Diabetes Ther (2024) 15:325–341
https://doi.org/10.1007/s13300-023-01503-4

REVIEW

Disease and Economic Burden of Poor Metabolic and Weight Control in Type 2 Diabetes in Spain: A Systematic Literature Review

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Received: August 18, 2023 / Accepted: October 23, 2023 / Published online: November 22, 2023
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ABSTRACT

Introduction: Poor metabolic control and excess body weight are frequently present in people with type 2 diabetes (PwT2D).
Methods: A systematic literature review was conducted to identify observational studies reporting clinical, economic, and health-related quality of life (HRQoL) outcomes associated with poor metabolic (according to HbA1c, blood pressure [BP] and low density lipoprotein cholesterol [LDL-C] levels) and/or weight control (defined by a body mass index [BMI] $\geq$ 30 kg/m^2) in adults with T2D in Spain, including articles published in either Spanish or English between 2013 and 2022 and conference abstracts from the last 2 years.
Results: Nine observational studies were included in the analysis. Poor glycemic control (HbA1c $\geq$ 7%) was associated with cardiovascular disease (CVD), increased requirements for antidiabetic medications, higher and more frequent weight gain, a greater probability of hypoglycemia and dyslipidemia, and worse health-related quality of life (HRQoL). Uncontrolled BP in PwT2D was related with the presence of CVD, worse metabolic control, and higher BMI and abdominal perimeter values. Poor LDL-C control or dyslipidemia was associated with CVD, hypoglycemia, and elevated HbA1c and triglycerides levels. The presence of a BMI $\geq$ 30 kg/m^2 was related to CVD and hypoglycemia, a higher prevalence of metabolic syndrome and worse BP control. Direct medical costs were found to be higher in PwT2D when coexisting with HbA1c levels $\geq$ 7%, uncontrolled BP or obesity. Increased total costs, including productivity losses, were also detected in those who presented uncontrolled BP and a BMI $\geq$ 30 kg/m^2, and when poor weight control existed together with HbA1c $\geq$ 8% and poorly controlled BP.
Conclusion: Gathered evidence supports the high clinical, economic and HRQoL burden of

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-023-01503-4.

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poor metabolic and/or weight control in PwT2D in Spain and reinforces the importance of prioritizing its control to reduce the associated burden, at both the individual and healthcare system levels.

Keywords: Type 2 diabetes mellitus; Burden of illness; HbA1c; Obesity

Key Summary Points
Despite existing evidence demonstrating that the presence of poor metabolic control and excess body weight negatively impact T2D, we have no knowledge of a systematic literature review that aggregates and summarizes its clinical, economic and quality of life burden in the Spanish population with T2D
The present systematic literature review identifies and describes available evidence reporting quantitative data regarding clinical, economic and quality of life outcomes in Spanish adults with T2D and poor metabolic control or obesity compared to those controlled and with normal weight
Available evidence supports a high clinical, economic and HRQoL burden associated with poor metabolic and/or weight control in adults with T2D in Spain
Addressing metabolic control and excess weight would reduce the burden that T2D imposes on individuals and the healthcare system

DIGITAL FEATURES

This article is published with digital features, including infographics, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24420694.

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent chronic diseases worldwide, with type 2 diabetes (T2D) accounting for approximately 90% of total diagnosis [1]. The prevalence of T2D in Spain is the second-highest in Europe [2], and the country ranks third in diabetes-related health expenditure [3].

Micro- and macrovascular complications are the major cause of morbidity and mortality in people with T2D (PwT2D) [4, 5] and are also responsible for most of medical costs incurred by patients [6]. Accordingly, a holistic, person-centered treatment approach is now being advocated with the goal of avoiding or delaying complications in the long term while maintaining PwT2D's quality of life. This includes the management of blood glucose levels (HbA1c), weight, cardiovascular risk factors and comorbidities [7].

The achievement of glycemic control early in the course of the disease has proven to confer protection against the onset and progression of microvascular and macrovascular complications [8–10]. In line with this, a general objective of HbA1c < 7 is recommended, although more stringent targets are reasonable if they can be achieved safely, mainly in PwT2D with longer life expectancy [7].

In Europe, 50.9–98.6% of PwT2Ds have obesity [11]. There is a high correlation between excess body weight and T2D, with men and women with obesity having a 7- and 12-fold higher risk of developing T2D, respectively, than those with a normal body weight [12]. However, obesity is not only an important environmental factor involved in the etiopathogenesis of T2D but is also highly associated with the development of its complications [13]. Weight gain increases the risk of cardiometabolic complications [12], and weight loss has been demonstrated to improve risk factors for cardiometabolic disease and PwT2D's quality of life [14]. Current treatment guidelines positioned weight loss as a primary target in the management of T2D in many cases and advocate for a minimum weight loss of 5 to 10% to obtain metabolic improvements [15]. In

general, outcomes are better with greater weight loss, and reductions of higher magnitude (10–15%) have shown disease-modifying effects leading to diabetes remission [16].

Despite recommendations, keeping adequate levels of HbA1c, blood pressure (BP) and lipids is still challenging, and PwT2Ds often have poor metabolic control, with no significant improvements observed over the past few years. A cross-sectional study using yearly clinical data from 2007 to 2018 revealed that almost half of the Spanish population with T2D in Catalonia was under HbA1c targets. The proportion of PwT2D with HbA1c < 7% exhibited minimal changes over the years, barely shifting from 54.9% in 2007 to 55.9% in 2018. Additionally, the simultaneous attainment of all three targets (HbA1c, BP and lipids) showed improvement from 12.5 to 20.1% until 2013, but remained constant thereafter and was found to be insufficient [17]. Although lifestyle modifications, such as diet and increased physical activity, are recommended for PwT2D at all disease stages, they are challenging and often fail to achieve glycemic targets and weight loss goals; therefore, glucose-lowering medication with weight loss efficacy is often required [18, 19].

Evidence reporting outcomes associated with poor metabolic and/or weight control in T2D in our country exists, but studies focused on clinical, economic or HRQoL variables and no comprehensive systematic literature review summarizing all these aspects is available. Therefore, we set out the present systematic literature review to gather all available evidence describing the clinical, economic and HRQoL burden of poor metabolic and/or weight control in PwT2D in Spain.

METHODS

Search Strategy

A comprehensive search strategy was carried out in international (MEDLINE/PubMed) and Spanish (*Medicina en Español, Índice Bibliográfico Español en Ciencias de la Salud*) databases and complemented with an extensive search of the gray literature. Terms used for this purpose are included in Supplementary Text 1.

Ethical approval was not required since this article is based on previously conducted research and does not contain any new studies involving human participants or animals.

Eligibility Criteria

Observational studies reporting clinical, economic and HRQoL outcomes based on the degree of metabolic/weight control in Spanish PwT2D were selected. Poor metabolic control was defined following the American Diabetes Association (ADA) as poor glycemic control (HbA1c ≥ 7%[53 mmol/mol]), and/or poorly controlled BP and/or hypertension (BP ≥ 140/90 mmHg) and/or poorly controlled low-density lipoprotein cholesterol (LDL-C) or dyslipidemia (LDL-C ≥ 100 mg/dl) [20]. Articles using alternative definitions for hypertension and dyslipidemia were also evaluated and included in the review. Poor weight control was defined as the presence of obesity, determined by a body mass index (BMI) ≥ 30 kg/m^2.

Studies published in English and/or Spanish in the last 10 years (2013–2022) which were conducted in Spain or in several countries but provide data specific for the Spanish population with T2D were included. Conference abstracts from the last 2 years (2020–2022) were also considered in the review.

Clinical trials, economic evaluations, opinion articles, letters to the editor and narrative or systematic literature reviews were excluded as well as observational studies focusing on specific drugs.

Study Selection

The review was performed using search filters and standardized terms and followed the "Preferred Reporting Items of Systematic Reviews and Meta-analysis: The PRISMA Statement" guidelines [21]. Two reviewers independently screened all identified articles for the full-publication review. Discrepancies were resolved by consensus or with the involvement of a third team member.

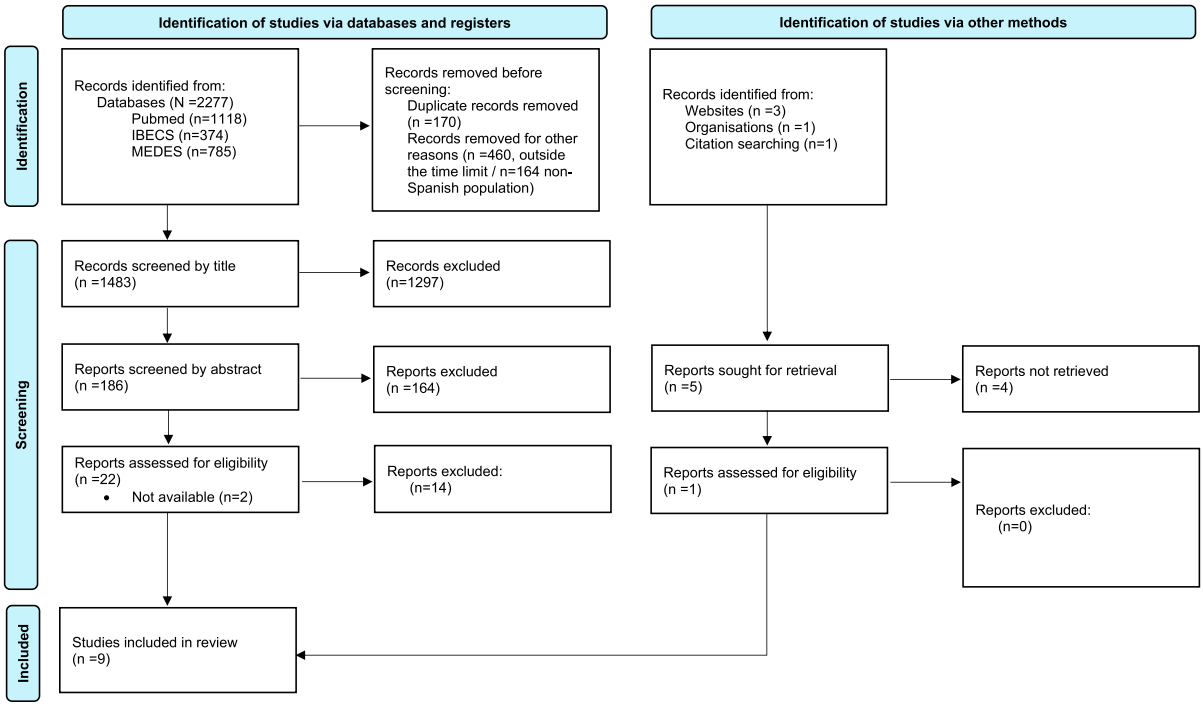


Fig. 1 PRISMA flow diagram depicting literature screening and inclusion process

Assessment of Study Quality

The quality of included publications was assessed using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) quality score [22], with 22 points (100%) being the maximum score.

Data Extraction

Data were directly extracted from each study, and no formal statistical analysis was performed. Study variables analyzed in this review included: design (observational [case series or case study]; analytical [cross-sectional; case-control; retrospective and/or prospective cohorts]), sample size, main objectives and a summary of the most relevant results obtained by variable analyzed (clinical [macro- and microvascular complications, CVD, mortality, etc.], HRQoL and economic outcomes [healthcare resource use/associated medical costs/loss of productivity]).

RESULTS

A total of 2282 potentially relevant titles were initially recovered. After duplicate removal (n = 170) and eliminating articles for other reasons, such as being outside of the defined time limit (n = 460) or not containing Spanish specific data (n = 164), 1488 titles were selected. Following analysis of the titles and abstracts, 1465 publications did not include information related to the search objective and 23 articles were considered for full-text review, 9 of which met study selection criteria and were finally included (Fig. 1).

Description of Studies Included in the Review

Of the nine selected observational studies, four had cross-sectional [23–26] and four retrospective [27–30] designs. Study design was not specified for one of the selected publications [31].

There were five studies that met ADA criteria for poor metabolic control [23–25, 28, 31].

Table 1 Characteristics of the observational studies included in the systematic literature review

Author and date	Title	Objective	Design	Population	STROBE
Sicras-Mainar et al. (2014) [27]	Clinical and economic characteristics associated with type 2 diabetes	To evaluate clinical characteristics (comorbidities, metabolic syndrome, therapeutic control, hypoglycemia and CVD) and to analyze healthcare resource use and costs in PwT2D according to certain comorbidity patterns in routine clinical practice in Spain	Retrospective	3760	20/22 (90.9%)
de Pablos-Velasco et al. (2014) [23]	Quality of life and satisfaction with treatment in subjects with type 2 diabetes: Results in Spain of the PANORAMA study	To assess quality of life and treatment satisfaction in PwT2D in Europe. It also aims to study the degree of metabolic control, treatment, and management practices by healthcare professionals	Cross-sectional	751	18/22 (81.8%)
Pérez et al. (2014) [24]	Glycemic control in patients with type 2 diabetes mellitus in Spain	To evaluate the degree of glycemic control in people with PwT2D in Spain and to identify factors associated with glycemic control	Cross-sectional	5382	18/22 (81.8%)
Alonso-Morán et al. (2015) [31]	Incidence of severe hypoglycaemic episodes in patients with type 2 diabetes in the Basque country: impact on healthcare costs	To describe the annual rate of severe hypoglycemia episodes and to estimate healthcare resource use and costs for individuals who have suffered such events	Descriptive	134,413	15/22 (68.2%)
Barquilla García et al. (2015) [25]	Blood pressure control in a population of hypertensive diabetic patients treated in primary care: PRESCAP-Diabetes Study 2010	To determine the degree of BP control in hypertensive-diabetic people in primary care and to investigate factors associated with poor BP control	Cross-sectional	3993	18/22 (81.8%)

Table 1 continued

Author and date	Title	Objective	Design	Population	STROBE
Mata-Cases et al. (2016) [28]	Direct medical costs attributable to type 2 diabetes mellitus: a population-based in Catalonia, Spain	To estimate healthcare resource use and additional costs for the Spanish National Health System (in 2011€) attributed to T2D compared to a control group of non-diabetic subjects matched for age, gender and managing physician, randomly selected from a population database	Retrospective	253,622	17/22 (77.3%)
Diaz-Cerezo et al. (2020) [29]	Resource use and costs in patients with poorly controlled type 2 diabetes mellitus and obesity in routine clinical practice in Spain	To compare healthcare resource use and costs in PwT2D with poor glycemic control and obesity versus those controlled without obesity in routine clinical practice in Spain	Retrospective	7975	20/22 (90.9%)
Díaz Vera et al. (2020) [26]	The prevalence and risk factors associated with dyslipidemia in type 2 diabetic patients in the Autonomous Region of Cantabria	To evaluate the prevalence and risk factors associated with dyslipidemia in the population with T2D in the region of Cantabria	Cross-sectional	680	17/22 (77.3%)
Orozco-Beltrán et al. (2022) [30]	Adherence, control of cardiometabolic factors and therapeutic inertia in patients with type 2 diabetes in the primary care setting	To estimate the prevalence of good adherence to all medications used to control diabetes, hypertension, and dyslipidemia and to analyze cardiometabolic control and its associated factors in PwT2D in the primary care setting in Spain	Retrospective	457	15/22 (68.2%)

CVD cardiovascular disease, *T2D* type 2 diabetes mellitus, *BP* blood pressure

Additionally, one defined the presence of poor BP control as PwT2D on antihypertensive therapy or with systolic/diastolic BP values ≥ 130/85 mmHg [27], one considered PwT2D with dyslipidemia as those on lipid-lowering therapy or with LDL-C values > 160 mg/dl [26], and an additional one did not provide a definition for dyslipidemia [27].

Regarding the correct communication of the information, two of the nine studies had 90.1%

Table 2 Poor glycemic control in the Spanish population with T2D: results of studies comparing clinical and HRQoL outcomes in PwT2D and poor glycemic control versus those with T2D and controlled HbA1c levels

Variable analyzed	Not controlled	Controlled	Difference	Publication
Insulin needs (% of patients)	77.0	23.0	$p < 0.0001$	Pérez et al. 2014 [24]
Combination (% of patients)				
Two antidiabetics	59.4	40.6	$p < 0.0001$	
Three antidiabetics	70.5	29.5	$p < 0.0001$	
Four antidiabetics	77.0	22.6	$p < 0.0001$	
Weight gain (kg, mean)	3.7	3.1	$p < 0.001$	
Weight loss (kg, mean)	− 3.7	− 4.5	$p = 0.0014$	
Quality of life (ADDQoL [+ 3-(-9)])	− 2.1	− 1.7	$p = 0.007$	de Pablos-Velasco et al. (2014) [23]
Treatment satisfaction (DTSQ [36-0])	28.1	30.1	$p < 0.001$	
Fear of hypoglycemia (HFS-II [0–72])	12.7	10.2	$p = 0.030$	
Medical attention for hypoglycemia (% of patients)	8.9	4.6	$p < 0.0001$	Pérez et al. (2014) [24]

ADDQoL Analysis of Diabetes-related Quality of Life, *DTSQ* Diabetes Treatment Satisfaction Questionnaire, *HFS-II* Hypoglycemia Fear Subscale

of STROBE items adequately reported [27, 29], followed by three others with 81.8% [23–25] and two additional one with 77.3% [26, 28]. Lower STROBE percentages (68.2%) were found for two of the selected publications [30, 31] because of the absence or lack of clarity around essential study aspects, such as study design, variables, statistical methods or sample size (Table 1).

Poor Metabolic Control in T2D

Poor Glycemic Control

Six of the nine selected studies compared clinical ($n = 4$), economic ($n = 4$) and HRQoL ($n = 1$) variables between adults with T2D and HbA1c levels < 7% with those who had poor glycemic control (HbA1c ≥ 7%) [23, 24, 26–28, 31] (Table 2 and S1).

Poor glycemic control in individuals with T2D was found to be associated with the presence of CVD (OR = 2.8) [27], hypoglycemia (OR = 1.6 in PwT2D 7% < HbA1c ≤ 8% vs. HbA1c < 7%) [31] or dyslipidemia (OR = 1.7) [26] (Fig. 2). Individuals with T2D and uncontrolled HbA1c levels had higher insulin needs (77.0% vs. 23.0%) and received combined therapy more often, with 70.5% and 77.4% requiring three or four antidiabetic medications, respectively, compared with 29.5% and 22.6% in those HbA1c < 7% [24]. Annual changes in body weight were significantly different between HbA1c controlled and not controlled groups, with those above glycemic control targets experiencing weight gains of higher magnitude (3.7 kg vs. 3.1 kg) and more frequently compared to HbA1c < 7% ones [24]. Available evidence also indicates poorer HRQoL, according to the Analysis of Diabetes-related Quality of Life (ADDQoL), reduced treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [DTSQ]) and increased fear of hypoglycemia (Hypoglycemia Fear Subscale [HFS-II]) in PwT2D with HbA1c > 7% [23].

Total direct medical costs were significantly higher in PwT2D who were HbA1c ≥ 7%

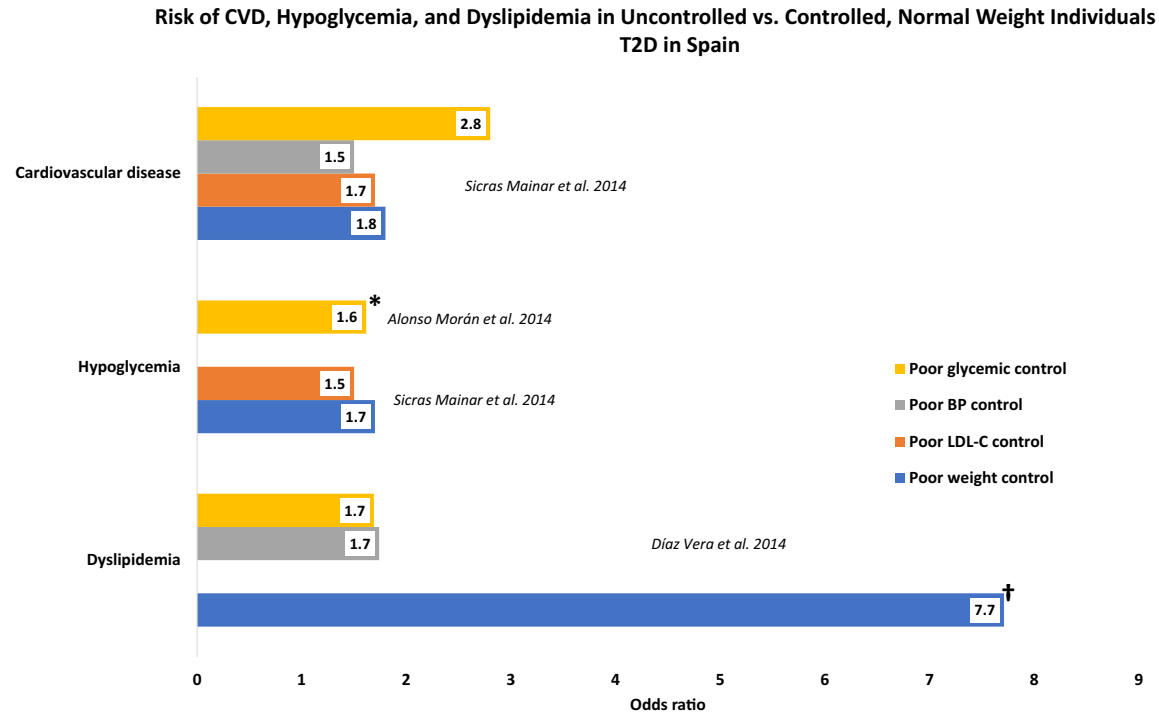


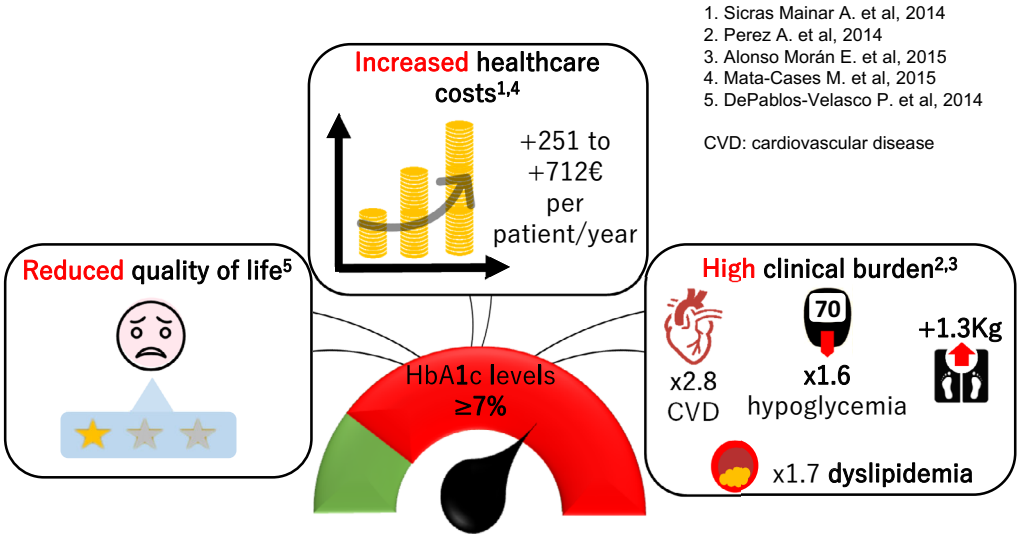
Fig. 2 Risk of CVD, hypoglycemia and dyslipidemia in uncontrolled vs. controlled normal weight individuals with T2D in Spain. *Results for 8% ≥ HbA1c > 7% group compared to HbA1c controlled individuals with T2D (HbA1c < 7%). Additional comparisons also available: 9% ≥ HbA1c > 8% vs. HbA1c < 7%, OR = 1.5; HbA1c > 9% vs. HbA1c < 7%, OR = 2.2. † Risk of dyslipidemia in those with a BMI ≥ 30 kg/m^2. Orozco Beltrán et al. 2022 found a higher risk of dyslipidemia (OR = 1.6) in those of normal weight (BMI < 30 kg/m^2)

compared to those HbA1c < 7% with an additional cost per person-year ranging from + 251€ to + 712€ [27, 31] (Fig. 3). Hospitalization and medication costs were the main variables contributing to the yearly cost increment [28], which was observed to rise with poorer HbA1c control [31]. In addition, a higher proportion of patients required medical attention because of hypoglycemia episodes during the year prior to the analysis among those with poor glycemic control (8.9% vs. 4.6%) [24].

Infographic 1

Disease and economic burden of poor metabolic and weight control in Type 2 Diabetes in Spain: a systematic literature review

Antonio Pérez, Jennifer Redondo-Antón, Irene Romera, Luís Lizán, Miriam Rubio-de Santos, Silvia Díaz-Cerezo, Domingo Orozco-Beltrán.



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Poor Blood Pressure Control

Three studies investigated clinical variables associated with poor BP control [25–27], one of which also examined its economic burden [27] (Table 3 and S2).

An association was identified between suboptimal BP control and the presence of CVD (OR = 1.5) or dyslipidemia (OR = 1.7) in individuals diagnosed with T2D [26, 27]. In addition, PwT2D and uncontrolled BP had worse metabolic control, higher BMI (30.9 vs. 30.2 kg/m^2) and superior abdominal perimeter values (104.1 cm vs. 102.3 cm) [25].

The presence of poor BP was linked to significantly higher direct and total medical costs, which also accounted for productivity losses [27]. Total annual direct costs in PwT2D and uncontrolled BP were + 554€ higher (Fig. 3) compared to BP controlled ones, mainly driven by primary care cost (2831€ vs. 2238€).

Poor LDL Cholesterol or Dyslipidemia

The clinical burden of poor LDL-C control or dyslipidemia in PwT2D was evaluated in two of the selected publications [26, 27] (Table 4 and S3). Findings revealed that poorly controlled LDL-C or dyslipidemia was associated with the presence of CVD (OR = 1.7) and hypoglycemia (OR = 1.5) [27] (Fig. 2). Additionally, higher HbA1c levels (7.0 vs. 6.7) and triglycerides values (145.8 vs. 90.2) were observed in PwT2D who had dyslipidemia [26].

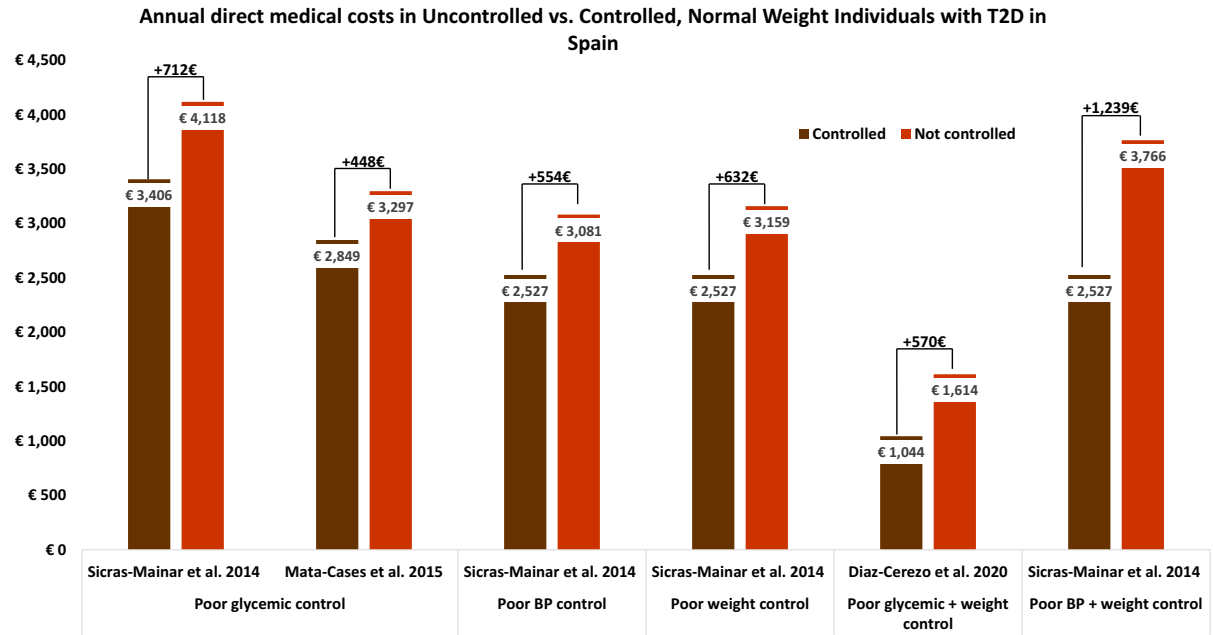


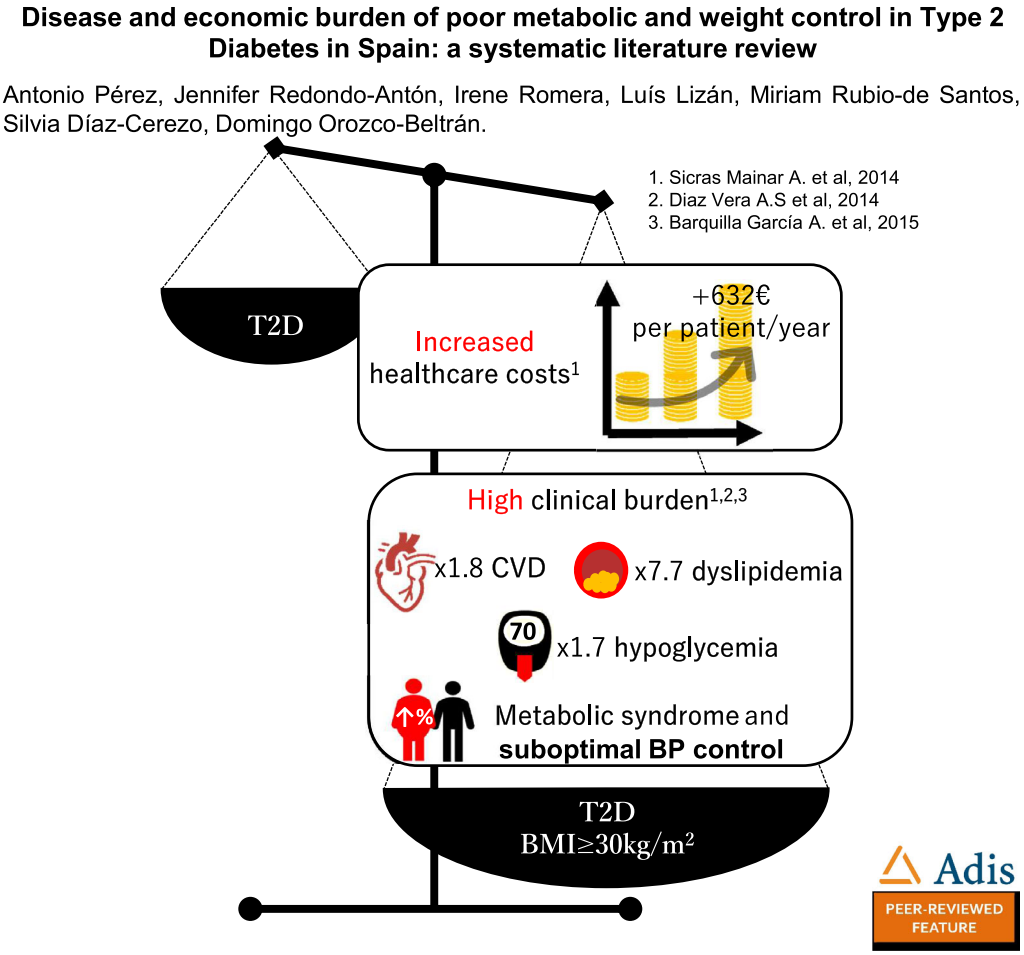
Fig. 3 Annual direct medical costs in uncontrolled vs. controlled normal weight individuals with T2D in Spain. Studies reporting total direct costs are included in this graph. The studies exhibited heterogeneity in the variables considered for calculating total direct cost. Alonso Morán et al. (2014) also analyzed the economic burden of uncontrolled HbA1c showing additional costs per person-year in different groups vs. HbA1c < 7% population: 7% < HbA1c ≤ 8%, + 251.5€; 8% < HbA1c ≤ 9%, + 561.8€; HbA1c > 9%, + 447.5€. Differences between controlled and not controlled subgroups were significant

Poor weight control in T2D

A total of four studies analyzed clinical outcomes in PwT2D and poor weight control compared to those of normal weight [25–27, 30] (Table 5 and S4). The presence of a BMI ≥ 30 kg/m^2 in PwT2D was linked to CVD disease (OR = 1.8) and hypoglycemia (OR = 1.7) (Fig. 2). A higher proportion of PwT2D were found to have metabolic syndrome (75.8% vs. 31.2%) [27] and suboptimal BP control (53.0% vs. 47.6%) [25] among those with poor weight control. Accordingly, a BMI < 30 kg/m^2 was associated with a reduced risk of inadequate BP control (OR = 0.6) [30]. Contradictory findings were observed for the relationship between body weight and dyslipidemia. One study revealed higher likelihood of dyslipidemia in people with obesity (OR = 7.7) [26], whereas another study suggested that those with normal weight (BMI < 30 kg/m^2) are more likely to have uncontrolled LDL-C values (OR = 1.6) [30].

Economic outcomes associated with poor weight control were assessed in one of the studies [27], which revealed significantly higher direct (3159€ vs. 2527€) and total medical costs (4915€ vs. 3431€) in PwT2D and a BMI ≥ 30 kg/m^2, mostly due to increased primary care costs (2794€ vs. 2238€) [27] (Fig. 3). In addition, using a linear regression model, poor weight control was found to be associated with increased direct costs [27].

Infographic 2



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Additional Findings

Poor Glycemic and Weight Control

Healthcare resource use and associated direct and total medical costs were higher in PwT2D HbA1c ≥ 8% with a BMI ≥ 30 kg/m^2 than in those HbA1c < 7% with normal weight, mainly driven by an increase in primary care medical visits, medicines and hospitalization costs (Fig. 3 and table S5) [29].

Poor BP and weight control

PwT2D with uncontrolled BP and a BMI ≥ 30 kg/m^2 showed a higher prevalence of metabolic syndrome, with percentages of people affected rising as BMI increase (only T2D group: 31.2%; T2D-high BP-overweight group: 78.7%; T2D-high BP-obesity group: 98.7%). In addition, a higher percentage of these PwT2D used antidiabetic medications or insulin compared to those controlled, following a similar trend (Table 6 and S5) [27].

Economic evaluations revealed an additional direct cost per person year of + 1239€ (Fig. 3) mostly driven by increased primary care costs (3355€ vs. 2238€) and significantly higher total costs (5201€ vs. 3431€) in PwT2D with poor BP and weight control [27].

Table 3 Uncontrolled BP in the Spanish population with T2D: results of studies comparing clinical outcomes in PwT2D and uncontrolled BP vs. those with T2D and controlled BP

Variable analyzed	Not controlled	Controlled	Difference	Publication
Metabolic control				Barquilla García et al. (2015) [25]
Basal blood glucose	141.3	133.4	$p < 0.001$	
HbA1c (%)	7.2	6.9	$p < 0.001$	
Total cholesterol	201.9	189	$p < 0.001$	
LDL-C	121.8	112	$p < 0.001$	
Triglycerides	158.6	144.7	$p < 0.001$	
Microalbuminuria	46.5	29.2	$p < 0.001$	
Estimated glomerular filtration rate	76.1	78.7	$p < 0.005$	
BMI	30.9	30.2	$p < 0.001$	
Abdominal perimeter	104.1	102.3	$p < 0.001$	
Dyslipidemia (% of patients)	87.2	79.7	$p = 0.017$	Díaz Vera et al. (2020) [26]

DISCUSSION

This systematic literature review provides a comprehensive summary of the influence of poor metabolic and weight control in Spanish adults with T2D using data from articles published within the last 10 years. A total of nine publications were identified, with seven of them exploring outcomes associated with the presence of poor metabolic control, while five addressed the burden of poor weight control in PwT2D. Retrieved article count was found to be low considering the extensive search period and the significance of the research question in the Spanish population with T2D. Data included in this review support that the presence of uncontrolled HbA1c levels, high BP, dyslipidemia and excess body weight in T2D pose a considerable burden on PwT2D and the healthcare system. This emphasizes the need to prioritize the management of these factors, considering the existing level of control in individuals with T2D in the Spanish setting. The fact that approximately half of the Spanish population with T2D remains outside control targets presents a clear chance for prevention strategies to mitigate the burden associated with this inadequate control [17].

Findings of this systematic literature review revealed an association between poor metabolic control and the presence of CVD, which aligns with existing literature across different research settings. Glycemic control has been described as a strong predictor of CVD and death in several long-term studies involving individuals with T2D [32–34].

Accordingly, data from the Swedish national Diabetes Register indicate considerable risk reductions for CVD and mortality associated with combined long-term improvement in HbA1c levels, systolic BP and ratio non-HDL: HDL in 13,477 PwT2D followed for a mean of 6.5 years. This study observed a 35% decrease in the risk of CVD linked to glycemic control, which rose to 56% when combined with BP control and further increased to 75% with the addition of non-HDL:HDL ratio control [35]. Therefore, data gathered in this review suggest that effective management of metabolic parameters could significantly reduce the risk of CVD and mortality among PwT2D.

The results of our study further support the well-established relationship between the

Table 4 Poor LDL-C control or dyslipidemia in the Spanish population with T2D: results of studies comparing clinical outcomes in PwT2D and poor LDL-C vs. those with T2D without dyslipidemia

Variable analyzed	Not controlled	Controlled	Difference	Publication
Metabolic control				Díaz Vera et al. (2020) [26]
HbA1c	7.0	6.7	$p < 0.030$	
Triglycerides	145.8	90.2	$p > 0.000$	

Table 5 Poor weight control in the Spanish population with T2D: results of studies comparing clinical outcomes in PwT2D and poor weight control vs. those with T2D and a BMI < 30 kg/m^2

Variable analyzed	Not controlled	Controlled	Difference	Publication
Metabolic syndrome (% of patients)	75.8	31.2	$p < 0.01$	Sicras-Mainar et al. (2014) [27]
Poorly controlled BP (% of patients)	53	47.6	$p < 0.005$	Barquilla García et al. (2015) [25]
Dyslipidemia (% of patients)	86.1	44.4	$p = 0.003$	Díaz Vera et al. (2020) [26]

Table 6 Additional findings

Variable analyzed	Not controlled	Controlled	Difference	Publication
Metabolic syndrome (% of patients)				Sicras-Mainar et al. (2014) [27]
Overweight	78.7	31.2	$p < 0.01$	
Obesity	98.7			
Use of antidiabetic medications (% of patients)				
Overweight	86.9	75.5	$p < 0.01$	
Obesity	89.3			

Clinical variables in PwT2D with poor weight control (overweight and obesity) and uncontrolled BP
Overweight: BMI 25–29,9 kg/m^2; obesity $\geq$ 30 kg/m^2

presence of obesity in T2D and the development of CVD [36]. Accordingly, weight gain has been linked to an increased risk of cardiometabolic complications, and weight loss has been demonstrated to improve risk factors for CVD in a direct and linear fashion in individuals with T2D [37, 38]. Weight management should be a priority in the treatment of T2D and needs to be addressed early, preferably using weight-beneficial agents, with the aim of achieving weight loss goals ranging from 5 to 15% for many people [7, 19].

The identified studies reveal increased costs linked to poor metabolic and weight control, with increments per person-year in direct costs ranging from + 251 to + 1239€. Previous studies have already explored the economic burden of poor glycemic control in PwT2D, showing that delays in treatment intensification and the persistence of a suboptimal glycemic state

translate into a significant increase in total annual costs [36, 39–41]. Liebl et al. reported that T2D costs are mainly driven by inpatient care for the treatment of complications (40–60% of total cost), with pharmacological therapy aimed at glycemic control accounting for 18% of the total cost. Therefore, early and strict glycemic control is required to prevent or delay these complications, promoting long-term health and reducing treatment costs [42]. Supporting the economic burden associated with the presence of excess body weight in T2D described in the present literature review, Karkare et al. found that weight loss was associated with significantly lower all-cause and T2D-related annual costs [43]. Weight control is crucial in T2D management programs, given its impact on people and the healthcare systems.

Our study presents some strengths, as the robust search strategy focused on collecting extensive and elaborated data from different databases. Therefore, most reviewed studies showed a high STROBE score, correctly reporting the information. Within the included studies, quantitative analyses of clinical, economic or HRQoL variables in controlled vs. uncontrolled PwT2D are presented, providing a comprehensive assessment of the extent to which poor control in T2D affects individuals and healthcare systems. Our study has limitations due to the observational nature of the investigations and the heterogeneity of the included studies (retrospective and cross-sectional designs). The definition of poor metabolic control among the studies included is inconsistent; therefore, the results may not be comparable. Thus, further high-quality prospective studies are necessary to accurately establish the consequences of poor metabolic control and/or weight control in Spanish adults with T2D.

CONCLUSION

Our study highlights the clinical, economic and HRQoL burden of poor metabolic and/or weight control in Spanish adults with T2D and reinforces the importance of prioritizing its control to reduce its associated burden, at both the individual and healthcare system levels.

ACKNOWLEDGEMENTS

The authors thank Marta Comellas, Neus Vidal and Patricia Felip, who received honoraria for their assistance in the project and medical writing and data analysis tasks.

Author Contributions. Irene Romera, Miriam Rubio-de Santos and Silvia Díaz-Cerezo contributed to the conception of the work. Jennifer Redondo-Antón, Irene Romera, Luis Lizán, Miriam Rubio-de Santos and Silvia Díaz-Cerezo contributed to the design and data analysis. Antonio Pérez, Jennifer Redondo-Antón, Irene Romera, Luis Lizán, Miriam Rubio-de Santos, Silvia Díaz-Cerezo, and Domingo Orozco-Beltrán contributed to data interpretation and manuscript writing. All authors participated in the critical revision of the manuscript and approved the final submitted version.

Funding. Lilly SAU sponsored this study and the publication of this article. The Rapid Service Fee was also funded by Lilly SAU.

Data Availability. All data generated or analyzed during this study are included in this published article/supplementary information files.

Declarations

Conflict of Interest. Antonio Pérez reports honoraria from Sanofi, Boehringer Ingelheim, Menarini, Novo Nordisk, Lilly, Pfizer, Amarin, Daiichi Sankyo, AstraZeneca, Almirall, Novartis, Merck Sharp & Dohme, Amgen, AMARIN and Esteve outside of the submitted work.Jennifer Redondo-Antón, Irene Romera, Miriam Rubio-de Santos and Silvia Díaz-Cerezo are employees and minor shareholders of Eli Lilly. Luis Lizán works for an independent scientific consultancy (Outcomes'10) that has received honoraria for conducting the systematic literature review and writing the manuscript for conducting the

systematic literature review and manuscript writing tasks. Domingo Orozco-Beltrán reports honoraria from MSD, Lilly and Novo Nordisk outside of the submitted work.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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