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ORIGINAL ARTICLE

Metabolic control and treatment regimens in patients with type 1 diabetes in Castilla-La Mancha, 10 years later: The 2020 DIACAM1 study

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KEYWORDS
Type 1 diabetes mellitus;
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Abstract
Objective: To evaluate degree of metabolic control and treatment regimens in patients with type 1 diabetes mellitus (T1DM) enrolled in the DIACAM1 study, after 10 years of follow-up under routine clinical practice conditions.
Patients and methods: A total of 1,465 patients enrolled in the DIACAM1 study, a multicentre, cross-sectional study conducted in Castilla-La Mancha in 2010, were analysed. Of these patients, 58 (4%) died during the 10-year follow-up period. Anthropometric, clinical, laboratory and treatment data were reviewed for 1,121 (76.5%) patients in active follow-up.
Results: Mean glycosylated haemoglobin (HbA1c) levels were 7.66% lower than in 2010 ($p < 0.001$), 26% of patients achieved HbA1c levels <7%, 24.4% were obese, 51.7% had dyslipidaemia and 33.6% had hypertension. The following were found to be predictive factors for good glycaemic control (HbA1c < 7%): good glycaemic control in 2010 (odds ratio [OR] 4.8); the use of intensified insulin regimens, including the Institute for Clinical Systems Improvement (ICSI) guideline and glucose monitoring (OR 2.8); no hyperlipidaemia (OR 1.97); and higher levels of education (OR 1.4). The recommended targets for lipid and blood pressure control were met by 76% of patients; 40% of the patients enrolled required drug treatment.

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Conclusions: Glycaemic control in patients with T1DM in Castilla-La Mancha improved after 10 years of follow-up. The use of intensified insulin regimens and technology applied to diabetes care appear to be determining factors in achieving this improvement. Despite the increase in the prevalence of cardiovascular risk factors, the majority of the patients achieved good lipid and blood pressure control.

PALABRAS CLAVE
Diabetes mellitus tipo 1;
Adultos;
Control glucémico;
Pautas de tratamiento con insulina;
Monitorización continua de glucosa

Control metabólico y pautas de tratamiento en pacientes con diabetes tipo 1 en Castilla-La Mancha, 10 años después. Estudio DIACAM1 2020

Resumen
Objetivo: Evaluar el grado de control metabólico y las pautas de tratamiento empleadas en los pacientes con diabetes mellitus tipo 1 (DM1) incluidos en el estudio DIACAM1, tras 10 años de seguimiento en condiciones de práctica clínica habitual.
Pacientes y métodos: Se han analizado los 1.465 pacientes incluidos en el estudio DIACAM1, estudio transversal multicéntrico realizado en Castilla-La Mancha en 2010. 58 pacientes (4%) fallecieron durante los 10 años de seguimiento. 1121 pacientes (76,5%) estaban en seguimiento activo y en ellos se han revisado datos antropométricos, clínicos, analíticos y tratamientos utilizados.
Resultados: El valor medio de la hemoglobina glicada (HbA1c) fue de 7,66%, significativamente inferior a la HbA1c en 2010 ($p < 0,001$), el 26% de los pacientes consiguieron HbA1c <7%, 24,4% tenía obesidad, 51,7% dislipemia y 33,6% hipertensión. Como factores predictivos de buen control (HbA1c < 7%) se hallaron: buen control glucémico en 2010 (OR 4,8), la utilización de pautas intensificadas de insulina, que incluyen ISCI y monitorización de glucosa (OR 2,8), la ausencia de hiperlipemia (OR 1,97) y alcanzar un nivel de estudios medio o superior (OR 1,4). El 76% de los pacientes cumplían los objetivos de control lipídico y tensional recomendados, precisando tratamiento farmacológico el 40% de los pacientes incluidos.
Conclusiones: Los datos de control glucémico global en pacientes con DM1 en Castilla-La Mancha han mejorado tras 10 años de seguimiento. La utilización de pautas intensificadas de insulina y la implementación del uso de tecnología aplicada al cuidado de la diabetes parecen ser factores determinantes para conseguir esta mejoría. A pesar del aumento en la prevalencia de los factores de riesgo cardiovascular un porcentaje amplio consigue buen control lipídico y tensional.

Introduction

Diabetes mellitus is one of the most pressing health problems worldwide due to the enormous personal, social and economic costs that it incurs. Type 1 diabetes mellitus (T1DM), though less prevalent than type 2 diabetes, is a growing health problem[1] that primarily affects a young sector of the population, in which blood glucose control and prevention of short- and long-term complications are keys to treatment.[2] Therapeutic management of patients with T1DM is under continuous development, and since the publication in 1993 of the Diabetes Control and Complication Trial (DCCT) study[3] and, after that, the results of the observational Epidemiology of Diabetes Intervention and Complication Trial (EDICT) study,[4] it has been clear that achieving and maintaining blood glucose levels as close as possible to normal causes significant reduction in the microvascular and macrovascular complications associated with the disease. To achieve this end, in the past decade, there have been major changes in the tools for treating T1DM. Advanced treatment education programmes and newly developed insulins have improved current insulin therapy regimens and brought them closer to physiologically normal patterns.[5] With new automated continuous subcutaneous insulin infusion (CSII) systems[6,7] and simplification of continuous glucose monitoring (CGM) devices,[8] technology has engendered great hopes for improving blood glucose control outcomes. However, this technification of treatment for T1DM has increased the complexity of treatments, and the need for greater specialisation and training of endocrinology and nutrition specialists, who must dedicate more time in their practice to optimising these therapies and making the most of their potential.[9]

In 2010, the DIACAM1 (DIAbetes tipo 1 en CAstilla la Mancha) study backed by the Sociedad Castellano Manchega de Endocrinología, Nutrición y Diabetes (SCAMEND) was designed in an attempt to determine the situation of patients with T1DM with regard to control and complications

in the Autonomous Community of Castilla-La Mancha. DIACAM1 documented the glycaemic control status, treatment regimens used and factors related to better glycaemic control in a representative cohort of patients with DM1 in this autonomous community.[10] After 10 years, the results of this cohort were reviewed to analyse whether there were changes in the degree of metabolic control and treatment patterns and to assess, where possible, the factors related to achieving metabolic control targets and how technology may be influencing this.

Patients and methods

The DIACAM1 study was an observational, cross-sectional, multicentre study of patients with T1DM in regular follow-up in endocrinology outpatient clinics in the eight health areas of Castilla-La Mancha (Albacete, Ciudad Real, Cuenca, Guadalajara, La Mancha Centro, Puertollano, Talavera de la Reina and Toledo). The selection criteria for the patients included in the study were previously reported.[10] The initial cohort (2009–2010) included 1,465 patients with T1DM 16 years of age or older, with more than five years since onset at the time of inclusion in the study.

This sample represented a third of the estimated population with T1DM over 14 years of age in the Autonomous Community. The sample size was calculated based on the diabetic population registry of Castilla-La Mancha primary care teams (Turriano, 2008 Castilla-La Mancha Health Department activity report), considering 5% of the population with T1DM and a prevalence of 0.31% in people over 14 years of age. A representative number of patients was established for each of the eight health areas, based on the registered resident population.

The study was approved by the Complejo Hospitalario de Toledo [Toledo Hospital Complex] Research Ethics Committee as the investigator-coordinating centre and patients gave their written informed consent to be included in the study.

Patients included in 2019–2020

This second review included all the patients studied in the first analysis, with the patients divided into four groups: *1. Patients in active follow-up (no.: 1,121; 76.5%)*: The patients included had visited outpatient endocrinology and nutrition clinics at least twice in the 12 months during which data collection occurred (June 2019–June 2020). Some patients having made remote visits during the months of lockdown triggered by the COVID-19 pandemic were considered. This group was included if they had recent laboratory results and anthropometric data. Pregnant women were excluded from the study. *2. Patients not in active follow-up (no.: 95; 6.5%):* This included women who had been pregnant in the year of data collection and patients who had confirmation of their vital status, but had not undergone follow-up in endocrinology and nutrition outpatient clinics in the past 12 months. *3 Patients with loss to follow-up (no.: 191; 13%):* This included patients in whom it was not possible to collect clinical information or information on their current life status. *4. Death (no.: 58; 4%):* This included patients with a record of their death over the course of these 10 years in their medical record.

Variables analysed

The same sociodemographic, clinical, anthropometric and analytical variables were collected in each patient as were collected in the original DIACAM study.[10]

The treatments received by each patient at the screening visit were assessed in terms of insulin therapy regimens and any other treatment related to the treatment of diabetes and cardiovascular risk factors:

- Insulin therapy: the current insulin therapy regimen was considered, divided into three types of regimen: *conventional* (if they were using two to three daily doses with a manual mixture or fixed premixes, with some sort of daily capillary blood glucose check and occasional self-adjustment of insulin doses), *multiple-dose insulin (MDI)* (if they were using a *basal-bolus regimen with four or more subcutaneous insulin injections per day*) and *CSII*. Whether they used associated CGM systems including Flash® monitoring was also recorded. Patients who used MDI or CSII + CGM or CSII alone were considered to belong to the *intensified or advanced insulin regimen* group. Daily total insulin dose, expressed in terms of IU/kg/day, and time elapsed since the last change in regimen were also assessed.
- Other treatments: data were collected on the use of hypotensive drugs, lipid-lowering drugs, antiplatelet drugs and anticoagulants as well as the use of metformin and other drugs related to diabetes treatment (DPP4 inhibitors, GLP-1 analogues and SGLT2 inhibitors).

As in the initial study in 2010, the following were recorded for each patient: ophthalmological complications (retinopathy of any degree, assessed in the latest eye fundus examination) and renal complications (nephropathy of any degree, assessed in the latest annual review if there was an increase in urinary excretion of albumin and/or a decrease in estimated glomerular filtration rate). Any signs, examination data or treatments for revascularisation suggestive of vascular complications at any level were also assessed.

Statistical analysis

Quantitative variables are expressed in terms of mean ± standard deviation. The descriptive analysis of the categorical variables is expressed in terms of percentages. Parametric tests such as Student's t test were used to compare means, and analysis of variance (ANOVA) was used to compare multiple variables with *post hoc* comparisons using Tukey's honestly significant difference (HSD) test. The difference between proportions in the qualitative variables was analysed using the chi-squared test. McNemar's test was used to analyse changes over time in categorical variables in paired samples in the two periods studied. To evaluate factors independently associated with good blood glucose control (defined as HbA1c <7%), a univariate analysis (chi-squared test) and a multivariate analysis (logistic regression) were performed using different

Table 1 Demographic characteristics of the DIACAM1 cohort in the two periods analysed.

	2010 DIACAM1 No. 1,465	2020 DIACAM1 No. 1,121
Male sex	51.5%	49.5%
Caucasian ethnicity and Spanish origin	98%	98.4%
Current age (years)[a]	39.4 ± 13.5	49.4 ± 12.8
Age at diagnosis of diabetes (years)	19.9 ± 11.8	21.1 ± 11.7
Time since diabetes onset (years)	19.4 ± 10.6	28.9 ± 10.0
Latent autoimmune diabetes	7.2%	7.2%
Level of education attained		
No education	6%	5%
Primary education	38%	38.5%
Secondary education	34%	35.5%
Higher education	22%	21%

Data is expressed in terms of mean ± standard deviation (quantitative variables) or percentages (categorical variables) for the patients included in each period.

[a] Age at the time of data analysis.

models, to calculate the adjusted odds ratio (OR) (95% CI). The threshold for significance that was adopted for all tests was $p < 0.05$. Data was analysed with the SPSS® statistics software package, ver. 20.

Results

The results analysed in this study corresponded to 1,121 patients in active follow-up and are presented jointly for the eight Castilla-La Mancha health areas.

Demographic and clinical characteristics

The demographic characteristics of the 2010 cohort and the current cohort appear in Table 1. Apart from current mean age (nearly 50), and mean time since onset of T1DM (nearly 30 years), the characteristics of the 2020 cohort were similar to the initial cohort. More than 40% of the patients included had no education or primary education only. The percentage of women included in this analysis increased slightly.

Blood glucose control and treatments used

As Table 2 shows, the mean HbA1c achieved in the cohort of active patients was significantly lower in the current analysis, although the percentage of patients with HbA1c <7% was not, as it remained stable. In the 2020 cohort, the percentage of patients with very poor blood glucose control (HbA1c >9%) was indeed significantly reduced. Nearly 68% of the patients from the 2020 DIACAM1 cohort had a HbA1c <8%.

Most patients included in the study used MDI or CSII insulin regimens, and less than 4% used conventional insulin regimens or insulin regimens with premixes. There was a significant increase in the number of patients who used CSII in these 10 years (Table 3). The DIACAM1 study did not assess the use of CGM, as only some patients on treatment with CSII used monitoring systems associated with insulin pump therapy. At the time when data from 2020 DIACAM1 patients in active follow-up was included, 26.9% of patients used CGM associated with a basal-bolus insulin regimen or CSII (Table 4). Patients with glucose monitoring had better metabolic control compared to patients without CGM, regardless of the type of insulin therapy used (Table 4). Patients who used an intensified insulin regimen were younger, had less time since T1DM onset and required a lower insulin dose than those on a conventional regimen (Table 4).

As adjuvant treatment for diabetes, 89 patients (7.9%) used metformin (21% in latent autoimmune diabetes versus 6.9% in classic T1DM, $p < 0.01$). In addition, 12 patients (1.1%) used other antidiabetic agents (eight used SGLT2 inhibitors, two used GLP-1 receptor analogues and two used DPP4 inhibitors, with no differences between latent autoimmune diabetes and classic T1DM).

Table 5 presents the univariate analysis of the factors associated with achieving better blood glucose control. Among the variables associated with HbA1c <7%, we found that if we classified patients by level of education into ''secondary or higher education'' versus ''no or primary education'', then 30.4% of the former group versus 19% of the second group had good control. The current age of the patients was significantly different; patients with HbA1c <7% were 2.3 years younger than patients with HbA1c ≥7%. There were no differences for achieving target HbA1c with respect to patient gender or with respect to time since disease onset. When prior blood glucose control in 2010 was assessed, both the HbA1c value and the percentage of patients who achieved HbA1c <7% in 2010 were better in those in the good-control group (50.4% versus 18.8%; $p < 0.001$). Patients with good control had less retinopathy (33.1% versus 43.2%; $p < 0.01$). The subgroup with on-target HbA1c preferentially used an intensified insulin regimen (defined as MDI with a sensor or CSII with or without a sensor) 34.9% versus 20%; $p < 0.001$. With respect to classic cardiovascular risk factors, patients with on-target HbA1c were more likely to be of a normal weight ($p < 0.05$), were less hypertensive ($p < 0.05$), were less likely to smoke ($p < 0.001$) and had less hyperlipidaemia ($p < 0.001$).

In the multivariate analysis (Table 6), the variables independently associated with better blood glucose control were in Model 1, which included factors related to demographics,

Table 2 Results for blood glucose control, lipids, blood pressure and weight in the DIACAM1 cohort, comparison after 10 years.

	2010 DIACAM1	2020 DIACAM1	p Value
HbA1c (%)	7.75 ± 1.13	7.66 ± 1.06	<0.01
HbA1c < 7%	24.0%	24.8%	0.63
HbA1c < 8%	62.0%	67.7%	<0.001
HbA1c > 9%	12.3%	10.6%	<0.05
LDL-C (mg/dl)	102.4 ± 25.3	92.5 ± 22.6	<0.001
LDL-C < 100	46.1%	64.0%	<0.001
HDL-C (mg/dl)	58.4 ± 14.8	59.82 ± 15.7	<0.01
HDL-C > 50	67.1%	70.9%	<0.05
Triglycerides (mg/dl)	84.3 ± 56.9	89.1 ± 46.4	<0.01
Triglycerides < 150	92.4%	91.8%	0.58
SBP (mmHg)	125.8 ± 15.3	132.3 ± 16.9	<0.001
SBP < 140	80.5%	68.3%	<0.001
DBP (mmHg)	73.5 ± 10.1	76.6 ± 9.7	<0.001
DBP < 90	93.0%	89.8%	<0.05
Weight (kg)	72.8 ± 13.4	76.0 ± 14.9	<0.001
BMI (kg/m^2)	26.3 ± 4.2	27.4 ± 4.8	<0.001
Normal weight	41.3%	33.8%	<0.001
Obesity	15.3%	24.4%	<0.01

Data is expressed in terms of mean ± standard deviation (quantitative variables) or percentages (categorical variables).
The general objectives for control recommended by the ADA in 2019[11] were: LDL-C < 100 mg/dl, HDL-C > 50 mg/dl, triglycerides < 150 mg/dl, SBP < 140 mmHg and DBP < 90 mmHg.
DBP: diastolic blood pressure; HbA1c: glycosylated haemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure.

Table 3 Cardiovascular risk factors, treatments used and associated complications in the DIACAM1 cohort, comparison of the two periods analysed.

	2010 DIACAM1	2020 DIACAM1	p Value
HTN	21.7%	33.6%	<0.001
Hyperlipidaemia	35.2%	51.7%	<0.001
Active tobacco use	25.6%	23.8%	0.093
Obesity	15.3%	24.4%	<0.001
Treatment with antihypertensive drugs	27.0%	37.0%	<0.001
Treatment with lipid-lowering drugs	37.3%	49.1%	<0.001
Treatment with antiplatelet drugs	28.2%	26.8%	0.156
Insulin regimen			<0.001
Conventional-premixes	15.8%	3.9%	
Basal-bolus (MDI)	74.0%	82.8%	
CSII	8.9%	13.0%	
Other	1.3%	0.3%	
Microangiopathic complications			
Retinopathy (any degree)	31.4%	40.5%	<0.001
Nephropathy (any degree)	15.3%	18.3%	0.093
Macroangiopathic complications			
Any domain	5.9%	11.5%	<0.001

CSII: continuous subcutaneous insulin infusion; HTN: hypertension; MDI: multiple-dose insulin.

blood glucose control and treatment: attainment of secondary or higher education, use of intensified treatment regimens, and a history of good blood glucose control in 2010. In Model 2 which considered the prior variables and included classic cardiovascular risk factors, to the use of intensified treatment regimens, achieving good blood glucose control in 2010, the absence of hyperlipidaemia was added as an independent variable. Prior good blood glucose control in 2010 was the most powerful independent factor linked to good control in 2020; the likelihood of having a

Table 4 Treatment regimens and blood glucose control achieved in the 2020 DIACAM1 cohort.

Treatment regimen	No. (%)	HbA1c	HbA1c <7%	HbA1c <8%	HbA1c >9%	Insulin doses	Age	Time since onset
Conventional	43 (3.9)	7.9 ± 1.1	18.6%	58.1%	11.6%	0.72 ± 0.31	59.6 ± 14.1	33.1 ± 13.1
MDI	714 (64.2)	7.8 ± 1.1	20.0%	62.0%	13.4%	0.69 ± 0.26	50.3 ± 12.8	28.9 ± 9.9
MDI + CGM	210 (18.9)	7.3 ± 0.9[a]	36.2%[c]	80.5%[c]	4.3%[c]	0.65 ± 0.24[b]	46.5 ± 13.0[b]	29.0 ± 10.5[a]
CSII	56 (5)	7.6 ± 1.0[a]	28.6%[c]	71.4%[c]	10.7%[c]	0.52 ± 0.18[b]	46.3 ± 9.3[b]	27.8 ± 7.2[a]
CSII + CGM	89 (8)	7.2 ± 0.8[a]	36.0%[c]	84.3%[c]	0%[c]	0.54 ± 0.19*	45.8 ± 9.5[b]	27.3 ± 8.5[a]

CGM: continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion; HbA1c: glycosylated haemoglobin; MDI: multiple-dose insulin. HbA1c (%), age and time since onset (years) and insulin doses (IU/kg/day). Values expressed in terms of mean ± standard deviation.

[a] $p < 0.05$.

[b] <0.01 (T test for equality of means, comparison with respect to the conventional regimen and MDI).

[c] $p < 0.01$ (chi-squared test, comparison with respect to the conventional regimen and MDI).

HbA1c <7% was four times higher with a HbA1c in 2010 of <7% and 1.5 times higher on an intensified insulin therapy regimen (Table 6).

Cardiovascular risk factors and treatments used

After 10 years, the patients from the 2020 DIACAM1 cohort presented worsening of their cardiovascular risk profile, with the percentage of patients with obesity significantly increasing (Table 3). Patients from the 2020 cohort gained weight, a mean of 3 kg, and the percentage of patients with normal weight decreased significantly. A non-significant decrease by nearly 2% was seen in rates of active smoking. A significant increase in the percentage of patients with hypertension and hyperlipidaemia or requiring treatment for either of the two situations was also reported (Table 3). Table 3 summarises the changes in the treatments used to manage cardiovascular risk factors.

Table 2 shows mean levels of lipid and blood-pressure parameters, and the percentage of patients who achieved suitable control according to the objectives recommended by the American Diabetes Association (ADA).[11] There was a reduction in patients on antiplatelet drugs.

Associated complications

Table 3 shows the prevalence of microangiopathic and macroangiopathic complications in the DIACAM1 cohort after 10 years of follow-up. There was a significant increase in the prevalence of retinopathy and macroangiopathy (in any domain: cardiac, cerebrovascular or peripheral artery disease-related), with no demonstrated significant increase in the number of patients who had developed nephropathy.

Discussion

The prevalence of T1DM in Castilla-La Mancha is high,[12] and recently published data show that, in our Autonomous Community, T1DM accounts for 10% of visits made to outpatient clinics.[13] To determine the situation with regard to blood glucose control in this group of patients, 10 years ago, the DIACAM1 study was designed.[10] In 2010, the results obtained showed that a quarter of the people with T1DM included had good metabolic control, defined as a HbA1c under 7, and two thirds had acceptable control, defined as a HbA1c under 8%. The 2020 DIACAM1 study was designed to determine the degree of metabolic control and treatment regimens of the DIACAM1 cohort, after 10 years of follow-up under regular clinical practice conditions. After this period, the overall degree of blood glucose control improved in this cohort, but the proportion of patients who achieved the objective of a HbA1c below 7% remained stable.

These results show that, despite the advances achieved in the therapeutic management of patients with T1DM, clinical practice lies far from achieving the recommended objectives. Several recent cross-sectional Spanish national studies[14–16] have yielded outcomes similar to the DIACAM1 cohort, with just 25%–35% of the patients included in these studies achieving the overall objective of HbA1c <7%.

Table 5 Characteristics associated with good blood glucose control in the 2020 DIACAM1 cohort.

	HbA1c <7%	HbA1c ≥7%	p Value
Sex, female	52.3%	50.0%	0.498
Current age (years)	47.7 ± 12.1	50.0 ± 12.9	0.01
Time since onset (years)	28.9 ± 9.9	29.1 ± 10.7	0.753
Level of education			
Secondary or higher education	64.7%	52.6%	0.001
HTN, no	72.2%	64.45%	0.017
Hyperlipidaemia, no	64.3%	43.0%	0.001
Tobacco use, no	82.7%	74.0%	0.001
Obesity, no	76.5%	75.5%	0.765
Normal weight, yes	40.4%	31.8%	0.012
HbA1c <7% in 2010	48.7%	15.9%	0.001
2010 HbA1c (%)	6.45 ± 0.4	8.0 ± 0.9	0.001
Intensified treatment regimen	44.9%	27.5%	0.0001
Retinopathy, no	66.9%	56.8%	0.003
Nephropathy, no	87.7%	79.6%	0.003
Microangiopathy, no	64.1%	51.6%	0.001

Data is expressed in terms of mean ± standard deviation (quantitative variables) or percentages (categorical variables).
HbA1c: glycosylated haemoglobin; HTN: hypertension; Microangiopathy: presence of any degree of retinopathy and/or nephropathy.

Table 6 Results of two logistic regression models to determine the impact of the different factors on achieving HbA1c <7% in the 2020 DIACAM1 cohort.

	Model 1			Model 2		
	OR	95% CI	p Value	OR	95% CI	p Value
Age, <45 years	1.18	0.860–1.605	0.297	0.981	0.682–1.411	0.919
Level of education, secondary or higher	1.405	1.019–1.930	0.038	1.24	0.880–1.742	0.210
Treatment regimen, intensified	1.882	1.376–2.57	0.000	1.803	1.299–2.504	0.000
2010 HbA1c < 7%	4.92	3.67-6.74	0.000	4.484	3.214-6.256	0.000
Microangiopathy, no	1.23	0.934–1.690	0.189	1.114	0.791–1.569	0.536
HTN, no				0.952	0.641-1.412	0.806
Hyperlipidaemia, no				1.970	1.378–2.816	0.000
Tobacco use, no				1.332	0.901–1.971	0.151
Normal weight, yes				1.106	0.792–1.546	0.553

Model 1: this included insulin therapy regimen, blood glucose control in 2010 and microangiopathic complications (nephropathy and/or retinopathy) as independent demographic variables (no.: 1,048).
Model 2: to the above variables were added cardiovascular risk factors (no.: 976).
HbA1c: glycosylated haemoglobin; HTN: hypertension; OR: *odds ratio;* 95% CI: 95% confidence interval.

The DIACAM1 study was the first Spanish national multicentre study having prospectively analysed an extensive cohort of patients with T1DM, from the Spanish public health system, 10 years after their inclusion. Our results showed that even in patients with long-standing diabetes, it is possible to improve metabolic control outcomes. In a study by Carral et al.[15] after 10 years of follow-up of HbA1c, it was significantly reduced. The same happened in a study in Catalonia by Amor et al.,[14] but both studies analysed results in the context of a single-specialisation clinic with a programme aimed at comprehensive follow-up of patients with T1DM. Our results for improvement in blood glucose control over time contrasted with the findings published for the North American Exchange study,[17] which prospectively analysed an extensive cohort of patients with T1DM between 2010 and 2018 in the United States. The data from the latest analysis demonstrated little variation in HbA1c between the 2010-2012 cohort and the 2016-2018 cohort, with a worsening of control in the group of adolescents.[17] On a national level, with the objective of examining the degree of blood glucose control in the child/juvenile population with T1DM at a specialised referral practice, outcomes in nearly 300 patients were analysed,[18] a mean HbA1c of 6.7% was achieved, with ADA objectives attained in more than 90% of the children and youth included, far from the 17% published in the Exchange study.[17] In the SED1 study,16 while it was not designed to analyse a population under 18 years of age, this subgroup achieved a HbA1c of 7.6%, with 29% of youths achieving the target of a HbA1c under 7%; the results were similar in adults.

When we analysed determining factors in blood glucose control in our cohort, level of education attained was a factor maintained over the course of the 10 years of follow-up;[10] this determining factor was similarly reflected in the

recently published SED1 study[16] and could be an indirect indicator of the degree of adherence to the treatment education programme.[19]

An intensified insulin therapy regimen is the gold standard for achieving better blood glucose control. Since the results of the DCCT/EDIC study were published,4 the most physiologically normal insulin therapy regimens have been known to yield the best results. In the Exchange study, patients who used CSII achieved lower HbA1c levels.[17] Several recent studies in Spain[20] and in our Autonomous Community[21] have also demonstrated better blood glucose control outcomes in patients with CSII. The percentage of patients who use CSII in Spain is rising, although it is still lower than expected and the country is far from the CSII usage figures in Europe more broadly.[22] In 2010, just 9% of the patients included in the DIACAM1 cohort used CSII; the increase to 13% after 10 years was significant, but lower than that reported in other groups,16 representing an opportunity for improvement. Similar to the use of CSII, the use of CGM is associated with better blood glucose control outcomes.[16,17] The development of the Flash® glucose measurement system has represented a ''before'' and ''after'' in self-management of blood glucose in patients with T1DM. Its lower costs and benefits have allowed more patients to access CGM and increased the indications for it, ultimately making funding by the public health system possible for all patients with T1DM over 4 years of age. In Castilla-La Mancha, CGM has been funded since November 2019, leading in a certain way to the results obtained in this study. The results ended in June 2020, just six months after the start of public funding, and three months after the start of the COVID-19 pandemic, which has hindered the implementation of this monitoring system due to initial lock-downs at home. Some 27% of the patients from the 2020 DIACAM1 study used CGM and achieved better blood glucose control regardless of the insulin regimen used. Recently published data indicates that, although prescription of CGM is higher in patients who use complex insulin regimens or CSII, the impact on the improvement of blood glucose control is higher even with simpler insulin regimens.[23]

HbA1c is a marker of chronic hyperglycaemia. Metabolic memory not only leads to lesser development of microvascular and macrovascular complications, but also was the most powerful independent factor in our cohort in achieving suitable blood glucose control. Lower blood glucose exposure 10 years earlier would contribute to maintaining suitable blood glucose control today. This must influence the need to intensify therapeutic and educational measures to achieve good blood glucose control from the beginning, which will surely yield better long-term outcomes. Studies analysing series of patients with T1DM in regular periodic follow-up since the onset of the disease, with a structured educational programme and intensified treatment, have achieved good control as of the first few years, resulting in better overall blood glucose control and a lower rate of complications.[24]

The impact of classic cardiovascular risk factors on blood glucose control has been extensively studied in the DCCT/EDIC cohort[25] and in recent population studies of adult patients with T1DM.[26] The absence of active tobacco use in the initial DIACAM1 cohort was associated with better blood glucose control.[10] In the multivariate analysis of the 2020 cohort, an independent relationship was maintained between the achievement of HbA1c under 7% and the absence of hyperlipidaemia; this was consistent with the known effects of blood glucose control on lipid metabolism.[25] This inter-relationship between cardiovascular risk factors and blood glucose control should help develop intervention measures for managing comorbidities and reducing cardiovascular risk in patients with T1DM.[27,28]

Our patients with T1DM showed a worsening in their cardiovascular risk profile after 10 years of follow-up; however, this must be qualified. First, the prevalence of tobacco use improved, although not significantly. In addition, the intensification of lipid-lowering and hypotensive treatment regimens contributed significantly to the fact that the percentage of patients with hypertension and dyslipidaemia increased (as the use of these treatments is included in the definition of these risk factors). However, this intensification was key to the fact that the achievement of lipid and blood-pressure control targets improved compared to the 2010 DIACAM1 study, especially with respect to targets for lipid (LDL-C and HDL-C) control.

Weight gain due to ageing and associated with intensified insulin therapy itself has been known to be a complication since the first data from the DCCT study was released.[3] It requires a specific approach with education and exercise programmes, as well as, possibly, the use of drugs that contribute to weight loss.[29] In our cohort, the use of metformin remained constant at around 8% over the course of these 10 years; rates of incretin drugs and glucosuric drugs were around 1%. Concomitant use of other antidiabetic agents in the treatment of T1DM was not collected in most of the Spanish series analysed,[14,16,24] apart from a study by Carral et al.[15] in which 6.5% of the patients included used other antidiabetic drugs.

Our study had several limitations, some inherent to observational, cross-sectional studies and others resulting from the COVID-19 pandemic, which surely affected some of the anthropometric and laboratory data collected in the final months of the study (March to June 2020). In addition, collecting data from medical records did not allow us to gather reliable data on the incidence of episodes of severe hypoglycaemia. We believe the great strength of the 2020 DIACAM1 study, on the other hand, was that we managed to collect and analyse data for 80.5% of the patients in the initial cohort; this rate was similar to that achieved in other European multicentre studies.[30] Although it was far from the 96% rate achieved in the EDIC study, it constitutes an extensive cohort representative of the population with T1DM in Castilla-La Mancha.

Conclusions

The data for overall blood glucose control, estimated based on HbA1c in patients with T1DM en Castilla-La Mancha, did not differ from those documented elsewhere in Spain, and improved after 10 years of follow-up. The use of intensified insulin regimens and the implementation of the use of technology applied to diabetes care appear to be determining factors in achieving this improvement, and offer an opportunity to continue improving outcomes in blood glucose control and complications in DM1.

Conflicts of interest

The authors declare that they have no conflicts of interest in relation to the results of the study.

Appendix 1. Other participating investigators in the 2020 DIACAM1 study group

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