Management of type 2 diabetes in very old patients according to glycemic control and health status

Ricardo Gómez-Huelgas\textsuperscript{1,2}, José Mancera-Romero\textsuperscript{3}, Luis M. Pérez-Belmonte\textsuperscript{1,4}, María I. Luna-Moreno\textsuperscript{3}, Laura Ruiz del Moral\textsuperscript{3}, M. Rosa Bernal-López\textsuperscript{1,2}

\textsuperscript{1} Department of Internal Medicine, Regional University Hospital of Málaga, BioMedical Research Institute of Málaga, University of Málaga, Málaga, Spain
\textsuperscript{2} Center for Network Biomedical Research on Physiopathology of Obesity and Nutrition (CIBERobn), Institute of Health Carlos III, Madrid, Spain
\textsuperscript{3} Ciudad Jardín Health Center, Málaga-Guadalhorce District, Andalusian Health Service, Málaga, Spain
\textsuperscript{4} Center for Network Biomedical Research on Cardiovascular Diseases (CIBERcv), Institute of Health Carlos III, Madrid, Spain

Introduction

The prevalence of diabetes in the elderly is increasing worldwide with more than a third of patients aged 75 years or older having diabetes.\textsuperscript{1,2}

The great heterogeneity in the health status of older patients with type 2 diabetes (T2D) makes an assessment beyond glycemia or glycated hemoglobin $\text{A}_1c$ (HbA$_1c$) necessary.\textsuperscript{3} Current guidelines and several studies support the claim that factors such as the presence of comorbidities, dementia, depression, functional dependence, frailty, or polypharmacy must be taken into account when establishing glycemic targets for elderly patients.\textsuperscript{3,4} In recent years, several reports have highlighted that elderly patients with a complex health status managed with tight glycemic control and intensive antidiabetic therapy are more likely to be harmed, particularly because of drug-induced hypoglycemia.\textsuperscript{5,6} However, less strict glycemic targets in vulnerable elderly patients by analogy can lead to poorer glycemic control and undertreatment in those elderly patients who have robust health status and who require more strict targets.\textsuperscript{7}

There are scarce data in the available literature on management of very old patients with T2D.\textsuperscript{3,4} The objective of this study was to analyze the management of very old patients with T2D according to health status and glycemic control. We hypothesized that those patients would be managed without considering their health status, and therefore, be at high risk for drug-induced hypoglycemia. We also assessed factors associated with poor glycemic control.

Patients and methods

We carried out a cross-sectional, population-based study of all community-dwelling patients who were 80 years old or older with diagnosed T2D treated with antidiabetic therapy living in Málaga (Spain). We analyzed clinical, epidemiological, and laboratory variables as of April 2017. Patients with other types of diabetes, institutionalized patients, and patients in palliative care programs were excluded.

We used electronic health records from the Andalusian Health Service. To calculate sample size, we used an estimated proportion of hypoglycemia-inducing agents of 45\%, estimated proportion of patients with tight control in the elderly of 70\%,\textsuperscript{2,4} probability of type 1 error ($\alpha$ error) of 5\%, statistical power of 80\%, and loss of 5\%. Records with missing information about diabetes control and treatment were considered lost. With these parameters, a minimum sample of 324 patients was required. A simple random sample was extracted from all health records provided by the Andalusian Health Service using a random number table. Patients were excluded if there were insufficient data in their electronic medical records.

Dementia was determined using the Global Deterioration Scale and the Functional Assessment Staging. Functional dependence was determined using the Barthel index. Polypharmacy was defined as the use of 5 or more drugs at the same time.

Patients were grouped according to their health status: complex health status (CHS) and robust health status (RHS). CHS was defined as 1 or more of the following criteria: moderate-severe dementia, moderate-severe functional dependence, cardiovascular disease and / or advanced renal failure. RHS was defined as the absence of all these criteria. Patients were also categorized into 3 groups depending on their glycemic control.
level according to the treatment goals established for older adults in current guidelines: HbA$_1c$ level of less than 7.5% (tight control), HbA$_1c$ level of 7.5% to 8.4% (moderate control), and HbA$_1c$ level of 8.5% or more (poor control). Statistical analyses were performed using IBM SPSS Statistics for Windows, version 15.0 (IBM Corporation, Chicago, Illinois, United States). Quantitative variables were expressed as means (SD), and qualitative variables as absolute value and percentage. The t test and the $\chi^2$ test were used to compare quantitative and qualitative variables, respectively. Stepwise multivariate logistic regression analyses were performed to identify factors independently associated with glycemic control, with HbA$_1c$ levels established as the dependent variable and with controlling for the confounding effect of other variables. A 2-tailed $P$ value of less than 0.05 was considered significant.

The study was approved by the local authorities. Informed consent from the patients and authorization from the Institutional Research Ethics Committee of Málaga were not necessary because the information in the dataset were anonymous and their collection was mandatory. Data confidentiality and patient anonymity were maintained at all times.

**Results** We identified 25,958 individuals who were 80 years old or older. Of those, 7,359 (28.3%) had T2D. After random selection, 340 patients were included in the study. There were no losses. The sociodemographic, clinical, and therapeutic characteristics of all patients and subgroups according to HbA$_1c$ levels (<7.5%, 7.5–8.4% and ≥8.5%) are summarized in Supplementary material, Table S1. Most of very old patients had HbA$_1c$ levels of less than 7.5% (n = 249, 73.2%) and CHS was observed in 221 patients (65%). More patients with HbA$_1c$ level of less than 7.5% and of 7.5% to 8.4% were classified as having CHS than patients with HbA$_1c$ level of 8.5% or higher.

Metformin was the most frequent antidiabetic agent, followed by insulin and secretagogues. Metformin, secretagogues, and/or insulin were used more frequently in patients with HbA$_1c$ levels of less than 7.5% as compared with patients with HbA$_1c$ level of 7.5% to 8.4% or HbA$_1c$ level of 8.5% or higher. However, dipeptidyl peptidase-4 inhibitors and insulin alone were less commonly used among all our patients. More patients with CHS with HbA$_1c$ levels of 7.5% or less and of 8.5% or higher were treated with insulin alone or in combination with secretagogues than patients with RHS with the same HbA$_1c$ level. All data on antidiabetic therapy in each HbA$_1c$ control group by health status are shown in Table 1.

In the logistic regression analysis, longer diabetes duration (odds ratio [OR], 0.91; 95% CI, 0.85–0.97; $P < 0.01$) and dementia (OR, 0.19; 95% CI, 0.04–0.91; $P = 0.04$) were associated with a greater likelihood of HbA$_1c$ levels of 8.5% or higher (Supplementary material, Table S2). No other factors were related with glycemic control in very old patients with T2D.

**Discussion** In our study, more patients who were 80 years old or older with T2D had CHS and tighter control using high-risk hypoglycemia drugs (secretagogues and/or insulin) than patients with RHS. Longer diabetes duration and dementia were associated with a greater likelihood of HbA$_1c$ levels of 8.5% or higher. No other factors, including comorbidity, functional dependence, or health status, were related with the glycemic control in very old patients with T2D.
our study were managed without previous comprehensive clinical assessment to tailor glycemic targets.

There is a growing interest in optimal glycemic control in older people with T2D. Currently, most guidelines agree that the harm of intensive glycemic control (especially severe hypoglycemia) outweighs benefits in older people with T2D. In the elderly, the level of poor glycemic control has been defined as a HbA1c level of 8.5% or higher – level associated with higher mortality rates in patients with T2D aged 80 to 89 years in several studies. Functional and cognitive status, comorbidities, and polypharmacy are factors that should be considered when tailoring glycemic targets in the elderly. However, a limited number of studies have described management in very old patients that would consider their clinical characteristics. These studies have described the drug-induced hypoglycemia as a significant cause of emergency hospitalizations due to adverse drug effects in older adults with T2D, especially among patients older than 70 years with a more CHS. In addition, both hypoglycemia and hypoglycemia unawareness have been identified as risk factors of cognitive impairment, falls and fractures, cardiovascular diseases, and mortality, even in patients with poor glycemic control. Therefore, the main goal in elderly patients with T2D and CHS should be the prevention of symptomatic hyperglycemia and hypoglycemia by relaxing glycemic control and promoting the use of antihyperglycemic drugs that do not induce hypoglycemia. In our study, the only factors related to health status that were considered when tailoring glycemic targets were diabetes duration and dementia.

Metformin is considered a first-line oral antidiabetic drug for older patients. The high rate of metformin use found in our setting was similar to the rate reported in a previous observational study on patients aged 80 years and older. A large proportion of elderly patients are treated with insulin secretagogues and insulin therapies, even when they are tightly controlled. Our study shows that more patients with CHS had tight or moderate glycemic control than patients with RHS and more of those patients were treated with secretagogues and/or insulin. The use of dipeptidyl peptidase-4 inhibitors among the very old patients in our study showed no differences according to health status. These antihyperglycemic agents have been proposed as an effective and safe option for very old patients due to the low risk of side effects and hypoglycemia. A recent randomized controlled study of older vulnerable patients with T2D found that a glucose-dependent strategy (metformin and incretin-based therapies) may be preferable to a glucose-independent strategy (insulin and sulfonylurea therapies) in order to significantly reduce the risk of hypoglycemia.

The role of newer glucose-lowering agents, such as sodium-glucose transporter-2 inhibitor or glucagon-like peptide-1 receptor agonist, has not been specifically studied in elderly patients, but age subgroup analyses have suggested that the cardiovascular and renal effects from sodium-glucose transporter-2 inhibitors seemed to be greater in older patients with T2D, especially in patients with heart failure. Furthermore, glucagon-like peptide-1 receptor agonists have been shown to be more beneficial among younger patients.

This study has some limitations, including the retrospective nature of our data, and the use of electronic health records from the Andalusian Health Service as the source of data, given that unmeasured confounding factors cannot be excluded and only limited information can be obtained. Among the strengths of the study are: the adequate random selection of patients, robustness of the multivariate analysis, and significant number of clinical, epidemiological, and laboratory variables collected. Further specific research is needed to fully implement appropriate management for very old patients and to identify factors to consider when tailoring glycemic targets.

In conclusion, this study shows that a large proportion of very old patients with T2D have CHS and their glucose levels are tightly controlled using high-risk hypoglycemia drugs. Diabetes duration and dementia were the only factors associated with less strict glycemic targets. These findings suggest that a comprehensive medical evaluation is needed when tailoring glycemic targets in very old patients with T2D.

SUPPLEMENTARY MATERIAL
Supplementary material is available at www.mp.pl/pamw.

ARTICLE INFORMATION
CONFLICT OF INTEREST None declared.
OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

HOW TO CITE Gómez-Huertas R, Mancera-Romero J, Pérez-Belmonte LM, et al. Management of type 2 diabetes in very old patients according to glycemic control and health status. Pol Arch Intern Med. 2019; 129: 567-570. doi:10.20452/pamw.14867

REFERENCES
1 International Diabetes Federation. IDF Atlas. 8th ed. Brussels, Belgium: International Diabetes Federation; 2017. http://www.diabetesatlas.org/resources/2017-atlas.html. Accessed April 25, 2018.
2 Soriger F, Goyad A, Bosch-Cornas A, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia. 2012; 55: 88-93.
3 American Diabetes Association. Older adults: standards of medical care in diabetes -2019. Diabetes Care. 2019; 42: S129-S147.
4 Lipska KJ, Ross JS, Miao Y, et al. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med. 2015; 175: 356-362.
5 Makam AN, Nguyen OK. An evidence-based medicine approach to anti-hyperglycemic therapy in diabetes mellitus to overcome overtreatment. Circulation. 2017; 135: 180-195.
6 Sinclair A, Morley JE, Rodriguez-Malea L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for...
6 Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc. 2012; 13: 497-502.

7 Meneilly GS, Berard LD, Cheng AY, et al. Insights into the current management of older adults with type 2 diabetes in the Ontario primary care setting. Can J Diabetes. 2018; 42: 23-30.

8 Gómez-Huelgas R, Gómez-Peralta F, Rodríguez-Mañas L, et al. Treatment of type 2 diabetes mellitus in elderly patients. Rev Clin Esp. 2018; 218: 74-88.

9 Budnitz DS, Lovegrove MC, Shehab N, et al. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011; 365: 2002-2012.

10 Gómez-Huelgas R, Pérez-Belmonte LM, Rivera-Cabeo I, et al. Management of elderly patients with type 2 diabetes in long-term care and skilled-nursing facilities. Pol Arch Intern Med. 2019; 129: 137-140.

11 Hamada S, Gulliford MC. Mortality in individuals aged 80 and older with type 2 diabetes mellitus in relation to glycosylated hemoglobin, blood pressure, and total cholesterol. J Am Geriatr Soc. 2016; 64: 1425-1431.

12 Heller SR, Pratley RE, Sinclair A, et al. Glycaemic outcomes of an Individualized treatMent aPproach for oldER vulnerable patIents: A randomized, controlled stUdy in type 2 diabetes Mellitus (IMPERIUM). Diabetes Obes Metab. 2018; 20: 148-156.