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Diabetes: The influence of pharmacological treatment in disease control and underlying obesity

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Diabetes: The influence of pharmacological treatment in disease control and underlying obesity

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ABBREVIATIONS

ACeS – *Agrupamento de Centros de Saúde*

aGLP1 – *análogos do* glucagon-like peptide-1

AP – abdominal perimeter

ARS – *Administração Regional de Saúde*

BMI – body mass index

DM – diabetes mellitus

GLP1a – glucagon-like peptide-1 analogues

HbA1c – glycated haemoglobin

IMC – *índice de massa corporal*

iSGLT2 – *inibidores do co-transportador 2 de sódio e glicose*

PA – *perímetro abdominal*

SGLT2i – sodium-glucose cotransporter type 2 inhibitors

T2DM – type 2 diabetes mellitus

ABSTRACT

Background: There is no specific knowledge about the association between pharmacological treatment with drugs that promote weight loss and the control of both type 2 diabetes mellitus (T2DM) and associated obesity in the Primary health context in Portugal. Such a study is important because of the link between obesity and T2DM and the metabolic control of patients concomitantly affected by these two chronic diseases, which must be verified in large real world populations.

Aim: To compare the progression of obesity and the metabolic control between 2017 and 2019, according to pharmacological therapy (glucagon-like peptide-1 analogues (GLP1a) and/or sodium-glucose cotransporter type 2 inhibitors (SGLT2i) versus a group without any of these drugs) in the diabetic population in the general practice context in Central Portugal.

Methodology: Retrospective cohort study in 2021 of the T2DM population enrolled in Central Administrative Portuguese National Health Service Authority, the "*ARS do Centro"*. All data were anonymously obtained and provided by the Informatic Services of *ARS do Centro*, after ethics consent. Gender, age, time since the diagnosis, abdominal perimeter (AP), body mass index (BMI) and last glycated haemoglobin (HbA1c) evaluation in 2017, as well as all the same parameters registered in 2019 and drugs prescribed according to the e.registration official program, the *S-Clínico,* Diabetes sheet of each of the T2DM suffering people, were collected.

Results: Out of the 127062 T2DM patients of the *ARS do Centro* n=16012 (12.6%) were on medication in 2017, with no data regarding GLP1a users. Mean age was of 73.5±10.1 years, the time since diagnosis was of 8.7±4.2 years and 48.8% were males. HbA1C, BMI and AP values between both assessment points were independent of age and time since diagnosis, $|r_S| < 0.400$. A statistically significant difference was found in median HbA1c values between the two assessment moments, 2017 and 2019, both in the total sample and in the subgroups medicated with SGLT2i in the sample and per gender, with increasing values, ($p<0.001$). In the subgroups medicated with other drugs rather than SGLT2i, no statistically significant difference was observed, either globally ($p=0.983$) or per gender (M: $p=0.932$; F: $p=0.932$). The BMI in subjects under SGLT2i showed statistically significant negative variation ($p<0.001$) as in the group medicated with other drugs ($p=0.004$). The AP values showed significant increase between the two assessment points in the group medicated with drugs other than SGLT2i ($p=0.001$) and a statistically significant increase when compared with patients under SGLT2i ($p<0.001$).

Discussion: The out-comes burden of these two chronic diseases implies the need for further studies on therapies like SGLT2i and GLP1a, hence the importance of information about GLP1a to compare with other drugs and SGLT2i results. The alleged efficacy of new classes of anti-diabetic drugs must be verified in real world patients, therefore effectiveness must be the point to measure. It is possible that decreased BMI and AP are associated in a future decrease of HbA1c.

Conclusion: SGLT2i achieved a significant decrease in the BMI and prevented an increase in AP, when compared with other anti-diabetes drugs. Regarding HbA1c control, in a 2-year gap no decrease in growth dynamics was observed.

Keywords: Diabetes, Pharmacological treatment, Obesity, Retrospective cohort

RESUMO

Introdução: Atualmente, não existe conhecimento específico sobre a associação entre o tratamento farmacológico, usando fármacos que promovam a perda de peso, e o controlo tanto da *diabetes mellitus (*DM) tipo 2 como da obesidade associada, no contexto dos Cuidados de Saúde Primários Portugueses. Tal estudo é importante pelo impacto e conexão entre estas doenças crónicas e o controlo metabólico dos pacientes concomitantemente afetados. Esta interação deve ser avaliada numa coorte representativa da população atual.

Objetivo: Comparar a progressão da obesidade e o controlo metabólico entre 2017 e 2019, de acordo com a terapia farmacológica (análogos do *glucagon-like peptide 1* (aGLP1) e/ou inibidores do co-transportador 2 de sódio e glicose (iSGLT2) versus um grupo sem nenhum destes medicamentos) nos pacientes com DM tipo 2 inscritos na Administração Regional de Saúde (ARS) da região Centro de Portugal.

Material e métodos: Estudo de coorte retrospetivo em 2021 da população com DM tipo 2 inscrita na ARS do Centro. Os dados foram obtidos anonimamente e fornecidos pelos Serviços de Informática da ARS, após consentimento da comissão de ética. Foram pedidos género, idade, tempo desde o diagnóstico, perímetro abdominal (PA), índice de massa corporal (IMC) e última avaliação de hemoglobina glicada (HbA1c) em 2017, e os mesmos parâmetros relativos a 2019 e medicamentos prescritos de acordo com o programa oficial S-Clínico de Diabetes de cada uma das pessoas que sofrem de DM tipo 2.

Resultados: Dos 127062 pacientes em estudo, apenas 16012 (12,6%) estavam medicados com iSGLT2 ou outra medicação (não havia dados relativos aos aGLP1). Na amostra 48,8% eram homens e 50,2% mulheres. A idade média foi 73,47±10,08 anos e o tempo desde o diagnóstico de 8,67±4,22 anos. Relativamente aos valores de HbA1C, IMC e PA entre ambos os pontos de avaliação estes mostraram-se independentes da idade e do tempo desde o diagnóstico, uma vez que $|r_S|<0,400$. Foi encontrada um aumento estatisticamente significativo nos valores medianos de HbA1c entre 2017 e 2019 tanto no total como nos subgrupos medicados com iSGLT2 tanto total e por sexo ($p<0,001$). Nos subgrupos medicados com outros medicamentos em vez de iSGLT2, não foi observada diferença estatisticamente significativa, quer globalmente ($p=0,983$) quer por sexo (M: $p=0,932$; F: $p=0,932$). O IMC em sujeitos sob iSGLT2 mostrou variação estatisticamente significativa ($p<0,001$) tal como no grupo medicado com outros fármacos ($p=0,004$), no sentido da redução. Os valores do PA mostraram um crescimento estatisticamente significativo no grupo medicado com outros medicamentos que não iSGLT2 ($p=0,001$) e um aumento estatisticamente significativo quando comparado com os pacientes sob iSGLT2 ($p<0,001$).

Discussão: O peso destas doenças crónicas adensa a necessidade de mais estudos sobre terapias como iSGLT2 e aGLP1, daí a importância da informação sobre aGLP1 para comparar com outros medicamentos e os resultados dos iSGLT2. Os resultados do estudo são extremamente importantes para discutir a eficiência farmacológica, e alguns exigirão uma investigação mais aprofundada.

Conclusão: A terapêutica com iSGLT2 teve uma maior diminuição, estatisticamente significativa, no IMC e impediu um aumento no PA, quando comparado com outra medicação. Em relação ao controlo pela HbA1c, num intervalo de 2 anos, não foi verificada redução da dinâmica de crescimento com nenhuma medicação.

Palavras-chave: Diabetes, Tratamento farmacológico, Obesidade, Coorte retrospetiva

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterised by long periods of hyperglycaemia, resulting from defects in insulin secretion, its insufficient action or both. It is associated with several organs damage and failure. Two major types are described: type 1 diabetes mellitus, a deficit in insulin secretion and type 2 diabetes mellitus (T2DM), insulin resistance prevailing.(1-5)

T2DM prevalence accounts for about 90% of the diabetic population and its prevalence continues to increase.(2, 3) It consists of a variable degree of peripheral insulin resistance, culminating in periods of hyperglycaemia. Its pathogenesis, in the long term, will lead to a decrease in insulin production, which will become insufficient to suppress the body's needs due to the underlying insulin resistance.(4, 5) Nowadays, DM represents a major public health matter both in Portugal and globally.

Obesity, characterized by an increase in body fat, evaluated in clinical context by the body mass index (BMI). (6, 7) It is a major chronic disease worldwide with epidemic proportions and affecting all age groups.(3, 6, 8-12)

According to the Regional Health Profile for the Portuguese Central Region in Portugal (2018 edition) obesity was, in primary health care registrations, the fourth most frequent health problem with a prevalence of 10.2% and DM the fifth one with an 8.8% prevalence. There is a prevalence increase as age increases.(13)

The Portuguese National Health Service in Central Portugal comprises Local Health Units (two) and Primary Health Centres Clusters (six) differing in its administrative relationship with the board of the *Administração Regional de Saúde (ARS) do Centro,* the decentralised board of the Portuguese government.(13)

Different studies have shown that obesity is highly related to the insulin resistance in T2DM (3, 10, 14-17) and approximately 80-90% of these patients are overweight (BMI ≥ 25 kg/m^2 and BMI < 30 kg/m^2 (6)) or obese (BMI ≥ 30 kg/m^2(6)).(2, 3, 18) The underlying pathophysiology includes altered adipocyte metabolism, as a consequence of fat over-load or as a consequence of pharmacological treatment with drugs such as insulin or sulfonylureas, which favour the absorption of glucose and an increase in adipose tissue, predominantly

abdominal.(18, 19) There are current therapeutic options, e.g. glucagon-like peptide-1 analogues (GLP1a) and sodium-glucose cotransporter type 2 inhibitors (SGLT2i), that are able to reduce glucose intake or excrete glucose, allowing fat reduction.(18, 20-22)

GLP1a operates in a similar way as endogenous GLP1, produced by small bowel's cells. These incretin receptors are distributed across different tissues including the pancreas, gastrointestinal tract, central nervous system, among others. Incretin is responsible for stimulating insulin secretion from β-pancreatic cells and decreasing that of glucagon in α-pancreatic cells, by glucose decreased production in the liver, through a phenomenon dependent on blood glucose concentrations.(23-26) In the central nervous system, GLP1 regulates appetite by decreasing it, increasing satiety and leading to weight loss.(25, 26) Concomitantly, at gastrointestinal level, it has a predominant effect in delaying gastric emptying, such as decreasing small intestinal peristalsis, which leads to slower glucose absorption, lowering the post-prandial glucose peak.(23, 25, 26)

SGLT2i, also called gliflozins, act through an insulin-independent mechanism and may indirectly modify insulin secretion and action. Its primary mechanism stops renal reabsorption of glucose in the proximal convoluted tubule – segment S1 and S2 – by blocking the sodium-glucose cotransporter SGLT2. This process results in increased glucose excretion in the urine lowering blood glucose levels, leading to a negative energy balance, which results in body weight loss. (22, 27, 28) In addition, it has the potential to delay the development of diabetic nephropathy (21, 22, 28, 29), which improves the patients' life quality and is a positive clinical out-come in the diabetes treatment.

After conducting a state-of-the-art search, it was concluded that there were no data on the correlation between pharmacological treatment with drugs that promote weight loss and the management of both diabetes and associated obesity in T2DM patients in the jurisdiction area of Portuguese National Health Service, the *ARS do Centro*.

The present study aimed to compare the progression of obesity, measured by the BMI and abdominal perimeter (AP), and the control of this metabolic disease, between 2017 and 2019, according to their pharmacological treatment, GLP1a and/or SGLT2i versus a group without any of these drugs, in a group of patients diagnosed with T2DM in Portugal central region.

It was expected that obesity would be observed in the majority of T2DM patients. Simultaneously, an increase in obesity prevalence or worsening was expected in patients on

therapies that do not include GLP1a or SGLT2i. This trend should not be observed in individuals being treated with these groups of drugs, and a favourable outcome was expected. It was also believed that the reduction of obesity by BMI and AP would be associated with a decrease in the glycated haemoglobin (HbA1c) value regardless of the therapy.

METHODS

An observational, retrospective (historical) cohort study was obtained in the T2DM population in the Primary Health Care units of the *ARS do Centro*. A sample was retrieved as representative of the population with T2DM in Primary Health Care in the Central Region of Portugal. All the data in this study were anonymously obtained and provided by the Informatic Services of *ARS do Centro*. The data included refers to people diagnosed with the International Classification of Primary Care, second edition, (ICPC2) of non-insulin-treated diabetes from the six Primary Health Care Centres Clusters. T2DM patients out of these Primary Health Care Centres Clusters were not studied, namely Local Health Units of *Guarda* and *Castelo Branco*, due to their autonomy form the ARS do Centro. This study design was approved by the Ethics Committee of the *ARS do Centro* (Appendix 1).

Requested data variables were: gender, age, time since the diagnosis, AP, BMI, HbA1c in 2017 and for the year 2019 and drugs in the Diabetes program sheet of these same people for the years 2017 and 2019 (users of GLP1a and/or SGLT2i versus those without its use). These were the inclusion criteria to be met.

Regarding the descriptive analysis, the qualitative variables were characterised by absolute and relative frequency. Mean and standard deviation were used to characterise age and time since diagnosis. For the remaining variables was used median and quartiles of the distribution, given that they did not present a normal distribution globally or in any of the subgroups characterised regarding medication and gender. The adjustment of the sample distribution to a normal distribution was assessed, case by case, applying the Shapiro-Wilk test and observation of symmetry by the skewness ratio with its standard error, always concluding in asymmetry, justifying the application of non-parametric tests.

We assessed the correlation between the variables HbA1C, BMI and AP in 2017 and 2019, as well as that of the difference between those two assessments – 2017 and 2019 – with age and time since diagnosis using Spearman's correlation. It was assumed that there is correlation between the pairs under analysis when the correlation coefficient had values greater than 0.400, in absolute value ($|r_S| > 0.400$), regardless of the p-value associated with the correlation coefficient, given the sensitivity of its statistical test to a large sample size.

The Wilcoxon test was used to compare paired samples, both globally and in each group, while the Mann-Whitney test was used to compare the change between both moments regarding gender and medication. The interaction between gender and medication was considered with four levels, and the difference between the two moments regarding that interaction was assessed by the Kruskal-Wallis test.

The analysis was performed in SPSS, version 27, and was analysed at a 5% significance level.

RESULTS

Sample characterisation:

The data accomplished included 127062 individuals from *Agrupamento de Centros de Saúde* (*ACeS) Baixo Mondego, Baixo Vouga, Cova da Beira, Dão Lafões, Pinhal Interior Norte* and *Pinhal Litoral*. However, the sample was comprised by 16012 individuals from those 127062 in accordance with the inclusion criteria for medication: 12171 were medicated with SGLT2i (76.0%) and 3841 with other medication (24.0%). Other medication was considered to be: biguanides, thiazolidinediones, alpha glucosidase inhibitors, insulin, glinides and sulphonylureas. There were no cases with GLP1a in 2017 and we proceeded the study with iSGLT2 vs other drugs.

Of these 16012, data distribution revealed more than half of them were from the *ACeS Baixo Vouga* and *Baixo Mondego* (5188 (32.4%) and 3870 (24.2%) respectively), followed by *ACeS Dão Lafões* (2613 (16.3%)), *Pinhal Litoral* (2519 (15.7%)), *Pinhal Interior Norte* (1413 (8.8%)) and *Cova da Beira* (409 (2.6%)), no major discrepancies were found between the sample and the population of the *ARS do Centro*, equally distributed in terms of gender (Male: n = 7971, 48.8%; Female: n = 8041, 50.2%), age between 30 and 102 years (mean ± standard deviation: 73.5 ± 10.1 years) and time since diagnosis between 0 and 64 years (mean ± standard deviation: 8.7 ± 4.2 years).

The distribution of HbA1C, BMI and AP 2017 and 2019 is different across categories of medication, overall and per gender ($p<0.001$), except the distribution of BMI in 2017 in male subjects that are the same across different medication categories ($p=0.607$).

HbA1c:

Only 3600 individuals presented valid HbA1c values both in 2017 and 2019. This sample presents similar characteristics to the overall sample: (M: n = 1787, 49.6%; F: n = 1813, 50.4%), varying in age between 36 and 99 years (mean ± standard deviation: 73.2 ± 10.0 years) and time since diagnosis between 0 and 64 years (mean ± standard deviation: 8.6 ± 4.1 years). Of the 3600 patients considered, 2828 (78.6%) were on SGLT2i and the remaining 772 (21.4%) were on one of the other treatments.

Appendix 6 shows that the difference in HbA1c values between both assessment points, which seems to be independent of age and time since diagnosis, with most of the differences between HbA1C values concentrated between ±2.5%. No correlation was observed between initial and final HbA1C, or percentage difference with age (respectively r_S = -0.110, r_S = -0.108 and r_S = 0.007) nor with time since diagnosis (respectively r_S = 0.057, r_S = 0.041 and r_S = -0.025).

A statistically significant difference was found in median HbA1c values between the two assessment moments, 2017 and 2019, both in the total sample and in the subgroups medicated with SGLT2i in total or per gender, with increasing values, ($p<0.001$) (Appendix 3). In the subgroups medicated with other drugs rather than SGLT2i, no statistically significant difference was observed, either globally ($p=0.983$) or per gender (M: $p=0.932$; F: $p=0.932$) (Appendix 3).

As shown in Figure 1, Figure 2 and Appendix 3, there was a higher variance and upward trend with SGLT2i when compared to the group medicated with other drugs ($p=0.006$), showing a growth dynamic in SGLT2i of 0.014 and in other drugs of 0.003. It was also observed a gender/medication interaction in the variation between the two moments ($p = 0.044$) since there is a trend slightly downward in the group of female subjects medicated with drugs other than SGLT2i, which was not observed in the other three groups where there is an increase in HbA1c between 2017 and 2019 (Figure 2 and Appendix 3). As for total females medicated with SGLT2i the variation was statistically significant ($p=0.049$) unlike males ($p=0.054$), although with a similar effect size with a median magnitude of 0.10 (Appendix 3).

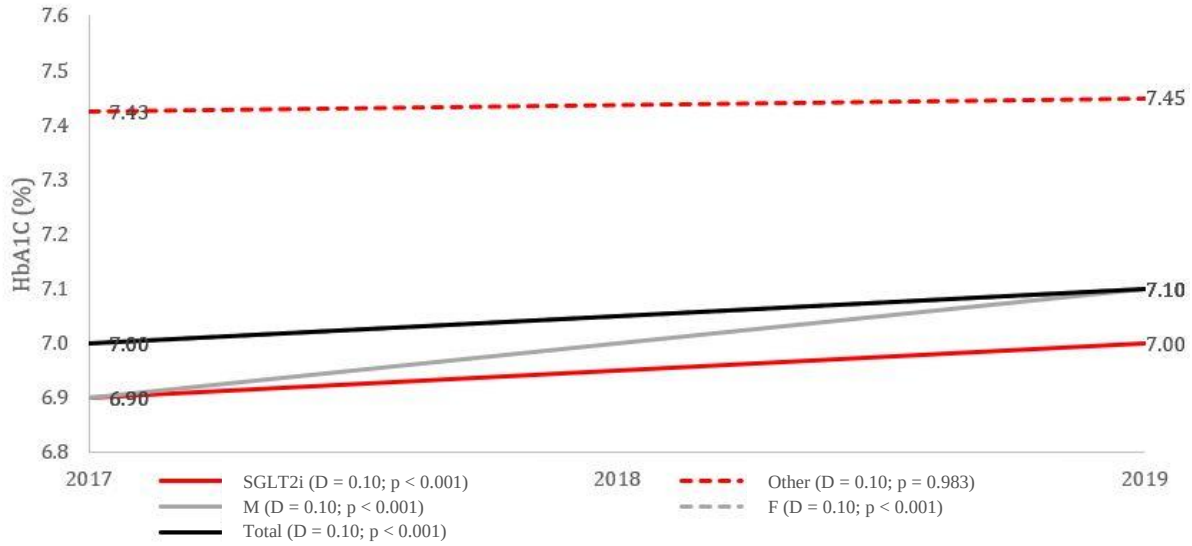

Figure 1: Variation of HbA1C values between 2017 and 2019, overall and according to medication or gender.

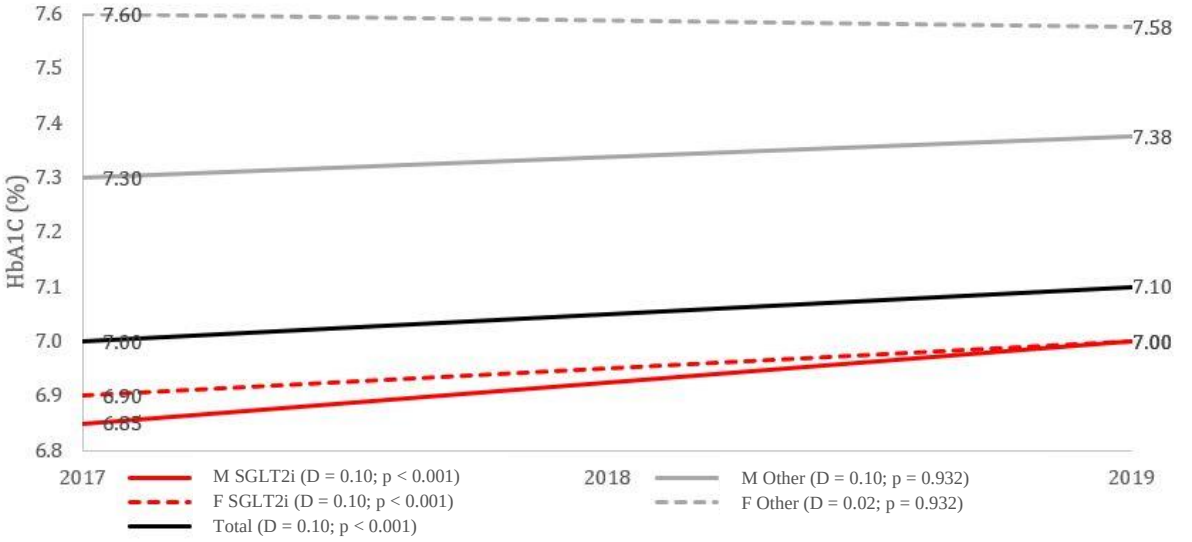

Figure 2: Variation of HbA1C values between 2017 and 2019, overall and according to medication and gender interaction.

BMI:

Of the 16012 only 4808 individuals had valid BMI values in 2017 and 2019. Like the HbA1c data, the study sample presents characteristics resembling the global sample: (M: n = 2362, 49.1%; F: n = 2446, 50.9%). Age ranged from 33 to 99 years (mean ± standard deviation: 73.2 ± 9.7 years) and time since diagnosis from 0 to 64 years (mean ± standard deviation: 8.8 ± 4.1 years). Of the 4808 patients considered, 3741 (77.8%) were on SGLT2i and the remaining 1067 (22.2%) were using one of the other drugs.

There was no substantial correlation between initial, final or BMI change with age (respectively r_S = -0.162, r_S = -0.173 and r_S = -0.036) nor with time since diagnosis (respectively r_S = -0.026, r_S = -0.021 and r_S = 0.006). Appendix 7 highlights that the difference in BMI values between the two assessment periods seemed to be independent from age and time since diagnosis, with most differences in BMI values concentrated between ± 5 kg/m^2.

Appendix 4 shows a statistically significant decrease in BMI in the group medicated with SGLT2i, both overall (p<0.001) and in each gender (M: p<0.001; F: p=0.007). In the group medicated with other drugs there was also a statistically significant reduction (p=0.004), contrary to what happened by gender with other drugs (M: p=0.177; F: p=0.932), however males and females overall showed significant decrease as well as the total sample (p <0.001) (Appendix 4).

As demonstrated in Figure 3, Figure 4 and Appendix 4, the reduction was larger in the group treated with SGLT2i (male and female) compared to the group medicated with other drugs, with growth dynamics of -0.015 and -0.005, respectively. It was also observed a gender/medication interaction in the variation between the two moments (p <0.001) (Appendix 4), because of a greater decrease in BMI, between the two assessments, in women (Figure 3 and Figure 4).

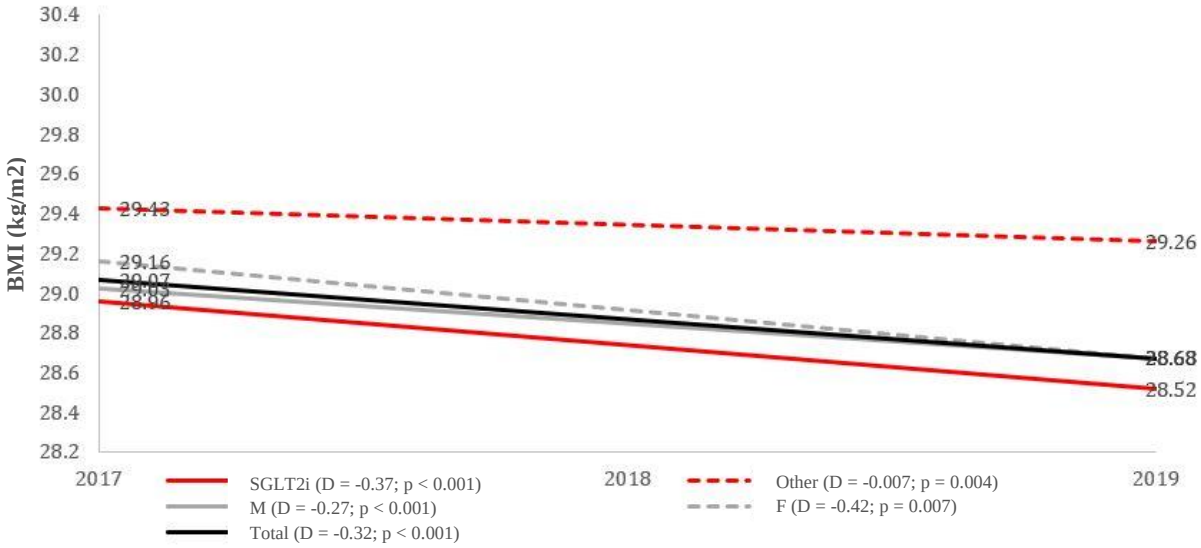

Figure 3 : Variation in BMI values between 2017 and 2019, globally and according to medication or sex

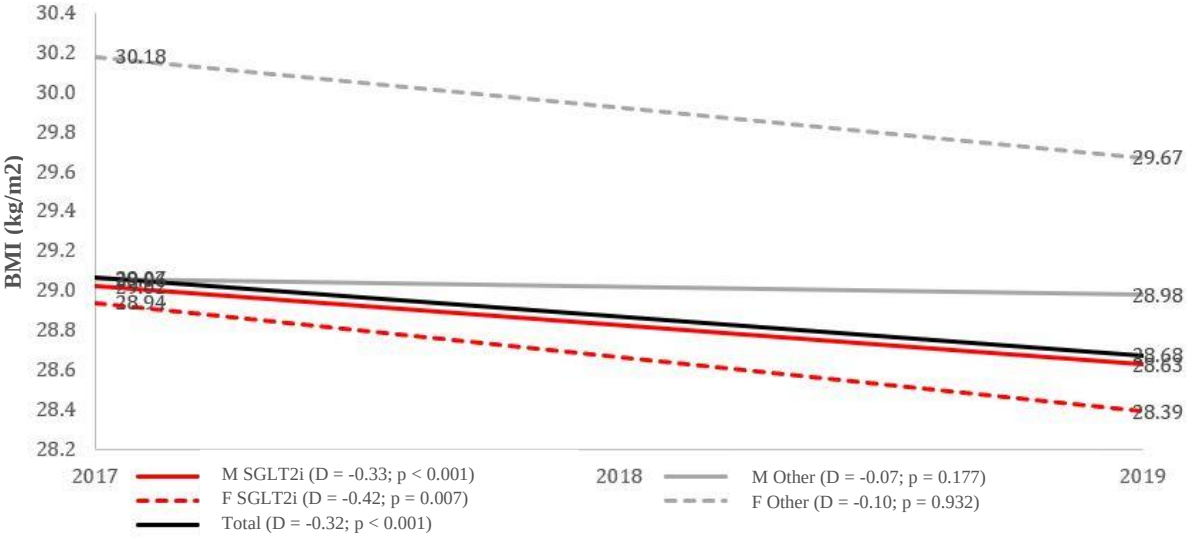

Figure 4: Variation in BMI values between 2017 and 2019, globally and according to medication and sex interaction.

Abdominal Perimeter:

The sample used to assess AP between 2017 and 2019 consisted of 4344 individuals, having similar characteristics to the overall sample (M: n = 2174, 50.0%; F: n = 2270, 50.0%), with age ranging from 36 to 101 years (mean ± standard deviation: 73.2 ± 10.1 years) and time since diagnosis from 0 to 64 years (mean ± standard deviation: 8.6 ± 3.9 years). Out of the 4344 patients considered, 3276 (75.4%) were on SGLT2i and 1068 (24.6%) on other drugs.

Appendix 8 demonstrates that the difference in AP values between the two assessment periods were independent of age and time since diagnosis, with most of the differences between AP values condensed between ± 20 cm. There was no substantial correlation between initial, final or AP change with age (respectively r_S = -0.004, r_S = 0.003 and r_S = 0.008) nor with time since diagnosis (respectively r_S = -0.039, r_S = -0.046 and r_S = -0.031).

Appendix 5 shows a statistically significant variation in AP values in the group medicated with drugs other than SGLT2i, both overall (p=0.001) and in males (p=0.010) showing an increasing trend in comparison to the remaining (Figure 5 and 6), even though the analysis for women was not statistically significant, it showed a value of p=0.052. In fact, it was observed an increase of 1.5 cm in median values o AP in males (growth dynamic of +0.010) and only 0.5 cm in females (growth dynamic of +0.005).

Regarding growth dynamics, SGLT2i showed a null value while other drugs presented a 0.007 growth.

No statistically significant variation was found in any of the analysis regarding SGLT2i.

An interaction gender/medication in the variation between 2017 and 2019 (p=0.003) was perceived, both genders presenting growing trends in AP, greater in male subjects (p=0.003) than in female ones (p=0.016) (Appendix 5 and Figure 5 and 6). A statistically significant increase in the group medicated with other drugs when compared with patients under SGLT2i was found (<0.001) (Appendix 4).

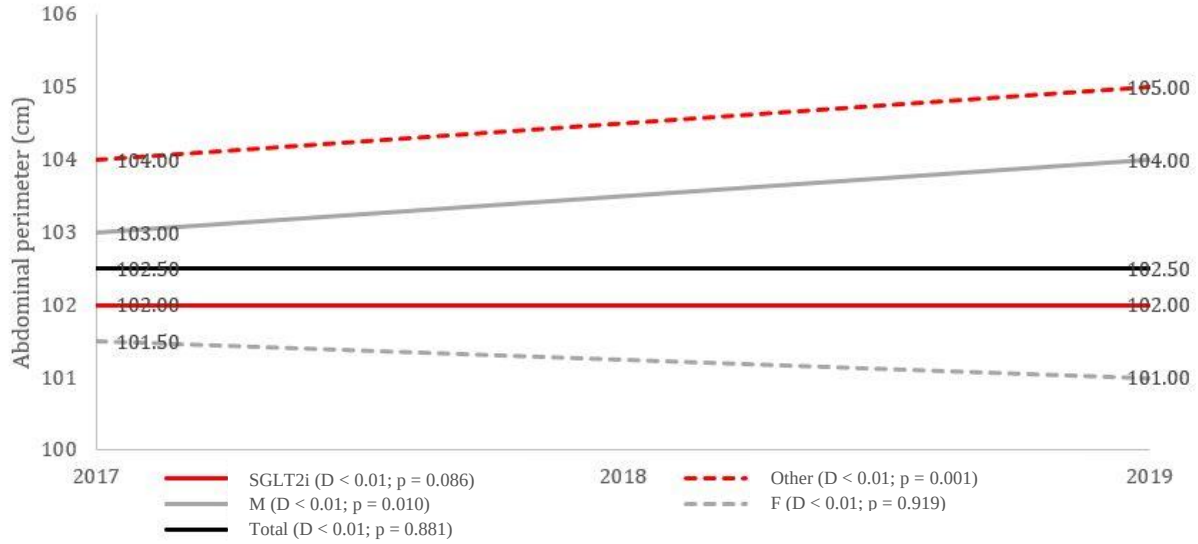

Figure 5: Variation of AP values between 2017 and 2019, globally and according to medication or gender

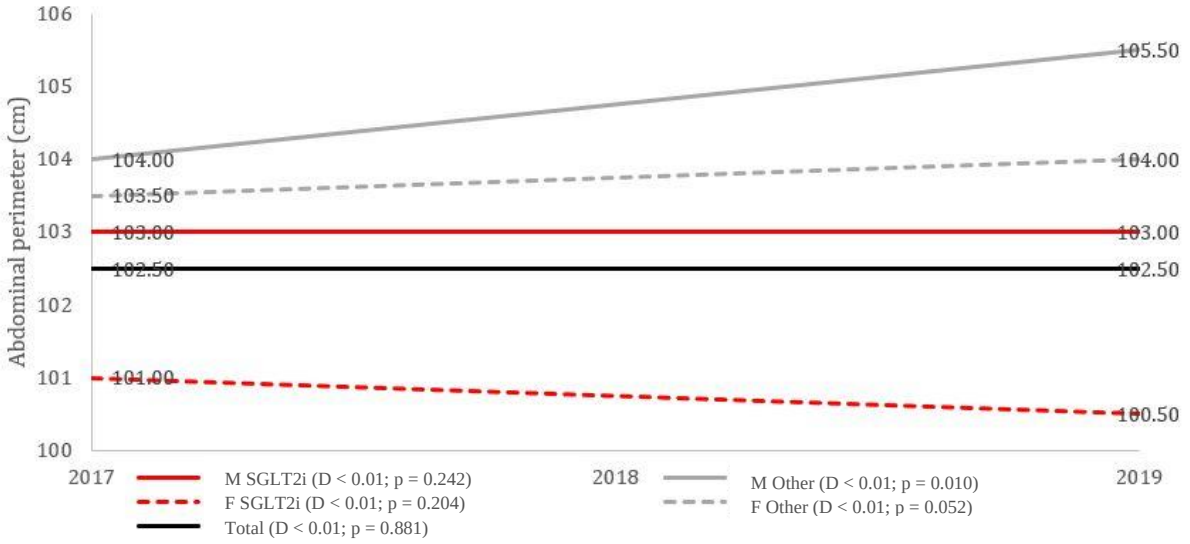

Figure 6: Variation of AP values between 2017 and 2019, globally and according to the interaction medication and gender

DISCUSSION

This study examined a sample of the population with T2DM in Portugal's central region. According to the inclusion criteria, from the 127062 individuals in the study, only 16012 were registered as being under pharmacological treatment. The 16012 studied individuals that were medicated with SGLT2i or other medication, only 3600 individuals presented valid HbA1C, 4808 valid BMI, 4344 valid AP values in 2017 and 2019. Therefore, we may be facing health professionals not registering the values in clinical appointments (a task to be performed both by nurses and doctors) or patients not regularly attending scheduled diabetes consultations. So, the problem of lack of recorded data is a dilemma to debate.

There were no data for T2DM patients on GLP1a in the two observation points. This absence of prescription could be understood by its high financial costs for acquisition and the need to be taken as an injection (daily or weekly subcutaneous administration) which involves patient counselling and training.(18, 30). The Portuguese inventory data indicators, *BI-CSP (Bilhete de Identidade dos Cuidados de Saúde Primários)*, reveals prescriptions of aGLP1 in 2019 and no records in 2017.(31) Still, this study´s goal was to compare 2017 to 2019. And so new studies will be important to assess data from diabetic patients undergoing GLP1a therapy, to compare its effectiveness as an antidiabetic drug, as well as its ability to decrease body mass vs other anti-diabetic drugs or even against SGLT2i results in the real world T2DM General Practice/Family Medicine context of follow-up.

The target control value for HbA1c may vary greatly from patient to patient due to concomitant diseases and other simultaneous morbidities, and also according to patient's age (patients with 65 years or older target value <7,0% and under 65 years target value <6,5%(32)). (2, 18). The present study showed no correlation between initial and final HbA1C values, or difference with age nor with time since diagnosis since the $|r_S|$ was always below 0.110 (Appendix 6). This was also observed for BMI (Appendix 7, maximum $|r_S| = 0.173$) and PA (Appendix 8, maximum $|r_S| = 0.046$). According to current studies these results were not anticipated. It was expected that younger and earlier diabetes diagnosis would present poorly controlled DM leading to higher HbA1c and BMI values as well as central obesity with greater AP values.(33-35)

Although SGLT2i have a larger positive variation in relation to the other drugs, this study only covers a two year observational period, so, even if there was a greater increase in HbA1c in patients under this therapy (with a growth dynamic of +0.014) when compared with other drugs (growth dynamic of +0.003) (Figure 1 and Appendix 3), one must consider the results in the

long term and the effects of the decrease of BMI and AP in HbA1c that may not be prompt, but eventually influence each other's growth dynamics. It is to be noticed that this growth dynamics influences values that, in the case of those with SGLT2i, was statistically lower in 2017.

In the SGLT2i users the difference is statistically significant, the effect observed in the median difference is never greater than 0.10% (Appendix 3), but the variation between these two points in time was from moderately controlled median values to borderline values (6.90% to 7.00%) (Figure 1). However, other drugs users, even with a lesser variation the values always varied in an uncontrolled range (from 7.43% to 7.45%) (Figure 1). Thus, it is important to continue to investigate these values.

Regarding the BMI, the presence of overweight or obesity is obvious in the sample, with more than 75% of records with values ≥25 kg/m^2 in both years (Appendix 4), as anticipated.(3, 6, 9, 10, 14, 18) As expected, and as discussed in other studies, the variation in the BMI was statistically significant in individuals medicated with SGLT2i, but also with other drugs globally, due to possible glycaemic control, and less exposure to long periods of hyperglycaemia.(34) Even though, the decrease was greater with SGLT2i (22, 27, 28) than with other drugs, the gap in median values in both was <1 kg/m^2 (SGLT2i 0.37 kg/m^2 and 0.07 kg/m^2 with other treatment (Figure 3 and Appendix 4)). However, one would expect a more obvious difference between the different treatments. The slight reduction observed with other drugs was not anticipated since we expected an increase in obesity prevalence or worsening in patients on therapies that do not include SGLT2i. This may be due to proper patient care to keep the disease under control, leading to a decrease in BMI and AP associated with improved HbA1c. The interaction gender/medication observed between the two moments showed that women had a greater reduction in BMI with both therapies, deserving further investigations. The distribution of BMI values in 2017 in male subjects is the same across different medication categories (p=0.607). As a bias we do not know the effect of the knowledge by patients of a new treatment, which has probably been biased to have thinning properties.

Concerning AP, a greater positive variation was observed in the group medicated with other drugs, showing a more pronounced upward trend globally and in males, which was not observed in the remaining groups (Figure 5 and Appendix 5). As for the gender/medication interaction, an increasing trend in males and females medicated with other drugs (bigger increase in men and in the need of further investigation) was observed, (Figure 6 and Appendix 5). This was anticipated since other drugs were not weight loss promoters, however, a decrease in AP would be expected in SGLT2i users accompanying the decrease in BMI (18,

19, 22, 27, 28) discussed above, instead of a plateau of this parameter. Nevertheless, we cannot exclude the presence of other comorbidities that may affect the AP or any other variable.

One must acknowledge that we are dealing with people that are patients, and they must be considered and treated as holistically as possible. Therefore, attention should be attracted to other variables that may alter treatment results, to individualised treatment prescription and to therapeutic inertia besides beliefs about medicines and diabetes(36, 37).

The aforementioned problems require a multilevel resolution, starting with doctor-patient relationship improvement, inclusion of patients in therapeutic decisions and monitoring the side effects of therapies to achieve better adherence to treatment, which should include a healthy lifestyle (diet and exercise) to enhance the effects of anti-diabetic drugs(38). This aims for better patient education, better control of both chronic diseases and quality of life. Furthermore, it is important to invest in more accurate medical records.

The main strengths of this study, a very large sample of T2DM patients from central Portugal, with specific criteria of inclusion, allows to understand the effects of treatments in a real clinical context and its effectiveness. As for the limitations, we should mention the fact that this is a retrospective study only seeking to know about differences occurring from medicines prescription. Therefore, adherence and maintenance in therapeutics, impact of socioeconomics in the control of T2DM and beliefs about medicines were not studied. There may be a criticism about the validity of the studied data, made by doctors and nurses in a e.registration support program (*S-Clínico*). Still if we are not to trust clinical records, then what should we trust? Nevertheless, a worrisome problem comes about the lack of existing data from many T2DM patients. So many computer resources existing, why are they not being exploited in the best way?

The present results are not similar to efficacy studies, but the time length is also different, these ones being shorter. Therefor more follow-up studies like this one must be made in the future, probably in other contexts and even with the ethical consent of patient’s randomisation.

CONCLUSION

SGLT2i attained a greater and significant decrease in the BMI, when compared with the effect of other anti-diabetic drugs. Still, the median variation was lower than 1 kg/m^2.

AP in SGLT2i users remained quite stable, in contrast to other drugs users, whose AP value worsened. However, an increase in obesity prevalence or worsening in patients on therapies that do not include SGLT2i was not observed.

In this two years observational study the effectiveness of SGLT2i as an anti-diabetic drug, to decrease HbA1c values when compared with other drugs did not reach clinical superiority. However, we should not take this value as the endpoint and think about the future of what these effects will be in the long term, as well as the influence and interaction between variables of the person suffering from Type 2 Diabetes.

Real world data must continue to be studied prospectively to draw fuller conclusions.

ACKNOWLEDGEMENTS

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I would also like to thank Doctor Conceição Saraiva, from the computer services of ARS do Centro, for the time spent collecting data, which enabled this work to be carried out.

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To Bárbara, Pedro, and Sara I am thankful to have you in my corner every step of the way.

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APPENDIX

1. Ethics committee approval

GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

ARSC ADMINISTRAÇÃO REGIONAL DE SAÚDE DO CENTRO, I.P.

COMISSÃO DE ÉTICA PARA A SAÚDE

PARECER FINAL: FAVORÁVEL	DESPACHO: Homologado o Parecer da Comissão de Ética 8/04/24 Conselho Diretivo da A.R.S. do Centro, I.P. Dr. José Reis Marques Presidente, Dr. João Rodrigues Vice-Presidente, Dr. Mário Antunes

ASSUNTO: **07/2021** - Título: "Diabetes: a influência da medicação farmacológica no controlo e na obesidade acompanhante"
Investigadores: Mariana de Miranda Pinto e Luiz Miguel de Mendonça Soares Santiago

Objetivos: Comparar num grupo de doentes com DM2, no período de 2017 a 2019, a progressão da obesidade a ser medida pelo Índice de Massa Corporal e pelo perímetro abdominal, e o controlo desta doença metabólica "em função da terapêutica farmacológica criando dois grupos, com iSGLT2 ou aGLP1 versus grupo sem algum destes medicamentos".
Todos os dados a ser utilizados no estudo serão anónimos e fornecidos pelos serviços informáticos da ARS. Os dados a serem fornecidos são os das pessoas com o diagnóstico de diabetes não insulino-tratada em Unidades de Cuidados de Saúde Primários. Os dados serão então analisados num estudo observacional, de coorte retrospetiva. Uma vez que a colheita dos dados é feita de modo anónimo, não haverá lugar ao consentimento informado. Acresce que o estudo longitudinal é um modo de testar a qualidade da prescrição feita em circunstâncias habituais.
Não existem custos adicionais.
Há autorização das instituições envolvidas.

O Relator e Presidente da CES da ARS do Centro,

Prof. Doutor Carlos Alberto Fontes Ribeiro

2. *ARS* Data Request

Entidade: Administração Regional de Saúde do Centro, I. P.

Formulário 2

À atenção do Coordenador do Gabinete de Sistemas de Informação e Comunicações

Pedido de Dados Estatísticos ao GSIC

Nome: Luiz Miguel de Mendonça Soares Santiago

Categoria Profissional: Médico

Coordenação: ○ Sim ◉ Não

Unidade de Saúde: USF Topázio

Email: LMSantiago@arscentro.min-saude.pt

Telemóvel: 9 6 6 2 2 5 7 7 3

Finalidade dos dados solicitados

☒ Investigação ☒ Apresentação em Congresso ☐ Tratamento de ficheiro ☐ Curriculum

Outra:

Inclui: ☒ Contagens ☒ Listas anonimizadas

Periodo a que se reporta os dados: 01/12/2017 a 31/12/2019

Prazo de disponibilização da informação: Quando possível

Descrição dos dados solicitados

Objetivo: Comparar num grupo aleatório de doentes com diagnostico de DM2, da ARS centro, no período de 2017 a 2019, a progressão da obesidade a ser medida pelo Índice de Massa Corporal e pelo perímetro peri-umbilical, e o controlo desta doença metabólica em função da terapêutica farmacológica criando dois grupos, com e sem iSGLT2 e ou aGLP1 versus grupo sem algum destes medicamentos.
Dados solicitados. Após homologação de parecer positivo da CE da ARS pelo respetivo CD, solicitam-se:
Em anonimato dados das pessoas com o diagnóstico ICPC2 de diabetes não insulino-tratada (Classificação ICPC2 T90) inscritas e seguidas, nos ACeS Pinhal Litoral, Baixo Mondego, Baixo Vouga e Dão Lafões. Os dados serão então analisados num estudo observacional, de coorte retrospetiva (histórica).
Dado requeridos: sexo, idade, hemoglobina A1c (HbA1c) dois primeiros em 2017 e dois últimos em 2019, perímetro abdominal (PA), índice de massa corporal (IMC), e fármacos constantes da ficha do programa de Diabetes de tais pessoas para os anos de 2017 e 2019.

Autorização do Superior Hierárquico

Local: Coimbra Data: 13/7/2021

Autorizado por *(quando aplicável)*: CD da ARS do Centro IP que homologou parecer da Comissão de Ética

Importante: Todos os campos do formulário são de preenchimento obrigatório.
Deve ser sempre e exclusivamente enviado para o mail do Coordenador do Gabinete de Sistemas de Informação e Comunicações.

ARS CENTRO, I.P. - Alameda Júlio Henriques, 3000-457 Coimbra

3. Table 1: Characterisation and comparison of HbA1C values in 2017 and 2019 globally and according to gender and medication

		N	2017		2019		p	Δ		p	p	p
Gender	Medication		min - max	median [Q1, Q3]	min – max	median [Q1, Q3]	[time]	min – max	median [Q1, Q3]	[gender*medic]	[gender]	[medic]
M	SGLT2i	1401	4.60 - 14.30	6.85 [6.30, 7.55]	4.55 - 12.85	7.00 [6.40, 7.65]	< 0.001	-5.70 - 4.80	0.10 [-0.30, 0.60]			
	Other	386	5.00 - 12.30	7.30 [6.55, 8.20]	4.20 - 13.60	7.38 [6.75, 8.15]	0.932	-4.25 - 5.80	0.10 [-0.65, 0.60]			
	Total	1787	4.60 - 14.30	6.90 [6.35, 7.70]	4.20 - 13.60	7.10 [6.45, 7.80]	< 0.001	-5.70 - 5.80	0.10 [-0.40, 0.60]			0.054
F	SGLT2i	1427	4.60 - 13.25	6.90 [6.30, 7.60]	5.00 - 12.50	7.00 [6.40, 7.70]	< 0.001	-6.30 - 4.80	0.10 [-0.30, 0.50]			
	Other	386	4.80 - 14.30	7.60 [6.75, 8.45]	5.30 - 14.75	7.58 [6.80, 8.50]	0.932	-8.85 - 4.75	0.02 [-0.60, 0.60]			
	Total	1813	4.60 - 14.30	7.00 [6.40, 7.85]	5.00 - 14.75	7.10 [6.45, 7.90]	< 0.001	-8.85 - 4.80	0.10 [-0.40, 0.55]			0.049
Total	SGLT2i	2828	4.60 - 14.30	6.90 [6.30, 7.60]	4.55 - 12.85	7.00 [6.40, 7.70]	< 0.001	-6.30 - 4.80	0.10 [-0.30, 0.55]		0.458	
	Other	772	4.80 - 14.30	7.43 [6.70, 8.30]	4.20 - 14.75	7.45 [6.75, 8.35]	0.983	-8.85 - 5.80	0.05 [-0.60, 0.60]		0.799	
Total	Total	3600	4.60 - 14.30	7.00 [6.35, 7.80]	4.20 - 14.75	7.10 [6.45, 7.80]	< 0.001	-8.85 - 5.80	0.10 [-0.40, 0.60]	0.044	0.453	0.006

4. Table 2: Characterisation and comparison of BMI values in 2017 and 2019 globally and according to gender and medication.

		N	2017		2019		p	Δ		p	p	p
Gender	Medication		min - max	median [Q1, Q3]	min – max	median [Q1, Q3]	[time]	min – max	median [Q1, Q3]	[gender*medic]	[gender]	[medic]
M	SGLT2i	1862	18.75 - 48.67	29.02 [26.45, 31.78]	17.75 - 46.84	28.63 [26.13, 31.45]	< 0.001	-12.52 - 6.02	-0.33 [-1.10, 0.45]			
	Other	500	14.82 - 43.58	29.06 [26.39, 32.36]	13.84 - 46.79	28.98 [26.17, 32.15]	0.177	-8.57 - 11.99	-0.07 [-0.95, 0.74]			
	Total	2362	14.82 - 48.67	29.03 [26.41, 31.83]	13.84 - 46.84	28.68 [26.13, 31.63]	< 0.001	-12.52 - 11.99	-0.27 [-1.09, 0.52]			< 0.001
F	SGLT2i	1879	13.16 - 66.16	28.94 [25.90, 32.45]	12.47 - 67.94	28.39 [25.44, 32.01]	0.007	-15.13 - 21.11	-0.42 [-1.46, 0.47]			
	Other	567	18.37 - 56.67	30.18 [27.09, 33.91]	17.40 - 56.29	29.67 [26.96, 34.02]	0.932	-12.86 - 6.70	-0.10 [-1.22, 0.80]			
	Total	2446	13.16 - 66.16	29.16 [26.15, 32.81]	12.47 - 67.94	28.68 [25.65, 32.46]	< 0.001	-15.13 - 21.11	-0.39 [-1.41, 0.58]			< 0.001
Total	SGLT2i	3741	13.16 - 66.16	28.96 [26.18, 32.03]	12.47 - 67.94	28.52 [25.82, 31.71]	< 0.001	-15.13 - 21.11	-0.37 [-1.26, 0.47]		0.012	
	Other	1067	14.82 - 56.67	29.43 [26.84, 33.29]	13.84 - 56.29	29.26 [26.58, 33.21]	0.004	-12.86 - 11.99	-0.07 [-1.07, 0.76]		0.372	
Total	Total	4808	13.16 - 66.16	29.07 [26.34, 32.35]	12.47 - 67.94	28.68 [25.96, 32.03]	< 0.001	-15.13 - 21.11	-0.32 [-1.21, 0.55]	< 0.001	0.014	< 0.001

5. Table 3: Characterisation and comparison of AP values in 2017 and 2019 globally and according to gender and medication

		N	2017		2019		p	Δ		p	p	p
Gender	Medication		min - max	median [Q1, Q3]	min – max	median [Q1, Q3]	[time]	min – max	median [Q1, Q3]	[gender*medic]	[gender]	[medic]
M	SGLT2i	1635	48 - 153	103 [97, 110]	76 - 146.5	103 [97, 110.5]	0.242	-39 - 40.5	< 0.01 [-2.75, 2.50]			
	Other	539	76 - 149	104 [98, 112]	71 - 144.5	105.5 [98, 113]	0.010	-17 - 25	< 0.01 [-2.00, 3.50]			
	Total	2174	48 - 153	103 [97.5, 111]	71 - 146.5	104 [97, 111]	0.762	-39 - 40.5	< 0.01 [-2.50, 2.75]			0.003
F	SGLT2i	1641	62 - 148	101 [94, 108]	61 - 180	100.5 [94, 108.5]	0.204	-48.5 - 70	< 0.01 [-3.00, 3.00]			
	Other	529	68 - 151	103.5 [97, 111]	67 - 166	104 [96, 112.5]	0.052	-35 - 28	< 0.01 [-2.00, 3.75]			
	Total	2170	62 - 151	101.5 [95, 109]	61 - 180	101 [94.5, 110]	0.919	-48.5 - 70	< 0.01 [-3.00, 3.00]			0.016
Total	SGLT2i	3276	48 - 153	102 [96, 109.5]	61 - 180	102 [95.5, 110]	0.086	-48.5 - 70	< 0.01 [-3.00, 2.75]		0.874	
	Other	1068	68 - 151	104 [98, 112]	67 - 166	105 [97, 112.75]	0.001	-35 - 28	< 0.01 [-2.00, 3.50]		0.800	
Total	Total	4344	48 - 153	102.5 [96, 110]	61 - 180	102.5 [96, 110]	0.881	-48.5 - 70	< 0.01 [-3.00, 3.00]	0.003	0.781	< 0.001

6. Dispersion diagram of the difference between HbA1c values ($\Delta_{2019\text{-}2017}$) and time since diagnosis or age (both measured in years).

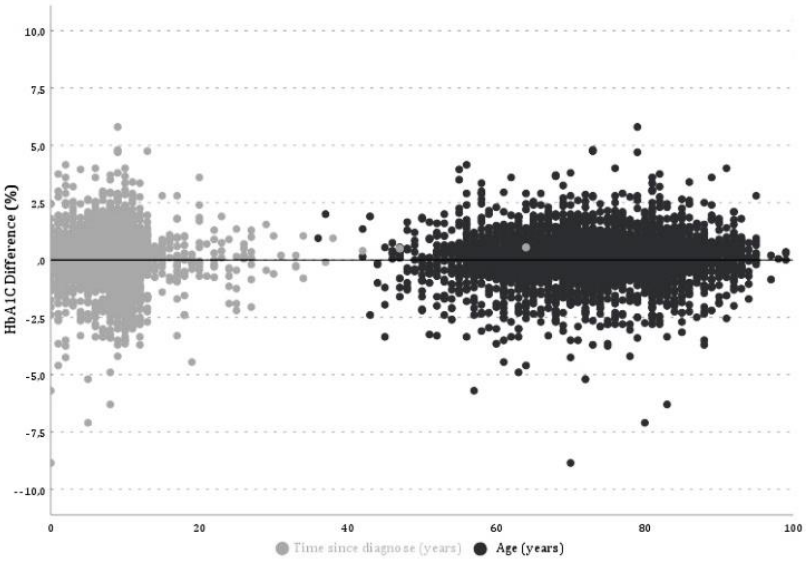

Figure 7: Dispersion diagram of the difference between HbA1c values ($\Delta_{2019\text{-}2017}$) and time since diagnosis or age (both measured in years).

7. Dispersion diagram of the difference between BMI values ($\Delta_{2019\text{-}2017}$) and time since diagnosis or age (both measured in years).

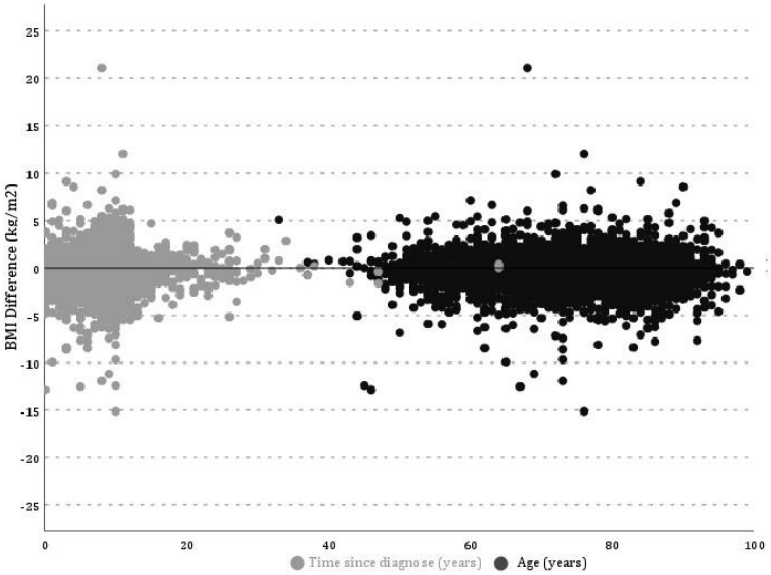

Figure 8: Dispersion diagram of the difference between BMI values ($\Delta_{2019\text{-}2017}$) and time since diagnosis or age (both measured in years).

8. Dispersion diagram of the Difference between AP values ($\Delta_{2019\text{-}2017}$) and time since diagnosis or age (both measured in years).

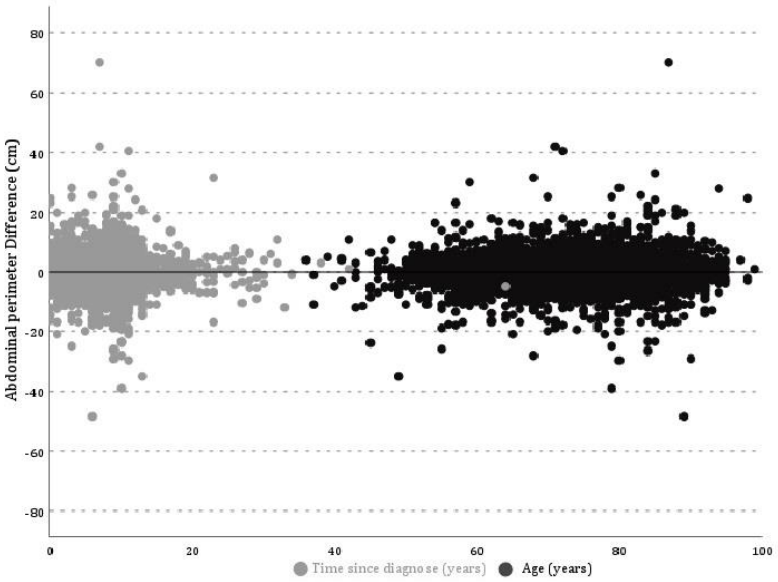

Figure 9: Dispersion diagram of the Difference between AP values ($\Delta_{2019\text{-}2017}$) and time since diagnosis or age (both measured in years).