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SPECIAL ARTICLE

Application of the changes in the Standards of Medical Care in Diabetes ADA 2021 to clinical practice in our country. SED-SEEN document☆

Aplicación de las novedades de los *Standards of Medical Care in Diabetes* ADA 2021 a la práctica clínica en nuestro país. Documento SED-SEEN

Manuel Gargallo Fernández[a,*], Sara Artola Menéndez[b], Maria José Picón César[c], Rebeca Reyes García[d], on behalf of the SEEN (MGF, RRG) and SED (SAM, MJPC)

[a] *Endocrinología y Nutrición, Hospital Universitario Infanta Leonor, Fundación Jiménez Díaz, Madrid, Spain*
[b] *Medicina de Familia, Centro de Salud José Marvá, Madrid, Spain*
[c] *Servicio de Endocrinología y Nutrición, Hospital Virgen de la Victoria, Málaga, Spain*
[d] *Unidad de Endocrinología y Nutrición, Hospital Universitario Torrecárdenas, Almería, Spain*

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Since 1989, the American Diabetes Association (ADA) has published its Standards of Medical Care in Diabetes (SMCD) in its January supplement. These standards currently constitute an international benchmark in the care and management of patients with diabetes mellitus (DM). It must be borne in mind, however, that the SMCD are prepared by an American scientific association and American experts, and therefore are essentially suited to medical practice in the United States. Obviously, the characteristics of American social and healthcare systems differ substantially from medical realities in Spain (in terms of public health, drug regulation agencies, population ageing, etc.). Hence, the ADA recommendations are not always applicable or useful in routine clinical practice in Spanish settings. In view of this, the Sociedad Española de Endocrinología y Nutrición [Spanish Society of Endocrinology and Nutrition] (SEEN) and the Sociedad Española de Diabetes [Spanish Diabetes Society] (SED) have taken the initiative of publishing this document evaluating the usefulness of the latest developments in the 2021 SMCD in the healthcare realities of people with DM in Spain. A group of sections with the greatest implications for Spanish clinical practice and the most new developments were selected for the purpose of this review.

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* Corresponding author.
E-mail address: gargallomgar@gmail.com
(M. Gargallo Fernández).

Technology in diabetes

Technologies applied to diabetes first appeared in the ADA recommendations in 2019, in a dedicated section. In 2021, the third edition of this nascent section already features interesting new developments.[1] The most significant is the indication established for continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) therapy.

It is proposed that both multiple dose insulin (MDI) and CSII therapy users may benefit from CGM. The evidence is stronger for real-time CGM (rt-CGM) than for intermittently scanned CGM (is-CGM), but both can help improve metabolic control and decrease episodes of hypoglycaemia. In the 2020 edition, CGM was only recommended in patients with type 1 DM (T1DM).

In the latest recommendations, CGM use depends not on the type of diabetes that the patient has but on the complexity of the patient's insulin treatment. Suitable use of these systems may aid in DM management, regardless of the form of insulin delivery. This is in line with the results of the DIAMOND study,[2] in which CGM in patients with type 2 DM (T2DM) being treated with MDI achieved a significant decrease in HbA1c by 0.3%.

Nevertheless, regional variations in Spain are such that is-CGM is funded in all patients with T1DM and rt-CGM is funded only in a percentage of patients with T1DM (in general, patients being treated with CSII). This means that patients with T2DM are not candidates for using this technology; as a general rule, many patients with T1DM being treated with MDI therapy are not candidates either. However, it is worth mentioning that on 25 November 2020, the Spanish Ministry of Health announced in a press release that funding for is-CGM (not rt-CGM) would be extended to insulin-dependent patients with neither T1DM nor T2DM who require intensive insulin therapy and perform at least six finger sticks per day.

Regarding CSII therapy, traditionally considered for T1DM only, this edition of the SMCD also proposes that it is useful in patients with T2DM who require MDI therapy and are capable of managing it.[3] In Spain, CSII therapy remains limited to T1DM, even with very low rates of use within this patient group;[4] therefore, the country is a long way from extending this indication to patients with T2DM.

Another interesting aspect of the SMCD is the inclusion therein of a more extensive section on the use of these devices in a hospital setting. As a result of the increasingly widespread use of technology in DM, it is quite likely that a patient with diabetes who requires hospitalisation is using CGM and/or CSII therapy. Though the level of evidence remains low, it is recommended that trained patients be allowed to continue to use the technology during hospital admissions under supervision.[5] In addition, experience with technology in DM, especially blood glucose sensors, has been gained in hospital settings over the course of the SARS-CoV-2 pandemic. Several publications with preliminary data from studies that were already in progress in relation to such use have emerged. Thus specific, agreed-upon protocols are needed in Spain so that this technology may be used in hospital.

Finally, the SMCD introduce a section on digital tools in DM management which may benefit patients with a very suitable level of evidence. This requires the development of appropriate safety and privacy standards.

Drug treatment of hyperglycaemia

Additional evidence is included on hybrid closed-loop CSII-CGM systems,[6] in patients with T1DM over 14 years of age: longer time in range, better blood glucose control and shorter time in hypoglycaemia compared to sensor-augmented pump systems.[7] In addition, in selecting one insulin administration system or another, it is recommended that the preferences of the person with T1DM, the cost and the capacity for self-care of the person with diabetes be considered. Use of CSII and, in particular, closed-loop systems in Spain is limited, thus restricting the applicability of these recommendations to the Spanish setting.

The initial drug treatment for T2DM is still metformin, combined with lifestyle changes. In cases of established cardiovascular disease (CVD) or indicators of high cardiovascular (CV) risk (age >55 years and left ventricular hypertrophy or coronary, carotid or lower-extremity stenosis >50%), kidney disease or heart failure (HF), the 2020 recommendations already recommended adding a glucagon-like peptide 1 receptor agonist (GLP1RA) with demonstrated CV benefits and/or a sodium-glucose transport protein 2 inhibitor (SGLT2I) with demonstrated CV benefits, regardless of degree of blood glucose control.

New additions this year include a pathway for choosing treatment for patients with HF with reduced ejection fraction (HFrEF) (<45%), in whom a SGLT2I with demonstrated benefits (dapagliflozin or empagliflozin) would have to be added, and another pathway for diabetic kidney disease with albuminuria, with a recommendation to add a SGLT2I with primary evidence on kidney disease progression (canagliflozin or dapagliflozin) or, failing that, a GLP1RA with evidence of CV benefits, and to combine the two if there is a high risk of CVD. In Spain, for administrative reasons rather than efficacy criteria, funding for GLP1RAs is limited to patients with a body mass index (BMI) >30 kg/m^2, thus limiting the application of these recommendations and depriving many patients of the benefits of these drugs.

A recommendation is included on the possibility of over-basalisation in basal insulin therapy in patients with any of the following clinical signs: basal insulin dose >0.5 U/kg, hypoglycaemia, wide variations in blood glucose levels, large differences between blood glucose levels before bed and basal blood glucose levels or large differences between postprandial and preprandial blood glucose levels. If over-basalisation is suspected, treatment should be re-evaluated on an individual basis. The section on injection therapy insists on the use of GLP1RAs as an alternative to basal insulin, but also in patients treated with basal insulin who do not meet their objectives.

Finally, the information regarding SGLT2Is has been updated. The need to discontinue them prior to any planned surgery to prevent the risk of ketoacidosis is included, and the United States Food and Drug Administration (FDA) warning about the higher risk of amputations with canagliflozin has been removed. Regarding GLP1RAs, specific mention is made of the CV benefits of liraglutide, semaglutide and dulaglutide; the kidney benefits (benefits for kidney end-

points, mediated primarily by improvements in albuminuria, for liraglutide, semaglutide and dulaglutide) have been updated; and it is recommended that caution be exercised in treating patients with reduced glomerular filtration rates (<30 ml/min/1.73 m^2) and that these patients be monitored for the onset of adverse gastrointestinal effects. Semaglutide is included in the FDA warning about the risk of thyroid C-cell tumours in animals, although the significance of the risk in humans has not been determined, and the information on pancreatitis has been updated (it has been reported in clinical trials, its causality has not been established and semaglutide should be suspended if pancreatitis is suspected).

Management of the patient with cardiovascular disease or cardiovascular risk

For the third consecutive year, this section of the SMCD[8] has been prepared jointly with the ADA and the American College of Cardiology (ACC). This means that the recommendations for the population with DM are adapted to those established by the ACC for the general population, which in some respects differ substantially from those established in Europe by the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)[9] as well as the Spanish guidelines issued by the SEEN[10] and the SED.[11]

In particular, with respect to lipid management, the SMCD recommend treating all subjects with DM 40–75 years of age with statins and considering said treatment in those under 40 years of age with risk factors, varying treatment intensity based on risk profile but independently of LDL cholesterol (LDL-C) levels. The European and Spanish guidelines, however, indicate treatment with statins based on target LDL-C levels depending on risk level, according to the traditional approach of treatment by objectives.

In relation to lipid-lowering therapy, this year's SMCD include a reminder of the benefits demonstrated by alirocumab in the ODYSSEY OUTCOMES study in subjects with DM in secondary prevention, and recommend the use of PCSK9 inhibitors (PCSK9Is) in cases of established CVD with persistently high LDL-C levels despite maximum doses of statins. In Spain, PCSK9Is are not funded in primary prevention in people with DM, but they can be used in secondary prevention, as recommended by the SMCD when LDL-C targets are not achieved with other treatments (statins and ezetimibe).

It should be remembered that, as a hygiene/dietary measure, the SMCD continue to recommend the Mediterranean diet as an initial step in lipid management. Obviously, Spain represents a good environment for enhancing this eating pattern.

Concerning HTN, this year, the need to start treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in cases with accompanying coronary disease is specified; this was already a common practice.

As regards antidiabetes therapy, messages to use drugs with demonstrated CV benefits (GLP1RAs and SGLT2Is), both in established CVD and in the presence of multiple risk factors for arteriosclerotic disease, are reiterated. This practice is universally included in all current guidelines, although perhaps it is not yet sufficiently widespread in Spain. It must be remembered that in Spain GLP1RAs are not funded for patients who are not obese; hence, patients with CVD and a BMI <30 kg/m^2 could not benefit from these treatments; in the absence of any contraindication, SGLT2Is would have to be used.

As mentioned above, the recommendation of using SGLT2Is is extended in patients with HFrEF.

The table of CV trials of the different drugs includes the data from the PIONEER-6 study corresponding to oral semaglutide. This drug, though authorised by the European Medicines Agency, has not yet been placed on the market in Spain.

One matter not addressed in the SMCD is that of patients with DM on cardiac rehabilitation units. According to a recent report from the ESC,[12] the treatment of these patients on such units was clearly deficient and barely consistent with guidelines throughout Europe. Therefore, collaboration between cardiology and endocrinology is needed on these units to ensure implementation of recommendations such as those in the SMCD.

Older/elderly adults

The SMCD contain recommendations for older people, including patients over 65 years of age. According to the World Health Organization (WHO), subjects of an age beyond the median survival at birth are considered elderly; in Spain, this designation corresponds to people 75 years of age and older.

This section maintains its recommendations on comprehensive evaluation of elderly people with DM of medical, psychological, functional and social determining factors, as well as detection of geriatric syndromes (i.e. polypharmacy, cognitive impairment, depression, urinary incontinence, falls and persistent pain) to establish the objectives for management and the treatment approach.[13]

Notably, a ''Neurocognitive Function'' section advises early detection of mild cognitive impairment which should be done in adults 65 years of age and older at the initial visit and annually. It recommends simple evaluation tools such as the Mini-Mental State Examination, Mini-Cog and Montreal Cognitive Evaluation.

It also recommends preventing potential episodes of hypoglycaemia, asking patients and caregivers in follow-up visits, and emphasising management of hypoglycaemia in elderly people with DM. Risk of hypoglycaemia can be stratified with validated risk calculators (e.g. the Kaiser Hypoglycemia Model). In elderly individuals with T1DM, and in those with T2DM on MDI therapy, CGM should be considered to reduce episodes of hypoglycaemia.

Regarding blood glucose targets, the SMCD continue to recommend personalisation in light of the heterogeneity of elderly people with DM. HbA1c levels of $\leq$7.0%–7.5% and postprandial glucose (PPG) levels of 80–180 mg/dl are considered to be targets in elderly people with few coexisting chronic diseases and intact cognitive function and functional status. In those with concomitant chronic diseases or cognitive or functional abnormalities, target HbA1c levels will be $\leq$8.0%–8.5%, while in very complex elderly people with

DM (who require chronic care or have end-stage chronic disease, moderate to severe cognitive impairment or cognitive impairment with two or more deficits in activities of daily living), the SMCD emphasise avoiding symptomatic hypoglycaemia and hyperglycaemia but not insisting on meeting HbA1c targets.

The level of recommendation is maintained in lifestyle management; optimal protein intake; and regular exercise, including aerobic activity and strength training for all elderly individuals with DM who can safely participate in these activities. In elderly people with T2DM, obesity and ability to exercise safely have been added to the recommendation of intensive lifestyle changes centred on changes in diet, physical activity and moderate weight loss (5%–7%).

Concerning drug treatment, the SMCD retain the recommendation of using drugs with a low risk of hypoglycaemia, avoiding overtreatment and de-intensifying complex treatments without losing personalised HbA1c targets.

They emphasise the algorithm to simplify the insulin regimen in elderly people.

With GLP1RA and insulin, which are injected (except for oral semaglutide, which is not marketed in Spain), some practical questions can be raised, since they require visual, motor and cognitive abilities to be administered appropriately. GLP1RAs may not be the most suitable drugs in elderly people with unexplained weight loss as they are associated with nausea, vomiting and diarrhoea.

Regarding SGLT2Is, the SMCD indicate that stratified analyses of randomised controlled trials (RCTs) of this drug group have found that benefits in older patients equal or exceed those in younger patients.

In the context of palliative care, the main objectives for end-of-life DM management are: general comfort, prevention of distressing symptoms and preservation of quality of life and dignity. Most drugs for T2DM can be discontinued.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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