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ORIGINAL RESEARCH

Are There Different Viewpoints About the Management of Type 2 Diabetes Mellitus and Comorbidities? A Multidisciplinary Spanish Qualitative Research

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ABSTRACT

Introduction: The aim of this study was to explore the vision of a large multidisciplinary group of physicians treating type 2 diabetes mellitus (T2DM) in Spain, with a special focus on controversial management aspects. The perceptions of primary care (PC) physicians and hospital care (HC) specialists were compared.

Methods: This was a mixed survey that included Delphi-like statements and opinion, attitude and behaviour (OAB) questions. The Delphi-like statements were assessed on the basis of the degree of agreement among respondents, and a descriptive analysis was performed on the answers to the OAB questions.

Results: A total of 296 participants responded to the first wave of the survey, of whom 293 responded to the second wave (211 from PC and 80 from HC, with two respondents for whom there were no data on specialty). A high degree of consensus (CNS $\geq$ 0.8) was obtained in all the statements. A proactive approach to detect prediabetes or T2DM in asymptomatic people was highly supported (80.4% of agreement). Introducing early treatment intensification was considered to favour the durability of glycaemic control and to delay the progression of the disease (80.4%). There was agreement on the statement that glycaemic variability constitutes a risk factor for chronic complications, although differences in the perceptions of HC physicians and PC specialists were identified (86.3 vs. 80.1%, respectively). More HC physicans than PC specialists considered comorbidities to affect the ability to self-care (95 vs. 82.9%, respectively).

Conclusions: The survey revealed that there was a high, albeit not universal, degree of agreement amongst PC physicians and HC specialists in relation to prevention, screening and diagnosis of T2DM; early treatment intensification; dysglycaemias; and the management of patients with comorbidities. The statement on the management of patients with comorbidities elicited the highest difference between PC physicans and HC specialists. The results of this survey indicate that there is room for

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improvement in terms of implementing strategies in these areas.

Keywords: Antidiabetic agents; Clinical guidelines; Comorbidities; Diabetes Mellitus, type 2; Drug therapy, combination; Prediabetes; Primary care; Qualitative research

Key Summary Points
Why carry out this study?
Type 2 diabetes mellitus (T2DM) is a complex disease with a large number of complications, and its management involves several specialists in addition to primary care (PC) physicians, and thus different approaches.
Knowledge and a correct approach regarding screening, prevention, diagnosis, early treatment intensification, dysglycaemia and comorbidities are crucial to avoid future complications in patients with T2DM.
The aim of the study was to analyse the perception of a large group of physicians involved in T2DM management on these subjects, and to identify differences between the perceptions of PC physicians and hospital care specialists.
What has been learned from the study?
This study shows that there is a high level of agreement amongst participants but that there is still room for improvement in terms of implementing strict glycaemic control, individualizing glycaemic control goals, and indication of early treatment intensification, mostly amongst PC physicians.
Further studies aimed at illuminating potential behavioural differences between different medical specialties in clinical practice would help to detect existing mismatches between knowledge and clinical behaviour regarding the management of T2DM.

INTRODUCTION

Although the pathophysiological changes that occur in patients with type 2 diabetes mellitus (T2DM) commonly remain undetected for several years before the disease is detected, i.e. during the long and asymptomatic pre-clinical phase of the disease, complications may have developed by the time of diagnosis [1]. Consequently, early detection of T2DM and the implementation of early and intensive interventions are relevant not only to prevent beta-cell dysfunction but also to intervene before the blood glucose thresholds currently set for T2DM diagnosis are reached to protect against potential cardiovascular (CV) risk factors [2, 3]. CV disease (CVD) accounts for one half of all T2DM-related deaths [4], and to address this issue, glucose-lowering drugs that have been developed over the past decade have been tested in CV outcomes trials that have included patients at high risk of CV disease, with the aim to evaluate CV endpoints [5]. Likewise, the most recent international recommendations have intensively focused on CVD to guide T2DM management, whilst other comorbidities and patient preferences been minimized despite that almost 80% of patients with T2DM have comorbidities other than CVD [6]. T2DM increases the risk of not only coronary artery disease, peripheral arterial disease and stroke, but also kidney failure, non-traumatic amputations and blindness [7–9].

Early treatment intensification strategies have been demonstrated to provide significant reductions in glycated haemoglobin (HbA1c) over both the short [6] and long term [10]. Moreover, a recent study comparing an early combination of vildagliptin plus metformin with metformin alone also showed a reduction in the time to treatment failure in the long term (5-year treatment period) in patients with recent T2DM and HbA1c levels of 6.5–7.5% [10]. This recent evidence has prompted an update of the recommendations in this regard [11, 12], indicating alternative strategies to keeping to the traditional sequential therapeutic approach of initiating treatment with metformin and adding a second hypoglycaemic agent only when glycaemic objectives are not achieved

[13], a clinical strategy often related to therapeutic inertia and lack of glycaemic control [14–17].

The complexity of T2DM and the variability and severity of its complications translate into the involvement of several specialists in the management of the disease and, thereby, into the convergence of different approaches. A wide variety of clinical guidelines exist in the field, although conformance and adherence to them are not always optimal, and clinical outcomes and related costs might be compromised [18–21].

The objective of the current study was to analyse the perception of a large group of physicians who are mainly involved in this area on certain controversial aspects of the management of T2DM, such as prevention, screening, diagnosis, early treatment intensification and management of dysglycaemia and chronic complications, as well as to identify differences between primary care (PC) physicians and hospital care (HC) specialists.

METHODS

A dedicated scientific committee consisting of three opinion leaders designed a survey to cover a number of issues covered in clinical practice guidelines. These individuals had different specialties (internal medicine, endocrinology and PC) and had wide clinical and academic expertise, as well as a broad spectrum of publications on T2DM. The survey included 25 Delphi-like statements and 13 questions on opinion, attitude and behaviour (OAB). Here, we report the results on a selection of 14 statements and five OAB questions. The OAB questions were either multiple choice or to be answered on a rating scale, and they were formulated within the context of some of the Delphi-like statements.

The survey was provided to a representative sample of 300 physicians from different regions of Spain. The selected participants were PC physicians and HC specialists whose usual practice included the management of T2DM. They were selected by a non-probabilistic directed sampling of convenience by conglomerates, according to proportional geographic and population distribution criteria.

The degree of agreement with the Delphi-like statements was evaluated in the first wave of the survey using a 5-point Likert scale (from 'totally disagree' to 'totally agree') and analysed using two metrics: the consensus value (CNS), applying the Tastle technique [22], and the collapse of the five Likert categories into three ('disagree', 'undecided' and 'agree'). The consensus threshold in the Delphi-like statements was CNS $\geq$ 0.70. Those statements that did not obtain a high degree of consensus (CNS $<$ 0.80) were re-evaluated in a second wave of the survey, either by modifying or inverting the composition of the statements. The percentages of answer were calculated for the multiple choice OAB questions, and the mean value was calculated for the rating scale OAB questions. The Mann–Whitney *U* test was used to evaluate differences obtained between the answers of PC physicians and HC specialists.

Compliance with Ethics Guidelines

The study was based on an on-line survey that did not require data on individual patients to be recorded nor involve the participation of patients. There was no evaluation of any specific medication as the main factor. Therefore, this study did not require ethical approval as none of the criteria of post-authorization studies (PASS, non-interventional PASS) covered by the Spanish Agency for Medicines and Health Products (AEMPS) were met. Data were collected by means of anonymous questionnaires in online format, completed by physicians in accordance with their usual practice. Participation was voluntary. The respondents expressed their consent to participate in the survey through logging into the secure online survey platform and actively clicking a consent box.

RESULTS

Participants

A total of 296 participants responded to the first wave of the survey, of whom 293 responded to the second wave (211 from PC physicians and

80 from HC specialists; for two responders there were no data on specialty). In terms of age, 21.6% of the participants were ≤ 45 years old, 31.0% were aged 46–55 years and 47.7% were older than 56 years. Of the participants, 65.5% were men and 67.9% had been in medical practice for ≥ 20 years. Regarding treatment protocols, 74.4% of the participants declared following the recommendations of clinical practice guidelines for the diagnosis and follow-up of T2DM, and 21.0% declared that they followed PC or hospital protocols.

Delphi Statements

After the second wave, the CNS reached a value of ≥ 0.80 for all of the statements included in the survey (Table 1). When responses were collapsed to three categories, similar results were obtained (Fig. 1).

Opportunistic screening strategies for the early diagnosis in asymptomatic patients were considered to be beneficial by 82.8% of participants. Similarly, 80.4% of participants considered periodic laboratory tests to be a convenient strategy for screening of prediabetes/diabetes in asymptomatic subjects. Agreement amongst participants was especially high regarding the consideration of lifestyle interventions as factors that delay or prevent the progression of prediabetes to diabetes (90.7%), and in the periodic determination of HbA1c to prevent long-term complications of T2DM (88.7%) (Fig. 1a).

Early strict glycaemic control was considered by 88.0% of participants as a means to reduce the prevalence of chronic complications and/or prevent disease progression. Slightly more than 95.0% of participants agreed that detection and control of hyperglycaemia in the asymptomatic stages of T2DM affects the prevention of complications, and 80.4% agreed that early intensification with combined therapy provides greater and longer-lasting benefits in terms of glycaemic control and delay of disease progression (Fig. 1b).

Glycaemic variability was agreed upon as a risk factor for chronic complications in and of itself (91.8% of participants), and postprandial hyperglycaemia was considered by 81.8% of participants to be a CV risk factor. The potential risk of severe hypoglycaemia was considered a key parameter for establishing the objectives of control and pharmacological management therapies of T2DM by 90.7% of participants (Fig. 1c).

The presence of chronic complications and comorbidities was considered to hinder selection between the different therapeutic options and combinations by 84.0% of participants. That comorbidities should be considered to affect the ability to self-care was agreed upon by 86.3% of participants, and 86.9% of participants were in agreement that psychiatric disorders affected antidiabetic treatment. The necessity of screening for corticosteroid-induced hyperglycaemia in patients with T2DM-COPD who receive medium or high doses of corticosteroids to treat the exacerbations was also agreed to by a high proportion of participants (91.1%) (Fig. 1d).

OAB Questions

A long life expectancy, good functional and cognitive status and a recent diagnosis of T2DM were chosen as factors that prompt individualization for stricter glycaemic control goals by more than 70.0% of the participants (Fig. 2a).

In patients lacking metabolic control despite the prescription of adequate treatment, the reasons for therapeutic failure seem to be multifactorial: comorbidities, functional factors, therapeutic regimen-derived factors and disease-derived factors were considered to be the most contributory factors (Fig. 2b).

Nearly 70.0% of participants expressed the view that independently of age, basal glycaemic control values are the main driver for treatment intensification (Fig. 3).

Among all participants, 85.8% declared using capillary glycaemia and a symptom diary to detect, monitor and assess the risk of hypoglycaemia, 64.5% admitted doing so by collecting data and information on the conditions associated with the risk of hypoglycaemia, 29.1% declared using continuous blood glucose

Table 1 Consensus degree obtained for Delphi statements

Statements	CNS (n = 291)	CNS PC (n = 211)	CNS HC (n = 80)	P value (MW)
Prevention, screening and diagnosis				
1. There are benefits derived from applying an opportunistic screening strategy for the early diagnosis of T2DM in asymptomatic subjects	0.82	0.82	0.82	0.619
2. Periodic laboratory testing (fasting basal glycaemia, HbA1c) is convenient for the screening of prediabetes/diabetes in asymptomatic subjects	0.80	0.80	0.81	0.748
3. Progression of prediabetes to diabetes can be delayed or prevented through lifestyle interventions	0.89	0.88	0.91	0.541
4. Periodic determination of HbA1c contributes to the prevention of long-term complications in patients with diagnosed T2DM	0.87	0.87	0.88	0.709
Early treatment intensification				
5. If performed early, during the first years after diagnosis of T2DM, strict glycaemic control reduces the prevalence of chronic complications and/or prevents progression	0.86	0.85	0.88	0.980
6. Detection and control of hyperglycaemia in asymptomatic stages of T2DM affects the prevention of complications	0.93	0.92	0.95	0.661
7. A first therapeutic step of early intensification with combined therapy following a diagnosis of T2DM provides greater and longer-lasting benefits for patients, by favouring the durability of glycaemic control and delaying the progression of the disease	0.81	0.81	0.82	0.675
Dysglycaemia				
8. Glycaemic variability (oscillation, frequency and intensity of fluctuations in blood-glucose concentrations) constitutes, in and of itself, a risk factor for chronic complications in patients with T2DM	0.81	0.79	0.85	0.019
9. Postprandial hyperglycaemia constitutes, in and of itself, a CV risk factor in patients with T2DM	0.80	0.79	0.82	0.421
10. The potential risk of severe hypoglycaemia is a key parameter to set the objectives of control and the pharmacological management of T2DM	0.89	0.88	0.93	0.097
Chronic complications and comorbidities				
11. The presence of chronic complications and comorbidities in the diabetic patient may hinder the election between the different therapeutic options and combinations	0.83	0.82	0.85	0.515
12. Comorbidity affects the patient's ability to self-care	0.84	0.81	0.91	0.000
13. The coexistence of serious psychiatric disorders in patients with T2DM affects antidiabetic treatment	0.85	0.84	0.87	0.168

Table 1 continued

Statements	CNS (n = 291)	CNS PC (n = 211)	CNS HC (n = 80)	P value (MW)
14. A specific screening for corticosteroid-induced hyperglycaemia (guidelines for self-measurement of capillary glycaemia) and the assessment of adjustments for the treatment of hyperglycaemia should be performed in patients with T2DM–COPD comorbidity, who receive medium or high doses of corticosteroids to treat the exacerbations of their pulmonary disease	0.87	0.85	0.91	0.021

CNS < 0.80 was considered to be high degree of consensus
CNS Consensus value, *COPD* chronic obstructive pulmonary disease, *CV* cardiovascular, *HbA1c* glycated haemoglobin, *HC* hospital care, *MW* Mann-Whitney *U* test, *PC* primary care, *T2DM* type 2 diabetes mellitus

monitoring and 12.8% declared using tests or questionnaires (Fig. 4a).

Excessive insulin dose, a reduction or delay in carbohydrate intake, inappropriate use of oral hypoglycaemic agents and an increase in physical exercise were the situations more commonly considered as potential causes of hypoglycaemia (Fig. 4b).

PC and HC Analysis

No differences were observed between PC physicans and HC specialists in any statement regarding prevention, screening and diagnosis and early treatment intensification. However, the degree of consensus was significantly higher amongst HC participants (86.3%) than among PC participants (80.1%) in terms of considering glycaemic variability as a risk factor for chronic complications.

The percentage of agreement was significantly higher among HC participants than among PC participants when the statement comorbidities affect the ability to self-care was considered (95.0 vs. 82.9%, respectively). Differences were also observed on the necessity of screening for corticosteroid-induced hyperglycaemia in the assessment of adjustments for the treatment of hyperglycaemia in patients with T2DM and chronic obstructive pulmonary disease (COPD) who receive medium or high doses of corticosteroids to treat exacerbations, with 95.0% of HC physicians versus 89.6% of PC specialists agreeing that such screeing was necessary.

DISCUSSION

Prevention, Screening and Diagnosis

Prediabetes is a clinical stage characterized by levels of fasting plasma glucose that are higher than normal but lower than those considered to indicate diabetes. Approximately 5–10% of patients with prediabetes ultimately develop T2DM each year [23]. Screening strategies, which are often carried out in the PC setting, were agreed upon by the participants in this study as being beneficial and convenient for detecting asymptomatic subjects. A periodic determination of HbA1c was also considered a convenient screening test in asymptomatic subjects and for the prevention of long-term complications in patients who already had a diagnosis of T2DM, as was having a degree of knowledge of the recommendations of the World Health Organization (WHO) [24, 25] and clinical practice guidelines [13, 26]. In light of the current delayed diagnosis of T2DM in clinical practice, the results reported here highlight the relevance of implementing screening strategies in high-risk individuals, as well as lifestyle interventions, in order to prevent or delay T2DM onset and avoid future

Fig. 1 Percentage of agreement obtained for Delphi statements (N = 291 participants)

complications, both of which are more likely to appear in the PC setting.

Early Treatment Intensification and Pharmacological Combination Treatment

Intensive glycaemic control is inversely related to the risk of microvascular events [27]. Delays in the intensification of treatment for T2DM due to clinical inertia have been shown to increase the risk for CV events [28]. Recent studies have demonstrated the benefits of achieving glycaemic control as early as within the first 12 months from diagnosis [29]. Nonetheless, a cross-sectional epidemiological study in Spain that included patients from 2007 to 2013 found a huge proportion of patients with records of deficient glycaemic control during the last year registered: 55.6% of patients were receiving monotherapy or no treatment at all, even though 44.8% presented HbA1c levels $> 7.0\%$ [30]. In our study, agreement on the statement that early treatment intensification following diagnosis is a strategy for providing greater and longer-lasting benefits for patients was high and, remarkably, similar across different PC and HC participants.

Recent international guidelines have included a general recommendation to consider early combination therapy at treatment initiation

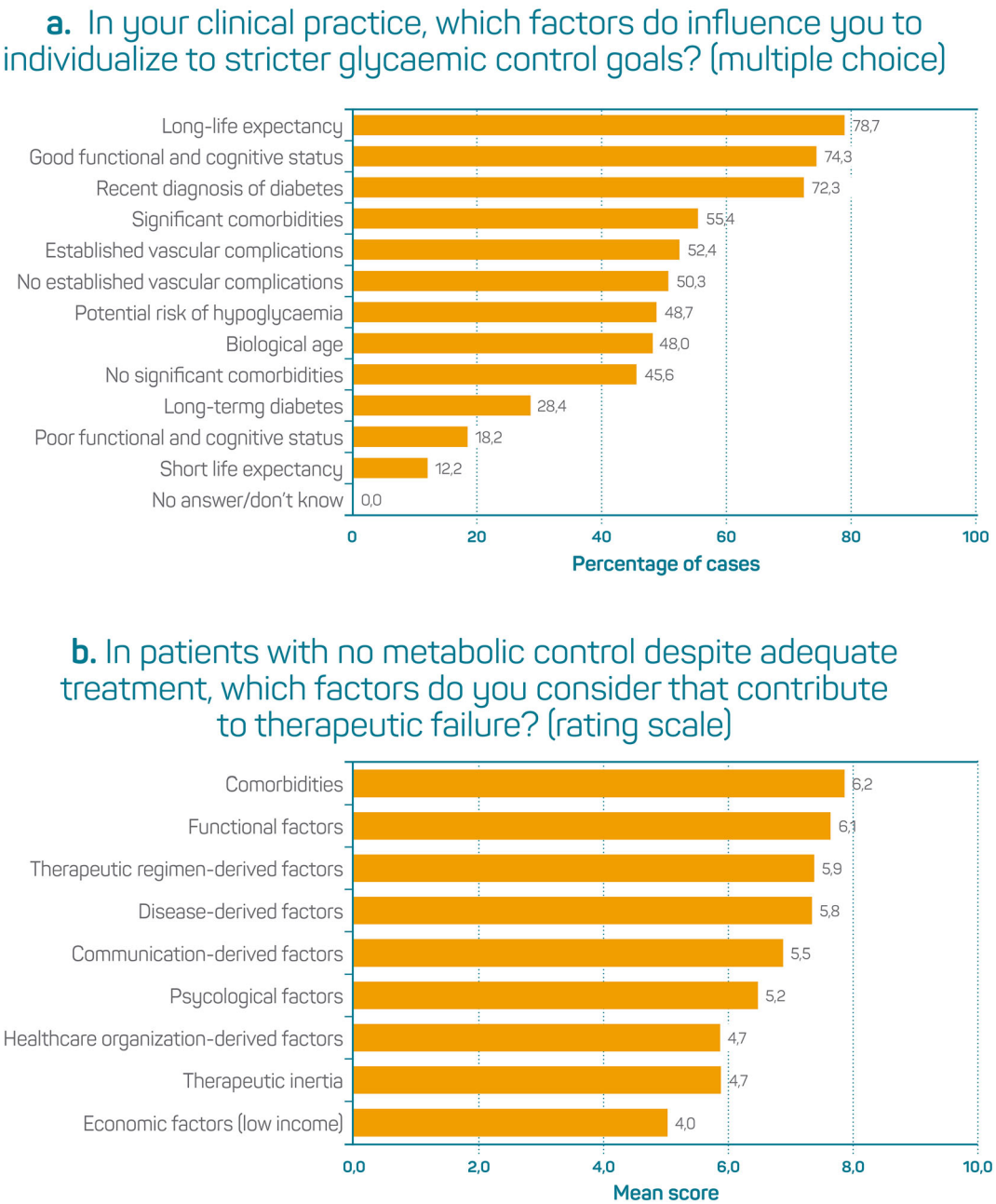

Fig. 2 Questions on opinion, attitude and behaviour (OAB) regarding strict glycaemic control (N = 296)

rather than a stepwise approach in order to extend the time to treatment failure [31, 32]. The VERIFY study was the first study to show that early intervention with a combination of hypoglycaemic agents as the first therapeutic step provides greater and longer-lasting benefits than a sequential approach: both the incidence of initial treatment failure and the time to treatment failure were significantly lower with the early combination of metformin and vildagliptin than with the sequential treatment regimen, whilst both arms were equally safe and well tolerated [10]. However, similar studies with other antidiabetic molecules, such as dipeptidyl peptidase-4 (DPP-4) inhibitors or those from different drug classes, are needed

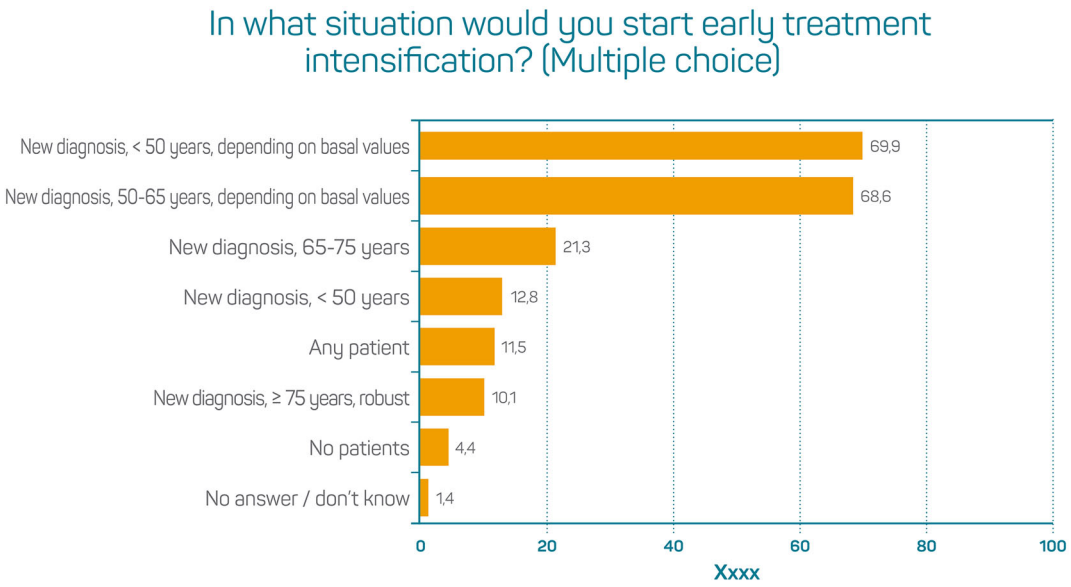

Fig. 3 OAB questions on early treatment intensification ($N = 296$)

and would likely result in stronger recommendations and a higher level of (or even universal) consensus on this issue. In this study, agreement the participants showed a high level of agreement when considering the statement on early treatment intensification following diagnosis as a strategy for providing greater and longer-lasting benefits for patients, and the level of agreement was similar across different specialties.

Despite the VERIFY study being performed in patients with a long life expectancy, good functional and cognitive status and recent T2DM diagnosis, 21.3, 25.7 and 27.7% of participants, respectively, did not believe that these three factors had an influence on individualization towards stricter goals for treatment. Similarly, although the patients included in the VERIFY study benefited from early combined treatment independent of their HbA1c levels, and current international guidelines recommend some antidiabetic classes independently of HbA1c levels in patients with CVD or renal disease [31], almost 70.0% of the panel considered basal values as the determinant for initiating a combined therapy after the diagnosis, probably prioritizing those patients with higher HbA1c values.

Dysglycaemia

Continuous glucose monitoring may help to measure and to avoid glycaemic variability and hypoglycaemia [33]. In this study, a large number of participants considered glycaemic variability to be a direct risk factor for the development of chronic complications in patients with T2DM. However, a good level of knowledge of glycaemic variability and of glycaemic monitoring techniques are not widely available, particularly in the PC setting, which could explain the significantly higher agreement amongst HC specialists than PC physicians. As such, the detection and avoidance of glycaemic variability could be an area for improvement.

In line with a number of epidemiological studies [34], postprandial hyperglycaemia was considered to be a CV risk factor by consensus in this study and, consequently, its monitoring and an individualized treatment strategy would be advisable: DPP-4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been shown to be effective in the reduction of postprandial hyperglycaemia [34–36].

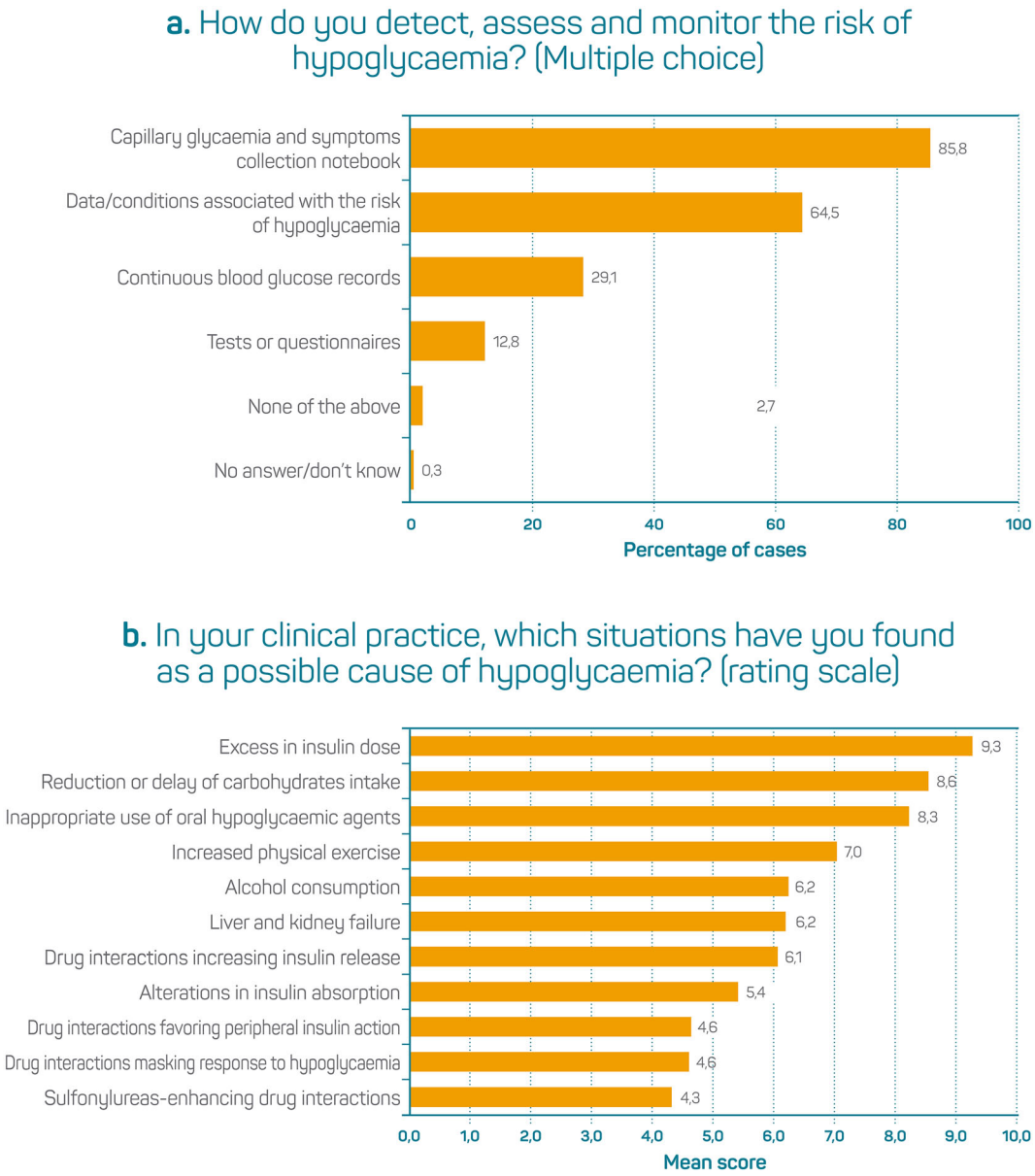

Fig. 4 OAB questions on the risk of hypoglycaemia ($N = 296$)

Severe hypoglycaemia is associated with adverse CV outcomes and all-cause mortality, and it is the most important safety concern in patients with diabetes [37]. More than 85.0% of participants declared assessing and monitoring the risk of hypoglycaemia by measuring capillary glycaemia and recording symptoms, and nearly 65.0% declared doing so by collecting data and recording associated conditions. In contrast, only a minority seemed to use continuous blood glucose monitoring, tests or questionnaires. The potential risk of severe hypoglycaemia was considered to be a key parameter for defining individualized objectives and choosing a pharmacological treatment for T2DM, with a high degree of agreement. The risk of hypoglycaemia is threefold higher in patients on insulin secretagogues and fivefold higher for those on insulin [38]. In fact, an excessive insulin dose and inappropriate use of

hypoglycaemic drugs were two of the situations most rated by participants as a cause of hypoglycaemia. The use of newer glucose-lowering agents with minimal risk of hypoglycaemia, such as DPP-4 inhibitors and GLP-1 receptor agonists, can be a useful strategy for avoiding hypoglycaemia [39].

Chronic Complications and Comorbidities

Almost 80% of patients with T2DM have comorbidities other than CVD [40]. In light of the findings of the trials completed over the past few years, the independent recommendations from the U.S. Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) for the approval of glucose-lowering molecules for the management of T2DM [41, 42] have been recently reviewed, and the inclusion criteria have been broadened to capture a wider range of comorbidities other than CVD amongst the selected patient populations [43]. The presence of chronic complications and comorbidities was considered to interfere with the assessment of the risk–benefit ratio for the available therapeutic options in a higher percentage of HC participants than PC participants. A plausible explanation could be the management of more complex patients in the HC setting. A better knowledge of the relevance of comorbidities by PC physicians and the selection of options with fewer safety concerns for patients with complications or comorbidities could be two advisable approaches for eliminating these differences.

Psychiatric symptoms are common in patients with T2DM [44, 45], and they worsen disease prognosis, treatment compliance, quality of life and clinical outcomes [46–49]. This also applies to cognitive dysfunction [50, 51]. However, nearly 13.0% of participants in this study did not express specific agreement when considering psychiatric disorders as comorbidities that affect antidiabetic treatment, with no significant differences between PC physicians and HC specialists.

Limitations of the Study

This study has a certain number of limitations. First, the sample of participants was selected, although this is a characteristic linked to the Delphi studies in general since they intend to include experts in the field. Second, Delphi questions are an excellent method by which to gain an understanding of opinions on complex situations in clinical practice, but they do not help to explain the reason for the answer given. To counteract this limitation, we included OAB questions derived from the Delphi statements in the survey. In addition to adding qualitative information, these OAB questions helped to check coherence and provided robustness to the methodology. The use of closed answers in OAB questions can lead to a certain bias due to having ignored other answer options. However, those options considered to be more relevant or frequent at the discretion of the scientific committee were included, and the option of including more answers or using an open field would have meant a questionnaire that was too long and the risks of excessive dispersion of the answers. There is the possibility of variable interpretation of the statements or response options according to each participant but, in any case, the questionnaire was reviewed by experts belonging to both the PC and the HC fields.

Last but not least, the study has detected a high degree of agreement amongst PC physicians and HC specialists in relation to knowledge of T2DM management, while differences in behaviour could be present due to the different clinical outcomes of patients addressed by each specialty. Therefore, existing mismatches between knowledge and clinical behaviour could have not been detected. In this regard, we suggest that further studies be conducted that highlight the potential behavioural differences between PC physicians and HC specialists in clinical practice.

CONCLUSIONS

Although high levels of agreement were obtained on all the issues assessed, this study

shows that there is still room for improvement in terms of implementing strict glycaemic control, individualizing glycaemic control goals and opting for early treatment intensification, with most improvement to be gained amongst PC physicians. Further studies to evaluate the consequences of the lack of glycaemia control and the benefits of early treatment intensification with combinations of glucose-lowering molecules are necessary, and the findings may possibly contribute to achieving higher levels of agreement among physicians and specialists and a transformation of clinical practice.

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Author Contributions. All authors have equally collaborated on the design of the study, interpretation of data and drafting and review of the manuscript.

Disclosures. Francesc Xavier Cos has taken part in advisory panels; has acted as a speaker for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk and Sanofi; and has been an investigator in clinical trials for Astra Zeneca, Novartis, Sanofi and Boehringer Ingelheim. Ricardo Gómez-Huelgas has taken part in advisory panels, lectures and studies for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Astra Zeneca, MSD, Janssen and Esteve. Fernando Gomez-Peralta has taken part in advisory panels for Abbott, Astra Zeneca, Esteve, Novartis, Novo Nordisk and Sanofi; has also been an investigator in clinical trials for Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi; and has acted as a speaker for Abbott, Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Esteve, Novartis, Novo Nordisk and Sanofi.

Compliance with Ethics Guidelines. The study was based on an on-line survey that did not require data on individual patients to be recorded nor involve the participation of patients. There was no evaluation of any specific medication as the main factor. Therefore, this study did not require ethical approval as none of the criteria of post-authorization studies (PASS, non-interventional PASS) covered by the Spanish Agency for Medicines and Health Products (AEMPS) were met. Data were collected by means of anonymous questionnaires in online format, completed by physicians in accordance with their usual practice. Participation was voluntary. The respondents expressed their consent to participate in the survey through logging into the secure online survey platform and actively clicking a consent box.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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