cédula Profissional n.º:

Contacto telefónico: 910910360 Endereço eletrónico institucional: up201905359@edu.med.up.pt

(acrescentar nº de investigadores, se apropriado ao projeto de investigação)

3. Promotor *(se aplicável)*:

CARACTERIZAÇÃO DA INVESTIGAÇÃO

1. Metodologia da investigação

☐ Qualitativa ☒ Mista (qualitativa+quantitativa) ☐ Outra. Qual? _____

Se quantitativa:

☐ Experimental ☐ Observacional ☒ Sem intervenção ☐ Com intervenção

Se experimental ou observacional com intervenção, qual o tipo de intervenção?

☐ Algoritmo de decisão diagnóstica/terapêutica ☐ Comunicação

☐ Outra. Qual? _____

2. Aleatorização dos braços de intervenção: ☒ Não ☐ Sim

3. Se observacional, qual o desenho?

☐ Coorte prospetivo ☐ Coorte retrospetivo ☐ Caso-controlo

☒ Transversal ☐ Ecológico ☐ Outro. Qual? _____

REALIZAÇÃO DA INVESTIGAÇÃO

Local onde se realiza a investigação: ☒ CHUSJ ☐ FMUP ☐ Outro

Serviço/ Departamento: Endocrinologia

Existem outros Centros onde se realizará a investigação? ☒ Não ☐ Sim. Quais? _____

ENTIDADE(S) QUE TUTELA(M) A INVESTIGAÇÃO

1. CHUSJ – Serviço: Endocrinologia

2. FMUP – Departamento: _____

3. Outra instituição. Qual? _____

ORIENTADOR *(se aplicável)*

Nome: _____

Afiliação: _____ Endereço eletrónico institucional: _____

PROFISSIONAL DE LIGAÇÃO *(se aplicável - ver anexo)*

Nome: _____ Serviço: _____

ENQUADRAMENTO DA INVESTIGAÇÃO

Em trabalho académico? ☐ Não ☒ Sim Conferidor de grau? ☐ Não ☒ Sim

Síntese dos objetivos:

O presente estudo transversal incide sob uma população de doentes com Diabetes Mellitus tipo 1 do CHUSJ. O principal objetivo do estudo é caracterizar, avaliar e relacionar a obesidade e patologias autoimunes com a doença em estudo.

Fundamentação ética *(incluir informação sumária sobre o estado da arte, ganhos em conhecimento/inovação, ponderação geral sobre benefícios/risco)*:

Não há nenhum risco ou incómodo evidente para os doentes cujos dados serão analisados neste projeto de investigação. Como benefícios espera-se alargar o conhecimento na área da diabetes, obesidade e autoimunidade.

PARTICIPANTES PREVISTOS PARA A INVESTIGAÇÃO

Estão definidos critérios de inclusão / de exclusão de doentes? ☐ Não ☒ Sim

Onde e como serão recrutados os participantes no estudo?
Registos clínicos informatizados de doentes com Diabetes Mellitus tipo 1 do CHUSJ.

Qual é o tamanho amostral? 1000

Está prevista a recolha de material biológico específico para a investigação?

☒ Não ☐ Sim. Identifique e justifique:

BENEFÍCIO/RISCO DECORRENTE DA PARTICIPAÇÃO

Descreva os benefícios previsíveis:
Aumento do conhecimento na área da diabetes, obesidade e autoimunidade.

Descreva os riscos/incómodos previsíveis:

Sem riscos/incómodos previsíveis

CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE

Prevê a obtenção de consentimento informado? ☐ Sim ☒ Não

Se não, justifique: Reutilização de registos de dados clínicos

Prevê informação escrita para os participantes? ☐ Sim. **Enviar modelo preenchido.**

☒ Não. Justifique: Reutilização de registos de dados clínicos

O modelo para obtenção de consentimento é o modelo institucional do CHUSJ? ☐ Sim ☐ Não

PROTEÇÃO DE DADOS PESSOAIS

Necessita consultar registos clínicos? ☐ Não ☒ Sim

Está previsto o tratamento de dados pessoais? ☐ Não ☒ Sim

Se sim, de que forma é garantida a pseudonimização dos dados recolhidos? *(codificação, uso de filtros, siglas...)*

De modo a garantir a confidencialidade e segurança dos dados, estes serão colhidos, armazenados e tratados anonimamente através da codificação dos números do processo. Apenas o investigador principal terá acesso à chave.

Descreva o património informacional a que pretende ter acesso *(v.g.: nome, idade, data nascimento, idade, morada, diagnóstico, história clínica, tratamento...)*:

Data e idade de diagnóstico, história familiar de Diabetes Mellitus tipo 1 e 2, anticorpos presentes na Diabetes, hemoglobina glicada. Doenças autoimunes (doença tiroideia, doença celíaca, insuficiência suprarrenal primária, lúpus, insuficiência ovárica primária e vitiligo) e seus anticorpos respetivos. Dados do estilo de vida, dados antropométricos, perfil lipídico, avaliação das tensões arteriais. Complicações macrovasculares e microvasculares. Fármacos anti-dislipidémicos, anti-diabéticos, anti-hipertensores e fármacos para a obesidade. Dados da bomba de insulina e da monitorização contínua de glicose.

Está prevista a criação de um Banco de Dados? ☐ Não ☒ Sim

Está previsto o registo de som ou de imagem dos participantes? ☒ Não ☐ Sim

O estudo envolve investigação genética? ☒ Não ☐ Sim

PROPRIEDADE INTELECTUAL

De quem será a propriedade intelectual da investigação e seus resultados?

☒ Investigador ☐ Promotor ☒ Serviço/CHUSJ ☐ Todos

DIVULGAÇÃO DOS RESULTADOS

Está prevista a divulgação dos resultados da investigação? ☐ Não ☒ Sim

Se sim, estão definidos critérios de publicação? ☒ Não ☐ Sim. Quais? _____

CONTRAPARTIDAS PARA OS PARTICIPANTES

Estão previstas contrapartidas para os participantes? ☒ Não ☐ Sim

Pela participação? ☒ Não ☐ Sim

Pelas deslocações? ☒ Não ☐ Sim

Pelas perdas salariais? ☒ Não ☐ Sim

Por outras perdas e/ou danos? ☒ Não ☐ Sim

EXAMES COMPLEMENTARES DE DIAGNÓSTICO

Estão previstos exames complementares de diagnóstico, para além dos inerentes à rotina assistencial?

☒ Não ☐ Sim. Quais? _____

Por quem serão suportados estes custos?

_____

PROTOCOLO FINANCEIRO

Existe protocolo financeiro com o CHUSJ? ☒ Não ☐ Sim

SEGURO

Este estudo prevê intervenção clínica que implique a existência de um seguro para os participantes?

☒ Não ☐ Sim *(se sim, junte cópia da respetiva Apólice)*

Data previsível para fim das credenciais de acesso: 30 /06 /2024

DOCUMENTOS ANEXOS *(em suporte digital)*

- [x] Pedido de autorização ao Presidente do Conselho de Administração do CHUSJ
- [x] Protocolo do estudo
- [ ] Caderno de recolha de dados (CRF)
- [x] Declaração Diretor(es) Serviço(s)
- [x] Informação Orientador
- [ ] Profissional de ligação
- [ ] Informação aos participantes
- [ ] Modelo de consentimento a utilizar
- [ ] Instrumentos de avaliação (*escalas, inquéritos*) _____
- [x] Curriculum/a vitae *(investigador/es)*
- [ ] Questionário para Encarregado de Proteção de Dados (EPD)
- [ ] Termo de Responsabilidade do Centro Académico Clínico *(para investigadores da FMUP que não pertençam ao CHUSJ)*
- [ ] Protocolo financeiro
- [ ] Outros: _____

TERMO DE RESPONSABILIDADE

Aceitação dos termos e condições de reutilização

Cumulativamente com as obrigações decorrentes da *Lei n.º 26/2016, de 22 de agosto*, maxime dos *n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12*, ao submeter o presente pedido, concordo e fico ainda juridicamente vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Após explicação do RAI do CHUSJ, embora a Lei 26/2016, de 22 de agosto, imponha como requisito a anonimização sem possibilidades de reversão, tal desiderato, é não só uma impossibilidade matemática já comprovada, como ainda resulta num prejuízo para a investigação, face à quantidade e à qualidade da informação a retirar à fonte, razão pela qual, concordando com o RAI, assumimos como compromisso a pseudonimização, o que impõe uma avaliação e gestão do risco, num quadro ético-jurídico que aceitamos e nos comprometemos a colaborar e respeitar;
- Não vou elaborar registos, suscetíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Comprometo-me a consultar os processos clínicos nos termos e locais que me forem indicados para o efeito;
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, poderá resultar no apuramento de responsabilidades disciplinares, civis e penais, e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.
- Independentemente de requerer a Certidão de Reutilização, DAta REuse Certificate for Research (DARE), comprometo-me a citar as fontes, sempre que publicitar, no todo ou em parte, resultados da presente investigação.

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Eu, João Sérgio Neves,

abaixo assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes na Declaração de Helsínquia (1960, e sucessivas emendas), da Organização Mundial de Saúde, da Convenção de Oviedo e das 'Boas Práticas Clínicas' (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CE de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CE o relatório final da investigação, assim que concluído.

Assinado por: **João Sérgio de Lima Soares Neves**
Num. de Identificação: 13590757
Data: 2023.10.08 23:12:28+01'00'

Data: 08 / 10 / 2023

CHAVE MÓVEL

COMISSÃO DE ÉTICA CHUSJ/FMUP

Parecer da CE, emitido na reunião plenária de 26 / 10 / 2023

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Centro Hosp. Univ. São João
Comissão de Ética
Manuel Vaz Silva
Presidente

RAI 23016505

RAI - Responsável pelo Acesso à Informação no Centro Hospitalar Universitário de São João (Art. 9º, Lei 26/2016 de 22 de Agosto)

SÃO JOÃO
Gabinete de Apoio ao RAI
Recebido em 21/11/2023
A funcionária

SÃO JOÃO
AUTORIZADO
RAI - Responsável pelo Acesso à Informação do Centro Hospitalar de São João (Art. 9º, Lei 26/2016 de 22/8)
21/11/2023

CENTRO DE EPIDEMIOLOGIA HOSPITALAR

ENCARREGADO DE PROTEÇÃO DE DADOS (EPD)
UNIDADE LOCAL DE SAÚDE SÃO JOÃO, E.P.E.
Paulo Alexandre Mota da Silva
Encarregado de Proteção de Dados do CHUSJ
epd@chsj.min-saude.pt

SÃO JOÃO

Ref.ª CES CHUSJ: **362 / 2023**

Título do Projeto Avaliação e caracterização de doentes com Diabetes Mellitus tipo 1 no Hospital de São João do Porto

Responsável pelo tratamento	João Sérgio Lima Soares Neves
Instituição	Unidade Local de Saúde São João (ULSSJOAO)
	Faculdade de Medicina da Universidade do Porto (FMUP)
Investigador	**Interno** Externo
Contacto telefónico	914837245 **Endereço Electrónico** u011761@chsj.min-saude.pt
Profissional de Ligação	Não aplicável
Amostra	1000

Análise de Risco Tolerável **Baixo** Elevado Muito Elevado

Parecer do EPD: **Data:** 06/02/2024

Finalidade: avaliar e caracterizar os doentes com Diabetes Mellitus tipo 1 do Hospital de São João do Porto e a sua relação com a autoimunidade e a obesidade.

Licitude: fundamento previsto no artigo 9(2)**(j)**, com as garantias do **89(1)** do **RGPD**, e artigo **31(1)** da **LERGPD**.

Categorias de dados pessoais: variáveis identificadas com detalhe na AIPD, datada de 23/11/2023, **ponto 13**, tendo presente o **princípio da minimização dos dados.**

Conservação: os dados serão alvo de **pseudonimização**, armazenados em **local seguro**, em área restrita com acesso limitado ao Investigador Principal, com acesso a ficheiros protegido por **palavra-passe**, efetuando-se a conservação até a conclusão da investigação, que se estima ser até **31 de julho de 2025**. Os dados recolhidos **serão destruídos** após a finalização do estudo.

Comunicação de Dados: **não há partilha** de dados pessoais.

Face ao exposto, e observadas as recomendações, entende-se que a presente AIPD apresenta os elementos necessários para assegurar que o **tratamento é realizado em conformidade com o RGPD.**

Recomendações:

1. Garantir medidas de segurança adicionais no transporte dos dados com recurso a dispositivos electrónicos de armazenamento (Laptop), nomeadamente através de medidas de cifragem e autenticação;
2. Garantir medidas de segurança adicionais (ex. transformar os dados com recursos a técnicas de generalização, perturbação e/ou como último recurso, a supressão de dados) para os dados que, ainda que pseudonimizados, contém elementos informativos que no seu conjunto possibilitam a re-identificação dos participantes, tendo presente a amostra em estudo (doentes seguidos em consulta de DM tipo 1), em particular na fase de disseminação ou publicação dos resultados (incluindo repositórios científicos);
3. Em caso de necessidade de extensão de prazo e/ou de qualquer alteração dos pressupostos atinentes ao presente parecer o Investigador Principal deverá solicitar a reapreciação do projeto de investigação junto do EPD.

Revisão AIPD:

☐ Data da próxima revisão: ___/___/_____ ☒ Não carece de revisão.

Anexos:

1. Processo CES n.º 362/2023
2. Parecer CES (20/10/2023)
3. AIPD (23/11/2023)
4. Protocolo de Investigação

Encarregado de Proteção de Dados
Assinado por: **PAULO ALEXANDRE MOTA DA SILVA**
Data: 2024.02.06 10:12:33+00'00'
Localização: ULS SÃO JOÃO

CARTÃO DE CIDADÃO

FACULDADE DE **MEDICINA**