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THE JOURNAL OF LATIN AMERICAN GERIATRIC MEDICINE EDITORIAL

Aging and diabetes: New challenges in an aging world

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The number of older adults across the globe is on the rise. Mexico, like other countries in the Latin American region, has witnessed this change in its population. Although the life expectancy has steadily increased over the past three generations, the prevalence and incidence of chronic conditions, such as diabetes, has followed a similar pattern. In Mexico, diabetes has been declared a public health priority since its treatment, especially the one focused on diabetes-related complications, represents an immense burden on health systems.

The management of diabetes is far more complex in older adults when compared to younger individuals. Problems such as multiple comorbidities as well as the presence of "geriatric syndromes" clearly increase the probability of worse adverse health-related outcomes for the elderly. Hence, it is paramount to raise awareness among healthcare professionals about the progressive increase of older adults living with diabetes as well as the challenges that the aging process imposes on the population.

The poor influence that the geriatric evaluation has on the management of chronic conditions in older adults is a cold truth. This also applies to diabetes management. Nonetheless, there is increasing recognition of the impact that age-related changes have on the diagnosis, treatment, and prevention of disease. All medical specialties should take into account such changes since this is a vital component for the adequate management of older adults.

In a combined initiative with the National College of Geriatric Medicine (CONAMEGER, from its Spanish initials), the Editorial Committee of the Journal of Latin American Geriatric Medicine summoned internationally renowned experts on the diagnosis and treatment of diabetes in older adults to share their knowledge and experience. This issue is the result of the kind collaboration from those summoned. The following articles convey useful information for those interested in the management of older adults in a comprehensive yet practical manner so it can appeal to healthcare professionals involved in primary care as well as specialists. We present five leading-edge original articles that will enhance our knowledge on diabetes in the older adult.

Frailty, as a central topic in geriatrics, is addressed from different standpoints. The work by Castro-Rodriguez, et al. shows the ramifications that frailty has on the decision-making process in the evaluation and management of the older adult with diabetes. When this syndrome is found, the patient will require a more exhaustive evaluation, including functional status assessment, in order to generate a tailored therapeutic strategy and to prevent complications in this already vulnerable population[1]. Likewise, Dr. Sinclair's

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group transmits a series of key messages to better tend to the frail, the diabetic, and the sarcopenic patient[2]. The knowledge shed by these two groups will surely be useful for our daily practice. These efforts join a previous collaboration of Dr. John Morley where he defines frailty as one of the "Giants of Geriatrics"[3].

By the same token, the work of Bourdel-Marchasson, et al. presents how a comprehensive geriatric assessment helps to better direct the management of older adults with diabetes and to once again implement a personalized approach that includes the caregivers[4].

One of the most frequent comorbidities found in the older adult with diabetes is hypertension. This topic is addressed by Tessier, et al. who proposes the rationale behind reaching adequate blood pressure goals, taking into account the clinical condition of the patient[5]. Finally, the work by the group preceded by Dr. Aguilar-Salinas, a renowned Mexican endocrinologist, brings attention to the benefits and drawbacks pertaining to the pharmacological treatment available for diabetes and its implications on older adults[6].

The Editorial Committee of the Journal of Latin American Geriatric Medicine is confident that this issue will prove useful to those who work with older adults. We invite our readers to share this issue with colleagues, students, and individuals interested in the matter, thus encouraging the practice of medicine with an evidence-based approach.

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THE JOURNAL OF LATIN AMERICAN GERIATRIC MEDICINE REVIEW ARTICLE

Comprehensive gerontological assessment: A tool to better address the needs of older people with diabetes

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Abstract

Diabetes is a very frequent disease in older subjects. However the heterogeneity of the patient's health status on the one hand and physiopathology, duration, and complications of diabetes on the other hand make diabetes management complicated. These patients may have severe comorbidities and are prone to present with falls, bladder incontinence, depression, and cognitive troubles. It is now recommended to perform a comprehensive gerontological assessment built to deal with the particularities of diabetes. Adapted therapeutic education for the patients and for the caregivers should be constructed based on this assessment. A better quality of life in a safer way may be expected from this procedure. (J Lat Am Geriat Med. 2017;3:4-9)

Key words: *Comprehensive gerontological assessment. Diabetes. Frailty. Older subjects.*

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INTRODUCTION

Diabetes mellitus prevalence increases with ageing[1]. In Europe, half of the people with diabetes are older than 65 years and a quarter older than 75[2,3]. In Latin America, the prevalence was even higher: in people older than 60 years in Panama, diabetes prevalence estimate was 16.5%[4] and Panama was in the lowest quartile for diabetes prevalence in adults in Latin America[5]. The increases in life expectancy and obesity prevalence result in a continuous increase in diabetes prevalence[1]. In 2000, 2.6% of the adult population in France was treated for diabetes; this proportion has increased to 3.5% in 2006, 4.39% in 2009[6], and 4.5% in 2012 (French scientific council for diabetes, June 2014). This rate may increase particularly in older populations. The estimate was a 2.2% increase in the 55-59 year-old class and 6-7% in those older than 80 years. The excess mortality associated with diabetes decreases with age but remains significant in those older than 90 years: standardized mortality ratio from 3.76 (95% CI: 2.71-5.21) in the 20-29 year old group to 1.11 (95% CI: 1.08-1.15) in those > 90 years[6]. However, this excess mortality was not as important as earlier with increased life expectancy with complications[7]. In Scotland, a decrease in diabetes incidence has been shown in the oldest (> 65 and > 75 years old)[8] in contrast to an increase in the youngest. Diabetes absorbs 10% of direct health costs in Europe[9]. Owing to the importance of diabetes in the daily life of numerous older subjects and the burden on our healthcare models, some reflections are in order to optimize the care of older people with diabetes.

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HETEROGENEITY OF OLDER PEOPLE WITH DIABETES

According to WHO, a subject is old when older than 65 years; however, the field of geriatrics better includes subjects older than 75 or 80 years. The health status varies in a large extent from one person to another. Rockwood, et al.[10] have described seven health status categories that are worsening from successful ageing to complete dependency (Clinical Frailty Scale; Table 1). The diagnosis of diabetes places the subject in the third category even if apparently healthy. Gradually, according to the accumulation of limitations, the needs of patients change along with their life expectancy. It is noticeable that robustness does not always mean greater life expectancy in the elderly; see for example the case of healthy nonagenarians.

Rockwood and Mitnisky have also developed the Frailty Index considering exhaustively symptoms, signs, diseases, and disabilities. Frailty in this model results from accumulation of multifactorial deficits through time[11]. Social frailty must be considered. Indeed, social isolation, low income or low educational levels are by themselves risk factors to suffer from functional decline, regardless of pathologies[12,13]. Another approach to frailty consists in a description of subjects at risk of severe events such as death, functional dependency, chronic disease decompensation, hospitalization, institutionalization, or geriatric syndromes (fall, incontinence, under-nutrition, dementia), or to present an adverse drug event. This is the epidemiological definition described by Fried, et al. It has been shown that this composite risk was predicted by a biological phenotype associating three or more of the five following criteria: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity[14]. The thresholds are defined according to gender and height, and finally are not easy to use in clinical practice. The frail patient according to these criteria could belong to the fourth of fifth category of Rockwood, et al. clinical frailty scale. Indeed, frailty phenotype excludes the subjects with severe functional dependency.

Diabetes is a frailty inducing disease with a premature ageing effect, more apparent in the youngest patients. The difference in functional dependency prevalence as compared with nondiabetics of the same age is lower in the octogenarian group than in the younger. The older patient with diabetes has numerous reasons to be frail according to the Rockwood and Mitnisky Frailty Index or according to the Fried phenotype[12,15]. Older people with diabetes have several reasons to be more frail than others of the same age: they more often have limitations for mobility or impaired gait[16] and a low activity level. Geriatric syndromes are more often present: falls[17], incontinence[18], and cognitive troubles[19]. Adverse drug events are also more frequent in older people with diabetes; hypoglycemia is a main cause of admission in the emergency department as well as accidents due to anticoagulants they are likely to receive[20].

Consistently, the quality of life is likely impaired with diabetes, in particular the physical quality of life[21]. The determinants of this poor quality of life were female gender, severe hypoglycemia events, limitations for instrumental activities of daily living, and hospitalization during the previous year. Specifically, poor mental quality of life was predicted by a poor satisfaction with social support and HbA1c in the range 8-10%. On the other hand, higher body mass index (BMI), lower income, and older age were associated with a poor physical quality of life. It is noticeable that poor quality of life is directly linked

Table 1. Clinical Frailty Scale

	Good health condition and frailty in older people[10]
1	Very fit: robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well: without active disease, but less fit than people in category 1
3	Well, with treated comorbid disease: disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable: although not obviously dependent, these people commonly complain of being “slowed up” or have disease symptoms
5	Mildly frail: with limited dependence on others for instrumental activities of daily living
6	Moderately frail: help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail: completely dependent on others for the activities of daily living, or terminally ill

Table 2. Main points of interest in the care of older people with diabetes[25]

Domains	1st round with Delphi method	2nd round
Hypoglycemia	5	3
Treatment	7	4
Diabetes in nursing homes	8	5
Comorbidities	1	2
Blood glucose targets	3	1
Family and caregivers	4	8
Education for health	2	5
Safety	5	3
Nutrition	Suggested by the experts	
Hypertension	Suggested by the experts	

to the diabetes disease and its consequences, but also to frequent associated conditions such as obesity or a less favorable socioeconomic condition[22,23].

As a consequence, taking into account frailty in older people with diabetes is necessary to optimize prevention and to provide a better quality of life.

The older patients with diabetes are also heterogeneous according to the physiopathology of the diabetes disease. The ENTRED 2007 cohort has shown that obesity was less frequent in the subjects older than 80 years as compared to the younger ones[2]. Pancreatic insufficiency rather than insulin resistance may precede diabetes in one subject in four older than 65 years, and this rate was described as increasing with age[24].

INTERNATIONAL CONSENSUS

International Association of Gerontology and Geriatrics (IAGG), European Diabetes Working Party for Older People (EDWPOP) and the International Task Force of Experts in Diabetes (ITFED)

An international consensus has determined and classified, in order of importance using the Delphi method, the main points of interest in diabetes management in people older than 70 years[25] (Table 2).

Among them, taking into account comorbidities is acknowledged as essential. Comprehensive gerontological assessment (CGA) is recognized as an efficient method to best manage comorbidities in the elderly and is recommended[15,25]. The CGA will additionally help to address the other points of interest underlined by the consensus.

COMPREHENSIVE GERONTOLOGICAL ASSESSMENT

Mental health

Mental health should be assessed as a priority because cognition is frequently impaired with diabetes, in particular executive functions that are necessary to the patient for self-management of diabetes: psychomotor speed, planning, attention[19]. On the other hand, diagnoses of either Alzheimer's or vascular type dementia imply adaptive care due to limitation in daily living activities. The risk of hypoglycemia is increased in subjects with dementia[26].

The Mini Mental State Examination (MMSE) is the first screening test for global function assessment. An abnormal blood glucose profile should be checked for because under or over treatment may impair cognition. Eventually, a memory clinic assessment will be proposed for the patient. An MMSE in the normal range or suggesting mild cognitive impairment should lead to checking the abilities of the patient for diabetes self-management using the clock drawing test[27] or timed money counting test[28]. Indeed an impaired clock drawing test predicts difficulties for insulin self-injections[27]. The timed money counting test was built to assess the quickness of the subject's decision making

as well as gestural abilities and vision. The assessor presents a banknote of 5 euros and coins, one of 2 euros, two of 1 euro, one of 50 cts and three of 10 cts. It is important to use the note and coins the patient is used to, replacing Euros with the appropriate currency. The subject has to announce the count as quick as possible. The threshold has been fixed at 45 seconds, and a higher time predicts limitations in self-injection capacities.

Cognitive assessment is also useful to adapt education for health.

During hospital stay, delirium is also to be screened, eventually using the Confusion Assessment Method (CAM)[29]. The blood glucose profile should be put in perspective[20] and, to optimize the mind functioning, treatment revision should have to maintain blood glucose in the range 80-200 mg/dl.

Depression is very frequent in older patient with diabetes[23,30] and could worsen their quality of life. The Geriatrics Depression Scale (GDS) is the most common tool used during CGA[31]. The care of depression will be organized and the troubles will be taken into account in the perspective of education for health.

Physical functioning and dependence

The functional assessment is a major component of CGA due to the high frequency of gait troubles and falls in older patients with diabetes[12]. Resulting from the assessment, promotion of physical activity or prescription for physiotherapy rehabilitation may be proposed. Blood glucose and blood pressure profiles should be carefully considered in case of a history of falls. It is difficult to state if blood glucose control can improve or not muscle functioning. It has been hypothesized that muscle quality is impaired due to neuropathy, peripheral arterial ischemic disease, insulin-resistance, and mitochondrial alteration due to hyperglycemia and oxidative stress. The decrease in muscle strength, obesity, and neuropathy may be a determinant of gait impairment with diabetes[32]. Indeed, muscle strength was shown as lower when HbA1c was higher and diabetes duration longer[12].

Functional assessment includes recording of basic and instrumental independence/dependence, gait and balance exam, and fall risk assessment.

Assessments for instrumental and basic activities for daily living dependency are followed by etiological search and are necessary to build the individualized care plan.

Gait and balance are assessed using SPPB (Short Physical Performance Battery), which includes gait speed in a four-meter distance, balance, and rising chair measures[33]. The risk of falling is predicted with a Timed get up and go test (TUG) over 20 seconds[34]. This test, similarly to SPPB, combines the three items above; the subject is instructed to rise from an arm chair to walk three meters followed by a half turn before to going back to sit in the chair. The TUG tests also the attention capacities, which are important determinants in the risk of falling.

Foot exam is an important part in the gait and falling risk assessment in older people with diabetes. A foot exam will include a podology risk assessment by searching for a decrease in 10 g-Weinstein monofilament sensitivity. The search for neuropathy with decreased sensitivity to vibrations is to include in the fall risk assessment. Edema, wounds, or mycosis should be specifically sought along with postural static impairment. Corrective actions, such as improvement of blood glucose control, anti-mycosis treatment, or advice for shoe fitting, are to be implemented as the result of assessment.

Bladder control may be improved with blood glucose control owing to expected decrease of polyuria linked to hyperglycemia.

Sensorial impairment, in particular far and near vision impairment, should be screened for. The rationale for vision testing is well known in subject with diabetes. Both visions are tested with current glasses under optimized lighting conditions. Distance vision testing uses a directly illuminated 3 m Snellen chart with the subject sitting. Near vision uses Jaeger or Parinaud testing. The subject is instructed to read a text with decreasing letter sizes held at a 30 cm distance from the eyes. A deficient subject is directed to a specialist.

Nutrition

Nutritional assessment is particularly important to consider. The BMI is generally higher in the older people with diabetes[23]. However, diabetes is not a protective factor against malnutrition, or may increase the risk of malnutrition, particularly in case of food restriction[35]. Indeed, it was shown in community-living older patients that those with diabetes were at risk of malnutrition according to the Mini Nutritional Assessment (MNA) in 26% compared to 0.1% in the others[36]. The diet of patients with diabetes should be purposive in order to meet the nutritional needs and to favor a safe blood glucose control, avoiding the inflation of antidiabetic drugs. Nutritional assessment includes a MNA interview[37], the search for weight loss or gain, and a

qualitative assessment of intake, swallowing capacities, and oral health. Based on this assessment, dietary advice is most often useful, and eventually modified texture and food fortification may be necessary. An oral health exam is mandatory in older people with diabetes due to frequent periodontal disease. Dental care should be organized whenever indicated. Finally, meals on wheels may be implemented in the framework of the individualized care plan.

Comorbidities

Comorbidity assessment starts with the exhaustive search for medical histories, physical exam, and paramedical investigations. Among them, cancer screening for the most frequent (breast, prostate, colon, lung) is to be done. Indeed, increased risk for cancer mortality was shown in people with diabetes[38]. However, there is no recommendation for screening investigations in this population and screening should be clinical. The place of diabetes in the patient's health status can be stated as main disease or associated condition. This is important in the perspective of goals for treatment and follow-up.

The diabetes complications assessment has also to be done to guide the choice of therapeutic objectives and hypoglycemic drugs[25,39]. The goals for treatment for other vascular risk factors must be reset, in particular the blood pressure control[40].

Pain is a frequent symptom in older people with diabetes, but may be due to other pathologies than diabetic neuropathy. A systematic screening for pain and a precise semiology description is mandatory before an antalgia care plan. Pressure ulcers occur with a higher rate in case of diabetes[20], justifying a careful skin exam during the CGA.

Routine biology includes renal function assessment. The question is what is the preferred formulae to use for glomerular filtration estimation. The Cockcroft and Gault formula is body-weight dependent and overestimates the creatinine clearance in obese subjects. The Modification of Diet in Renal Disease (MDRD) formulae is "skin color" dependent. The construction of the Chronic Kidney Disease Epidemiology Collaboration (CPK-EPI) formula seems more trustworthy because it avoids these two limitations, but none of these three formulas is validated in people older than 80 years. In frail or sarcopenia subjects, the creatinine level maybe lowered and the renal function overestimated. The clinical judgment is in this case of major importance to deal with the uncertainty.

Treatment conciliation, ideally with the pharmacist, and treatment revision come at the end of the CGA, taking into account the mental, functional and nutritional assessments, comorbidities, renal function, and generally the therapeutic goals and the iatrogenic risk. The different lists of potentially inappropriate medication in older may help the decision of treatment withdrawal or addition[41]. Vaccination updating and vitamin D supplementation complete the treatment revision.

Social

Needs for social support for patients and caregivers must be considered when building the care plan, based on functional dependency assessment. The social workers may help them to find financial support.

Education for health, adapted to the abilities of the older patient, can result from CGA. This education should ideally include caregivers.

The CGA frame should be adapted to the frailty status of the patient. In robust patients, with no comorbidity (category 3 according to Rockwood, et al.), CGA is not necessary. Conversely, in dependent patient (categories 6 and 7), the CGA should be focused on nutrition, pain, pressure ulcer risk, social needs, and treatment revision.

CONCLUSION

The CGA is a useful tool to deal with the complexity of the health status in older patients with diabetes. It is possible to hope for care that is both rational and efficient to improve the quality of life of the patient and also more efficient from our healthcare system's point of view.

DECLARATION OF INTEREST

The authors have no conflict of interest to declare concerning the topic and the content of this paper.

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Impact of frailty in older patients with diabetes mellitus: An overview

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Abstract

Diabetes and frailty are two conditions that frequently occur concurrently and are increasingly prevalent in the older patient. We review the concept, epidemiology, and consequences of frailty and the implications of the presence of frailty in the management of diabetes. Frailty is associated with decreased quality of life, a risk of falls, new or increased disability, hospitalization, and increased mortality. All of these factors affect the management of diabetes in older patients. It is important to rule out frailty in all diabetic patients aged > 70 years; if frailty is suspected, a comprehensive and multidisciplinary medical and functional assessment of the patient should be conducted to develop an individualized treatment plan. This plan should include nutritional measures, physical activity, and education on self-care and diabetes; drugs should not be used without a clear indication. Antihyperglycemic drugs that may cause excessive weight loss and/or are associated with high risk of hypoglycemia should be avoided. (J Lat Am Geriat Med. 2017;3:10-9)

Key words: *Diabetes. Hyperglycemia. Frailty. Sarcopenia. Older people.*

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AGING OF THE POPULATION

Increasing life expectancies and declining birth rates mean that the segment of the population comprising people aged > 60 years is growing at a rapid rate in most countries. Worldwide, it is estimated that this population will increase from 600 million to two billion between 2000 and 2050[1].

This demographic change poses a major challenge to society, which must adapt to improve the health and functional capacity of older people[1]. Taking into account that increasing life expectancy is currently a very difficult problem due to the long life expectancies now existing in many countries, the new challenge is to improve quality of life; that means to improve functional status (WHO Report on Aging and Health). In this context, frailty, which is considered to be the most characteristic clinical condition of an aging population predisposing to the development of disability, is particularly important[2].

This article provides an overview of the concept, epidemiology, and consequences of frailty, as well as the implications of the presence of frailty in the management of diabetes, summarizing and updating the information provided in a previous one[3].

FRAILTY: CONCEPT AND EPIDEMIOLOGY

Frailty can be defined as a situation of extreme vulnerability to the effects of low-intensity stressors. It results from difficulty maintaining homeostasis due to loss of functional reserve[2].

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Attempts to arrive at an operative and universal definition of frailty have not yet been successful. Experts from different disciplines collaborating on the "Frailty Operative definition-Consensus Conference" project (2012) concluded that frailty is a multidimensional syndrome that affects physical function (i.e. gait and mobility), nutritional status, and mental health and cognition, and is the result of a decrease in physiological reserve and resistance to stressors[4]. In a similar sense, representatives from six international societies (the International Association of Gerontology and Geriatrics; the Society on Sarcopenia, Cachexia and Wasting Diseases; the International Academy of Nutrition and Aging; the European Union Geriatric Medicine Society; the American Medical Directors Association; and the American Federation for Aging Research) have defined frailty as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death."[5]

CAUSES AND CONSEQUENCES OF FRAILTY

Although frailty involves disorders in different physiological systems of the body, endocrine, immune, musculoskeletal, and cardiovascular systems are the main ones. Frailty becomes apparent when a (currently not accurately defined) level of decline in physiological reserves occurs[6,7].

Several longitudinal studies conducted in older populations have demonstrated an association between frailty and deterioration in quality of life, and a risk of falls, new or increased disability, hospitalizations, nursing home entry, and mortality[8-10].

FRAILTY, COMORBIDITY, AND DISABILITY

Frailty is different from comorbidity and disability, even though these concepts overlap. Instead, comorbidity is one of the etiological factors of frailty, and disability is a result of frailty (Fig. 1).

Interactions between frailty and various chronic diseases, such as anemia, cardiovascular diseases, chronic renal disease, cancer, HIV infection, cognitive disorder, Parkinson's disease, depression, and diabetes mellitus, have been identified[6]. However, six chronic diseases/conditions have been shown to be most significantly associated with the development of frailty and its progression towards disability: heart failure, ischemic heart disease, OCFA, osteoarthritis, dementia/cognitive impairment, and diabetes mellitus.

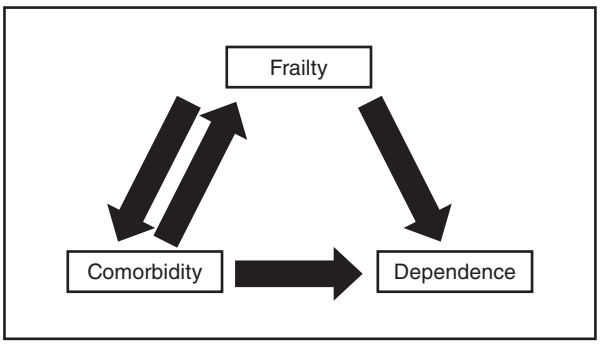

Figure 1. *Relation between frailty, comorbidity, and dependence.* (adapted with permission from Cobo, et al.[3]).

The diabetes/frailty association is of particular importance for the following reasons: (i) both disease states are commonly encountered in the older patient; (ii) both entities share several common mechanisms[11-13], which could explain their frequent coexistence; (iii) diabetes accelerates the aging process and therefore places the individual at greater risk of becoming frail[13]; and (iv) the presence of frailty in diabetic patients increases the likelihood of complications[14], functional deterioration[15,16], and mortality[17] and therefore impacts the management of these patients[18].

FROM DIABETES TO FRAILTY

Epidemiology

The prevalence of diabetes increases with the presence of frailty. The Cardiovascular Health Study showed that the prevalence of diabetes was 18.8% in individuals without frailty, 24.5% in individuals with pre-frailty, and 32.4% in individuals with frailty[19]. Likewise, the presence of frailty is higher in patients with diabetes. Data from this study indicate that frailty is present in 25% of individuals with diabetes, and pre-frailty is present in 18.2% compared with a prevalence of frailty of 6.9% in the whole sample who were aged ≥ 65 years. A study that evaluated the progression of frailty and pre-frailty in an older cohort living in the community found that the presence of diabetes in women with pre-frailty reduced by 50% the likelihood of their frailty improving[20].

Pathophysiology

Sarcopenia, defined as a reduction in muscular mass and function (strength or performance)[21], is considered

a key component of frailty and may represent the pathophysiological link between diabetes and frailty[22]. Data from several studies reviewed by other authors[11,13,22,23] show a close relationship between diabetes, insulin resistance, the chronic low-grade inflammation characteristic of diabetes and sarcopenia, and/or muscle deterioration. Many studies have shown that muscle strength and quality decrease in patients with diabetes, and this decline becomes more pronounced the longer the patient is affected with diabetes and the poorer their glycemic control. Insulin resistance is associated with a decrease in muscle strength, most likely due to a decrease in protein synthesis, increased degradation, and a resultant loss of muscle mass. At the same time, insulin resistance in aging patients can lead to mitochondrial alterations that result in a decrease in production of the energy required for muscle contraction and an increase in oxidative stress.

Insulin-like growth factor type 1 plays an important role in protein synthesis, and levels of this molecule decrease with age and in patients with diabetes. This decrease is related to the development of frailty, functional decline, and disability in the older patient. Research on markers related to inflammation in frail and non-frail individuals indicates that the frailest subjects have elevated levels of high-sensitivity C-reactive protein, a soluble biomarker of inflammation[24], and other pro-coagulant factors. Patients with diabetes also have elevated levels of cytokines, such as tumor necrosis factor alpha and interleukin-6, that stimulate proteolysis and apoptosis in muscle cells. This pro-inflammatory setting can indeed change some pathophysiological pathways like the one driving to vascular disease[25,26].

These mechanisms provide a direct association between diabetes and sarcopenia/functional impairment and explain most of the attributable risk of disability in older patients with diabetes. However, other factors can explain the relationship between these two entities, including atherosclerosis, depressive illness, and cognitive decline[12,27].

FRAILTY AS A COMPLICATING FACTOR IN T\HE MANAGEMENT OF PATIENTS WITH DIABETES

Screening and diagnosis of frailty

According to the international consensus on frailty (Frailty Consensus: A Call to Action), "all persons aged 70 years or older, as well as any person with a significant weight loss (≥ 5% over the past year) due to chronic illness should be screened for frailty."[5] Given the significant repercussions that frailty has on older individuals (especially patients with diabetes), and the implications for the management of diabetes, the International Diabetes Federation (IDF) also recommends screening every patient with diabetes who are aged ≥ 70 years for frailty and functional status[28].

Functional status is an important prognostic factor in older patients. Consequently, a comprehensive functional assessment that quantitatively encompasses the physical, cognitive, and emotional status of the patient should be a critical part of the clinical evaluation of older patients with diabetes[29].

The international consensus on frailty endorses validated instruments to assess the presence of frailty, including the FRAIL questionnaire, the CHS Frailty Screening Measure (corresponding to the Fried Phenotype), the Clinical Frailty Scale (a tool recommended by the IDF) (Table 1), and the Gérontopôle Frailty Screening Tool[5].

As recommended by the IDF and treatment guidelines for older diabetics, multidimensional and, whenever possible, multidisciplinary assessments of older patients with diabetes should be performed to collect information about medical, functional, cognitive, emotional, and social functioning of the patient[28-30]. This assessment is a dynamic and structured diagnostic process that detects and quantifies the problems, needs, and abilities of the older individual in four key areas: clinical, functional, mental, and social. This assessment can then be used to develop an interdisciplinary plan for intervention, treatment, and long-term monitoring, thereby enabling the patient to maintain a high degree of independence and an acceptable quality of life[31]. At a minimum, the evaluation should assess the patient's functional capacity, cognitive function, and mental health[28]. Table 2 lists the evaluations and instruments proposed by the IDF that can be used with minimal training in daily clinical practice.

Screening and diagnosis of diabetes

Given the elevated prevalence of diabetes in older patients and because approximately 40% of cases of diabetes remain undiagnosed, all older patients should be periodically evaluated to detect diabetes. These evaluations are especially warranted in certain groups, including in all patients admitted to a nursing home[28]. The IDF recommends using the same diagnostic criteria for diabetes that are used for the general population; however, only the simplest possible tests should be used in frail patients.

Table 1. Operational criteria of the frailty phenotype

Characteristic	Measure
Unintended weight loss (in the past year)	– > 4.5 kg (communicated) or ≥ 5% in the past year (objectified)
Weakness	– Grip strength (adjusted for sex and BMI) in the lowest quintile
Self-reported exhaustion	– Communicated by means of two statements of the CES-D* depression scale: "I felt that everything I did was an effort" and "I could not get going" The individual would report always or almost always (3-4 days/week or greater)
Slowness	– Walking time 4.57 m (adjusted for sex and height) in the lowest quintile
Low physical activity	Energy expenditure: – Men: < 383 Kcal/week – Women: < 270 Kcal/week
Presence of frailty – Frail: at least three criteria are met – Pre-frail: one or two criteria are met – Not frail: no criteria are met	

*Center for Epidemiologic Studies-Depression Scale (CES-D) is a 20-item instrument that assesses symptoms of depression in DSM-IV.
BMI: body mass index; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (fourth edition).
Adapted with permission from Fried, et al.

THERAPEUTIC MANAGEMENT OF DIABETES IN OLDER FRAIL PATIENTS

Clinical trials evaluating treatments for diabetes typically exclude frail patients and patients with multiple comorbidities or functional disabilities. Therefore, no evidence-based recommendations for the treatment of these patients are available. Additionally, until recently clinical practice guidelines did not contain specific recommendations for the management of these patients[18,32]. Current guidelines for managing diabetes in the older patient recognize the need to consider frailty, comorbidities, and functionality when making decisions[28-30,34]. Other factors should also be considered, including cardiovascular disease, advanced microvascular disease, undetected hypoglycemia, and other individual aspects of the patient (resources and support systems)[35,36].

Glycemic control objectives

There is widespread consensus that the objectives of glycemic control in the frail older patient should be individualized and that the strict control of glycemia (for example, HbA_{1c} < 7%) is associated with a risk of hypoglycemia and functional decline[18,28-30,32]. Because the estimated time to achieve benefits from intensive glycemic control is at least eight years (United Kingdom Prospective Diabetes Study), the available guidelines currently recommend less stringent control objectives (HbA_{1c} < 8.0-8.5%) in frail patients or patients with a limited life expectancy (< 5 years) (Table 3).

Diabetes treatment

Below, we summarize the limited information available for treating older patients with diabetes that considers the frailty of the patient.

Non-pharmacological interventions

Nutrition

A nutritional evaluation that can detect malnutrition or weight loss and provides an appropriate and individualized nutritional plan should be performed. Food with high protein and energy content may be necessary to improve the nutritional and functional status of the patient[28,36].

Performing physical activity and exercise

This is an important component of the treatment plan for diabetic patients. Light resistance and balance training can be performed to improve physical performance, strengthen the lower body, and prevent

Table 2. Instruments for evaluating frailty and its components and/or associated areas

Dimension	Instrument
Frailty	– Fried Frailty Phenotype – Frailty Index – 7-point Clinical Frailty Scale – 9-point Clinical Frailty Scale* – Frailty Trait Scale – FRAIL Screening Questionnaire – Groningen Frailty Indicator – Tilburg Frailty Indicator – The Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI)
Functional decline (performance-based)	– Short Physical Performance Battery (SPPB) – Timed Up and Go (TUG) test – 4-meter gait speed test – Institute for Diabetes in Old People (IDOP) 3-steps package (Walking/Balance/Mobility).
Disability	– For performing Basic Activities of Daily Living: Barthel Index*/Katz Index – For performing Instrumental Activities of Daily Living: Lawton and Brody Scale
Cognitive and emotional assessment	– Mini Mental State Examination – MiniCog or Montreal Cognitive Assessment Tool (MoCA) – Pfeffer Scale (Portable Functional Assessment Questionnaire) – Yesavage Geriatric Depression Scale*
Quality of life	– EuroQoL EQ-5D
Risk of hypoglycemia	– In-depth assessment of history to identify risk factors*
Ability to provide self-care	– Revised self-care inventory (SCI-R)
Nutritional evaluation	– Nutritional Mini-evaluation-Abbreviated version (MNA-SF) or Malnutrition Universal Screening Tool (MUST)
Pain	– Pain thermometer (VAS) – Modified Resident's Verbal Brief Pain Inventory (M-RVBPI)

*Tools recommended by the IDF for the management of the older patient with type 2 diabetes.
IDF: International Diabetes Federation; VAS: visual analog scale.
More information about these tools can be found in Ministerio de Sanidad SS, e Igualdad (2014) and International Diabetes Federation (2013).

the deterioration of the patient's functional status[28,31]. Interventions focused on physical activity have been shown to be effective in delaying and even reversing frailty and disability[37] and improving cognitive status and emotional wellbeing[38]. According to a systematic review of studies on frail older patients, the best strategy for improving frailty and preventing falls involves implementing interventions designed to address strength, endurance, and balance[39].

Diabetes and education on self-care

Education on self-care should take into account mental and physical functional disorders, comorbidities, impaired vision or hearing, manual dexterity, and social setting. Education should be provided to both health professionals and caregivers[29,40]. Recommendations from the Diabetes Care Program of Nova Scotia indicate that it may not be necessary to routinely measure plasma glucose in patients who have remained stable with oral anti-diabetics or well-established doses of insulin alone[18].

Pharmacological measures

Antidiabetic drugs

Because renal disease is prevalent among older patients, renal function should be evaluated before

Table 3. Recommendations on the use of hypoglycemic drugs in patients with comorbidities associated with frailty

	Usage warnings in patients with comorbidities related to frailty (old age, renal disease chronic kidney disease hypoglycemic risk, etc.)*
Metformin	– Low risk of hypoglycemia – Adjust the dose during and after the addition or discontinuation of therapy with glucocorticoids, β2 agonists, and diuretics – Monitor the development of weight or muscle mass loss – Spread the dosage into two to three doses or slowly increase the dose to prevent gastrointestinal events
Sulfonylureas	– Avoid in older vulnerable populations. These drugs can cause hypoglycemia, weight gain, falls, cardiovascular problems, and cognitive disturbances – Use short-acting drugs such as gliclazide or glimepiride and avoid using long-acting drugs such as chlorpropamide and glibenclamide/glyburide
Glinides	– Use in older patients with erratic eating patterns – Lower risk of hypoglycemia than sulfonylureas
Pioglitazone	– Increased risk of heart failure, which limits the use of these drugs in older patients and patients with CKD. These drugs are also associated with an increased risk of fractures – Low risk of hypoglycemia
Alpha glucosidase inhibitors (acarbose and miglitol)	– Common side effects include digestive intolerance, flatulence, bloating, and diarrhea
DPP-4 inhibitors	– Good safety profile and low risk of hypoglycemia. Consider in situations of special risk and vulnerability (hospital discharge, frail older individuals, kidney failure, recurrent hypoglycemia, reduced intake, CKD, etc.) – When combined with sulfonylureas, reduce the dose to decrease the risk of hypoglycemia – Limited experience in older patients – Caution in patients with a history of pancreatitis and if suspected stop treatment
GLP-1 receptor agonists	– Associated with a low risk of hypoglycemia and weight loss – Limited previous use in patients aged > 75 years – Weight loss and gastrointestinal side effects should be considered. Assess potential weight loss in frail underweight patients – Caution in patients with a history of pancreatitis and if suspected stop treatment
Insulin	– The most common side effect is hypoglycemia; therefore, in older and frail patients who are more likely to experience hypoglycemia, it is recommended to start insulin therapy with a low dose of 0.1-0.2 U/kg body weight – The use of basal insulin analogs is recommended for their lower risk of hypoglycemia, especially at night
Inhibitors of SGLT2	– Good safety profile; limited experience in patients aged ≥ 75 years – In patients ≥ 75 years an increased risk for volume depletion should be taken into account – Associated with weight loss and blood pressure reduction; low risk of hypoglycemia – Urinary tract infection, genital infection, and reduced renal function should be monitored closely in older patients – Evaluation for the presence of ketoacidosis in patients experiencing signs or symptoms of metabolic acidosis is recommended; Discontinue SGLT2 inhibitors if ketoacidosis is suspected and if confirmed, take appropriate measures to correct the acidosis and monitor sugar levels

*Information on warnings can be checked in the corresponding Summary of Product Drug characteristics are as reported at http://www.aemps.gob.es/cima/ and at https://sinaem.agemed.es/CartasFarmacovigilanciaDoc/2015/DHPC_definitiva_glifozinas_09_07_2015.pdf for the inhibitors of SGLT2, unless otherwise indicated.
CKD: chronic kidney disease; DPP-4: dipeptidyl-peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose co-transporter 2.
Adapted with permission from Cobo, et al.[3].

starting a treatment regimen for diabetes. If the patient has adequate renal function, metformin is the drug of choice. Most recent consensuses[28,39], recommend that the dose of metformin should be reduced if the estimated glomerular filtration rate (eGFR) is between 30 and 60 ml/min, and it should not be used in patients with eGFR values < 30 ml/min. One of the most common problems with metformin encountered in the older patient is a high rate of gastrointestinal intolerance (which can occur in up to 30% of patients) and resultant anorexia and weight loss. This can lead to sarcopenia and declines in function, which would necessitate the discontinuation of this drug or a dose reduction. In this case, dipeptidyl peptidase 4 (DPP-4) inhibitors or sulfonylureas with a low risk of inducing hypoglycemia (like gliclazide) may be the drugs of choice[34]. If monotherapy with metformin is not sufficient to achieve the desired glycemic control, another drug must be added, preferably a DPP-4 inhibitor[28-30,34] in patients at a high risk of experiencing hypoglycemia (i.e. frail patients; patients recently discharged from hospital; patients with cognitive impairment, disability, or erratic intake; and patients in a residential care setting). In patients who cannot tolerate metformin, the combination of a DPP-4 inhibitor and a sulfonylurea with low risk of hypoglycemia is recommended. Similarly, according to the treatment algorithm for hyperglycemia in patients with type 2 diabetes published by the Network of Study Groups of Diabetes in Primary Health Care (Red de Grupos de Estudio de la Diabetes en Atención Primaria de la Salud – RedGDPS), patients aged > 75 years or frail patients should receive a DPP-4 inhibitor instead of a sulfonylurea to reduce the risk of hypoglycemia[41]. Furthermore, the RedGDPS algorithm emphasizes the need to consider potential renal dysfunction. Thus, in patients with GFR < 30 ml/min, the drug of choice would be a DPP-4 inhibitor (with dose adjustment, if required).[41]

Several studies[42,43] indicate that DPP-4 inhibitors (linagliptin and vildagliptin) are a safe option for diabetic patients aged > 70 years, and most guidelines list DPP-4 inhibitors as the drugs of choice for older patients in whom metformin is contraindicated[28,29,41,44], being an alternative to sulfonylureas, which in most cases are associated with an increased risk of hypoglycemia.

If a patient requires insulin treatment, the safest option is to add a long-acting insulin analog along with oral agents and provide educational information tailored to the patient and/or their caregivers[35]. In all cases, it will be necessary to evaluate factors such as the cognitive function of the patient, the presence of caregivers, the ability and degree of independence of the patient, and accessibility of healthcare[36].

Table 3 summarizes the main characteristics, precautions, and warnings of each group of diabetes medications when used in older and frail patients.

Drugs that could cause nausea or gastrointestinal discomfort or excessive weight loss should be avoided or discontinued. Thiazolidinediones have been associated with congestive heart failure, fluid retention, and bone fractures[45]. Insulin can have anabolic effects, and use of a single basal insulin is recommended if possible to avoid hypoglycemia associated with the use of a fast-acting insulin[18]. To choose the most appropriate drug, the ADA and the European Association for the Study of Diabetes also recommend following a patient-centered approach, taking into account the efficacy, cost, and adverse effects of the drug, its effects on the weight of the patient, associated comorbidities, hypoglycemia, resource availability, and preferences of patients or their caregivers[44].

It is important to periodically review other medications that the patient receives and, if possible, avoid polypharmacy because of its link with adverse events in the older patient. An evaluation of the indication of each drug should be performed. The STOPP-START (Screening Tool of Older Person's Prescriptions and Screening Tool to Alert doctors to Right Treatment) criteria are a useful tool that can be used to determine when to discontinue drugs that negatively affect older patients who are at increased risk of side effects (falls, functional impairment, urinary incontinence, sleep disturbances, weight loss, etc.)[46].

Prevention and management of complications associated with diabetes in the frail patient

Not all patients clearly fit into one category. Therefore, the preferences and characteristics of the patient and their caregivers are important factors to consider when developing individualized treatment plans. Treatment goals for the management of complications depend on the functional status of the patient, including their frailty, cognitive status, risk of hypoglycemia, and life expectancy[36].

The recommendations of the IDF and ADA for the management of certain complications and comorbidities associated with diabetes are summarized in table 4.

Interventions to address patients' cardiovascular risks are necessary to prevent or delay cardiovascular

Table 4. Objectives for the management of complications and comorbidities associated with diabetes in the frail older patient with diabetes mellitus

	IDF recommendations, 2013	**ADA recommendations, 2015**		**Other consensuses***	
	***Functionally dependent patient/frail patient**	***Patient with a complex or intermediate health status**	***Patient with a very complex health status**	***Frail patient (EDWPOP)**	***Frail patient (Spanish consensus, type 2 diabetes in the older patient)[47]**
HbA_{1c}; FG	HbA_{1c} ≤ 8.5%	HbA_{1c} < 8% FG: 90-150 mg/dl Bedtime glucose: 100-180 mg/dl	HbA_{1c} < 8.5% FG: 100-180 mg/dl Bedtime glucose: 110-200 mg/dl	HbA_{1c} 7.5-8.5% FG: 136-162 mg/dl	HbA_{1c} 7.6-8.5% (If functionally or cognitively impaired or short life expectancy)
BP	< 150/90 mmHg	< 140/90 mmHg	< 150/90 mmHg	< 150/90 mm Hg	< 150/90 mmHg Avoid < 120/70 mmHg
Dyslipidemia	Use statins, especially in patients with established CV disease Do not use in combination with fibrates Monitor side effects on muscles Control objectives can be less strict	Consider statins unless contraindicated or poorly tolerated	Consider statin therapy (as secondary prevention rather than primary prevention)	Consider statins as secondary prevention	Consider statins as secondary prevention, with a control objective of LDL-C < 100 mg/dl
To reduce the risk of hypoglycemia	Avoid FG < 110 mg/dl Use drugs with low hypoglycemic potential Educate caregivers and family to recognize and treat hypoglycemia Enroll the patient in an emergency call program	Perform routine screening for cognitive dysfunction because of its association with hypoglycemia Monitor episodes of hypoglycemia Accommodate control objectives according to patient needs		Avoid FG < 110 mg/dl Use drugs with low hypoglycemic potential Special interest in hypoglycemia unrecognized by the subject	In all cases, avoid hypoglycemia Monitor risk factors that increase the risk of hypoglycemia

*Functionally dependent and frail patients (IDF): They are characterized by a combination of significant fatigue, recent weight loss, severe restriction of mobility and strength, and a greater risk of falls and hospitalization. Individualize glycemic control objectives, taking into account the patient's functional status, comorbidity, CV disease, history, and risk of hypoglycemia and microvascular complications. Patients with a complex or intermediate health status (ADA): Multiple chronic diseases coexist or a limitation exists for performing more than two IADL or mild or moderate cognitive impairment. Patients with intermediate life expectancy, high risk of hypoglycemia, vulnerability, and risk of falls.
Patients with a very complex health status (ADA): Presence of advanced-stage chronic disease or severe cognitive impairment or lack of independence in more than two IADL. Patients with limited life expectancy in whom the benefit of treatment is uncertain.
European Consensus (EDWPOP). Frail patient: Dependent patients with multi-systemic disease who have been hospitalized, including those with dementia in whom there is a high risk of hypoglycemia and in whom it is key to avoid metabolic decompensation.
Spanish Consensus (Treatment of type 2 diabetes in the older patient): Frail patient: Patient with multiple comorbidities, a high risk of hypoglycemia, functional disability or life expectancy less than five years (less likely to benefit from reduced risk of vascular complications and more likely to suffer serious adverse effects such as hypoglycemia). Individualize therapy by performing a risk/benefit analysis of antidiabetic treatment based on the functional and cognitive status of the patient, comorbidities, risk of hypoglycemia, ability to take care of oneself, life expectancy, and quality of life.
ADA: American Diabetes Association; BP: blood pressure; CV: cardiovascular; EDWPOP: European Diabetes Working Party for Older People; FG: fasting glucose; IADL: instrumental activities of daily living; IDF: International Diabetes Federation; LDL-C: low-density lipoprotein cholesterol.
Adapted with permission from Cobo, et al.[3].

disease in people with diabetes. In this context, the ADA recommends preventive measures in all patients aged ≥ 60 years to address some of the main risk factors for cardiovascular disease (tobacco use, blood pressure, dyslipidemia, renal function, glycemic control, obesity, periodontitis, sleep apnea, and peripheral vascular disease)[40]. However, the role of cardiovascular disease as a prognostic marker of death and functional impairment in older patients with diabetes is controversial, especially in patients aged > 75 years[47] and a recent paper has shown that when frailty is taken into account, neither cardio or cerebrovascular diseases nor comorbidity (assessed by Charlson Index) are any longer prognostic factors for death or incident disability in this population[48].

Hypoglycemia is the main side effect of diabetes treatment in general older patients, and hypoglycemia can have serious consequences, including cognitive impairment, falls, fractures, and cardiovascular events. Therefore, it is recommended that family members and caregivers be educated to recognize and treat hypoglycemia[28] and that frail patients living in the community should be enrolled in an "SOS-call" program.

Additional research on the consequences of frailty in diabetic patients and the development of intervention programs specifically designed for these patients could help improve their clinical care. In this context, the MID-FRAIL study, which was funded under the 7th Framework Program of the European Union and led by Spain, provides an opportunity to explore the usefulness of a multidimensional intervention for frail and pre-frail patients aged > 70 years with type 2 diabetes[49].

CONCLUSIONS

The continued growth of the older population is coupled with an increase in the prevalence of frailty, ranging from less than 5% at 65 years old to more than 30% in people older than 80. Frailty is a multidimensional syndrome that is characterized by decreasing physiological reserve and resistance to low-intensity stressors. Frailty is associated with a decreased quality of life, an increased risk of falls, new or increased disability and hospitalizations, and increased mortality.

Frailty can be associated with various chronic diseases, especially diabetes. Both conditions are highly prevalent in older individuals, share pathophysiologic mechanisms and characteristics, and act synergistically to cause functional impairment in older patients. Moreover, frailty affects the management of diabetes in older patients, an issue that is increasingly being recognized in the therapeutic guidelines of major national and international scientific societies. Therefore, it is important to rule out frailty in all diabetic patients aged > 70 years. With this aim, current guidelines for the management of diabetes in older patients recommend the systematic assessment of frailty and functional status in people older than 70 using several validated evaluation tools, which can be administered during routine clinical practice as part of a comprehensive and multidisciplinary evaluation to establish an individualized intervention plan that requires less strict glycemic targets and a consideration of the life expectancy of the patient. The intervention plan should contain specific measures for addressing nutrition, physical activity, education on diabetes and self-care recommendations, and avoidance of polypharmacy. It is important to take precautions when using drugs to treat hyperglycemia that can cause excessive weight loss and/or an increased risk of hypoglycemia.

It is necessary to train health professionals to detect, diagnose, and manage frailty and its potential consequences.

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THE JOURNAL OF LATIN AMERICAN GERIATRIC MEDICINE REVIEW ARTICLE

Diabetes, frailty, and sarcopenia: Getting key messages to primary care physicians

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Abstract

Diabetes increases the risk of physical and cognitive dysfunction, eventually leading to the development of disability. This progression from diabetes to disability is only partially explained by diabetes-related complications and the associated comorbidities. The emergence of sarcopenia and frailty, as a new diabetes-related complication, is likely to be the mediator in the pathway from diabetes to disability. Sarcopenia and frailty share common pathogenetic mechanisms accelerated by the presence of diabetes. Both sarcopenia and frailty are dynamic in nature and can be reversed with timely intervention before progression to disability. Regular screening for sarcopenia and frailty by validated tools is required. A multimodal intervention, which includes adequate nutrition, exercise training, and good glycemic control, may help delay or prevent the progression to disability and an individualized intervention approach based on patients' functional level is recommended. (J Lat Am Geriat Med. 2017;3:20-5)

Key words: *Older people. Frailty. Sarcopenia. Diabetes mellitus. Management.*

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INTRODUCTION

With increased ageing of the population and urbanization of lifestyle, the epidemiology of diabetes is shifting towards old age and its prevalence is likely to reach an epidemic level[1]. The greatest proportional increase in the number of people with diabetes by age group is expected to occur in individuals between 60 and 79 years of age[2]. In this age group, frailty and sarcopenia are emerging as a third category of complication, in addition to the two traditional micro- and macrovascular diseases[3]. The development of frailty is associated with adverse outcomes; however, frailty is a dynamic process and can be delayed or prevented if intervention occurs in the pre-frail stage[4]. Therefore, on the one hand, regular screening and prevention of frailty is needed, and on the other hand, once frailty is developed, especially if associated with significant weight loss, hypoglycemic medications should be reviewed and de-intensified due to the increased risk of hypoglycemia[5]. This review investigates the link between frailty, sarcopenia, and diabetes and explores ways of prevention and management.

DIABETES AND FUNCTIONAL DISABILITY

Diabetes is associated with physical decline and disability, defined as difficulty in performing activities of daily living (ADL). The trend of disability with diabetes increases steadily with age from 13.5% for ADL and 8.8% for instrumental ADL among individuals aged

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50-59 years to 28.4 and 18.2%, respectively, among those aged ≥ 80 years[6]. Diabetes-associated disability is only partially explained by traditional diabetic complications or associated comorbidities, and diabetes itself does not directly cause disability[7,8]. This may suggest that other unmeasured factors, such as sarcopenia and frailty, which have a detrimental effect on physical functioning, may play a part in the pathway to disability in older people with diabetes (Fig. 1).

FRAILTY AND SARCOPENIA

Definition

Frailty and sarcopenia definitions are still not very clear, but current thought suggests that frailty is a state of increased vulnerability to physical or psychological stressors due to diminished physiological reserve[9]. The definition is based on the presence of three or more phenotypes[10] (Table 1). Sarcopenia is defined as loss of muscle mass that leads to reduced muscle strength and muscle function[11] (Table 2).

Pathogenesis

The biological process that underlies frailty is likely to be complex and multifactorial. The accumulation of deficits or physiological dysregulation across multiple physiological systems is likely to be associated with frailty[12]. Frailty is associated with sarcopenia and they overlap in their phenotype and pathogenesis. Sarcopenia is likely to result from an imbalance between anabolic and catabolic pathways that control muscle mass. Inadequate protein intake, reduced physical activity, and age-related reduction in growth and sex hormones are factors contributing to sarcopenia[13]. Although other chronic conditions may lead to frailty and sarcopenia, persistent hyperglycemia associated with diabetes is associated with increased oxidative stress, inflammation, and insulin resistance, which have deleterious effects on skeletal muscle, accelerating the progression to sarcopenia[14]. Other factors include mitochondrial dysfunction, increased advanced glycation end products, peripheral neuropathy, and reduction in motor neurons[15-17] (Table 3).

Implications

Frailty and sarcopenia are associated with functional decline, resulting in an increased risk of poor mobility, hospitalization, incident disability, and impaired performance of ADL[18-20]. They are also associated with

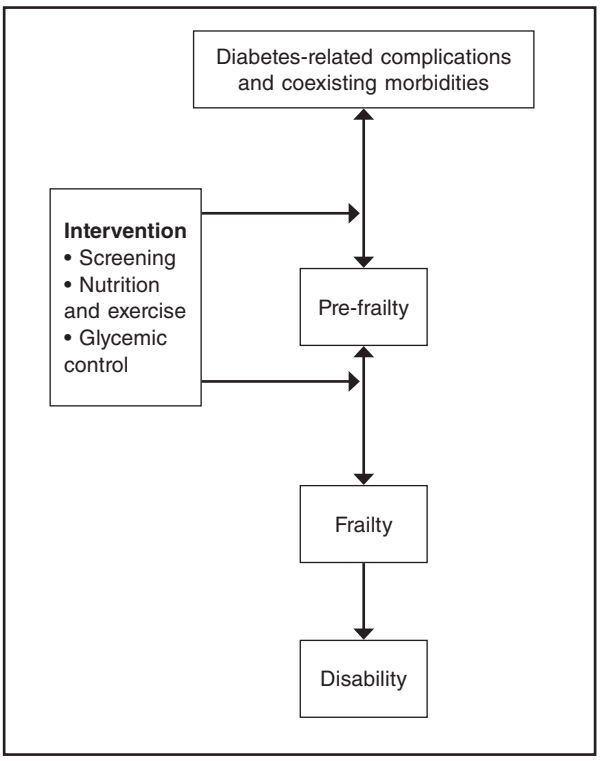

Figure 1. *Frailty as a mediator of the pathway from diabetes to disability. Intervention in the stage of pre-frailty may help to delay or prevent the progression to disability.*

Table 1. Frailty phenotypes[10]

1.	Unintentional weight loss (≥ 4.5 kg in the last year)
2.	Weakness (weak hand grip)
3.	Reduced physical activity (reduced weekly activities)
4.	Slow walking speed (slow walking time)
5.	Exhaustion (self-reported fatigue)

Presence of:
≥ 3 indicates frail state
1-2 indicates pre-frail state
0 indicates robust state.

Table 2. Sarcopenia phenotypes[11]

1.	Low muscle strength
2.	Low muscle mass
3.	Low muscle performance

Presence of:
Indicates pre-sarcopenia
Indicates sarcopenia
Indicates severe sarcopenia

Table 3. Pathogenesis of frailty and sarcopenia[12-17]

– Multisystem physiologic dysregulation
– Malnutrition and inadequate protein intake
– Sedentary life style
– Reduced growth and sex hormones
– Insulin resistance
– Increased oxidative stress
– Increased inflammation
– Persistent hyperglycemia
– Mitochondrial dysfunction
– Peripheral neuropathy
– Reduced motor neurons
– Increased advanced glycation end products

Table 4. Screening tool for frailty[25]

FRAIL Scale
1. Fatigued (self-reported)
2. Resistance (unable to climb a flight of stairs)
3. Ambulation (unable to walk a block)
4. Illness (having > 5 comorbidities)
5. Lost weight (> 5 kg in the last 6 months)
Presence of ≥ 3 is diagnostic of frailty.

Table 5. Screening tool for sarcopenia[26]

SARC-F Scale
1. Strength (difficulty lifting a weight of 10 pounds)
2. Assistance in walking (difficulty walking across a room)
3. Rise from a chair (difficulty to transfer from chair to bed)
4. Climbing stairs (difficulty to climb a flight of stairs)
5. Falls (number of falls in the last year)
Scores: answer none = 0, some difficulty = 1, unable = 2, no falls = 0, 1-3 falls = 1, ≥ 4 falls = 2. Score ≥ 4 indicates high risk of adverse outcomes from sarcopenia.

increased risk of cognitive decline, which will increase the risk of disability in instrumental ADL[21]. Frailty shares the cognitive dysfunction in the pathogenesis (such as increased oxidative stress and impaired repair) and risk factors (such as smoking, alcohol consumption, poor diet and low levels of physical activity)[22,23].

Also, frailty increases the risk of mortality in a dose-response manner independent of diabetes-related complications[24].

MANAGEMENT

Frailty and sarcopenia should be regularly screened for using validated tools as part of patient review[25,26] (Tables 4 and 5). An individualized approach for prevention and management based on the patient's functional level is recommended[27] (Table 6).

FIT PERSONS

In fit or pre-frail persons, the goals are to achieve tight metabolic targets, maintain function, and prevent deterioration into frailty. These patients are likely to be independent and living in the community.

Nutrition and exercise

Diabetes nutritional therapy may have a protective effect against the development of frailty[28]. There is a need for more protein intake, up to 20-30% of daily calories, to compensate for the diminished protein synthesis associated with old age[29]. The essential amino acid leucine promotes positive muscle protein balance and reduces sarcopenia[30]. Vitamin D supplementation increases muscle strength, especially in persons with vitamin D deficiency or those ≥ 65 years of age[31]. Exercise combined with adequate nutrition have synergistic effects compared to either alone. The combination of diet quality and physical activity was associated with maintenance of muscle strength in older Australian men (aged 67-84 years) with diabetes, but diet quality alone was not enough to preserve muscle strength when looked at in a secondary analysis of the longitudinal, observational NuAge study[32]. Adopting a healthy lifestyle of being physically active and achieving an ideal body mass index are associated with a lower risk of developing frailty[33].

Glycemic control

The role of tight glycemic control in the prevention of frailty or sarcopenia is less clear. Data from the Women's Health and Aging Study II has shown that uncontrolled diabetes (HbA1c ≥ 8.0%) was associated with the development of poor physical performance, low walking speed, and difficulty in walking compared to

Table 6. Management based on patient's functional level

	Fit	Frail	Disabled
Characteristics	Living in the community independently	Living in the community with some assistance	Fully dependent or living in care homes
Management	Adequate nutrition with high protein intake and resistance exercise training	Adequate nutrition with high protein intake and reasonable resistance exercise training	Adequate nutrition with high protein intake and resistance exercise training as tolerated
Glycemic control	Tight	Relaxed	Symptomatic
Target HbA1c	7.0-7.5% (53-59 mmol/mol)	7.5-8.5% (59-69 mmol/mol)	8.5-9.0% (69-75 mmol/mol) Short-term targets of RBG* > 4 <15 mmol/l is more relevant
Focus	Maintain independence	Maintain function	Maintain quality of life
Aim	To prevent deterioration into frailty	To prevent deterioration into disability	To prevent hospitalization

Fit: Patients living in the community independently; Frail: Patients living in the community with some assistance; Disabled: Patients fully dependent or living in care homes; RBG: random blood glucose.

tight glycemic control (HbA1c < 5.5 %)[34]. In the Korean Longitudinal Study of Health and Ageing, uncontrolled diabetes (HbA1c > 8.5%), rather than the presence of diabetes itself, was associated with poor muscle quality in older people with diabetes adjusted for age, body mass index, smoking, alcohol consumption, physical activity, and duration of diabetes[35]. Also, in the San Antonio Longitudinal Study of Aging, good glycemic control (HbA1c < 7%) was associated with better lower extremity performance compared to poor glycemic control (HbA1c > 7%)[36]. However, this has not been demonstrated in some other studies[37]. The occurrence of increased muscle mass or muscle atrophy depends on the balance between muscle protein synthesis and breakdown. Medications may have their beneficial or harmful effects on muscles through stimulation of anabolic or catabolic pathways respectively. Insulin sensitizers, through their anabolic effect, may have a beneficial effect in reducing sarcopenia and frailty. In a cohort study of 2,415 veterans with type 2 diabetes, mean (SD) age 73.7 (5.2) years, metformin was significantly associated with a decreased odds of frailty (OR: 0.66; 95% CI: 0.61-0.71; p < 0.0001) after a mean (SD) of 5.6 (2.3) years of follow up[38]. In another small observational study of 41 patients with type 2 diabetes, mean (SD) age 52.7 (10.4) years, metformin showed a significant reduction in total fat mass (–1.6 kg; p < 0.001) and a significant increase in the lean/fat ratio (0.1; p = 0.04), suggesting a favorable effect on body composition, which may have the potential to postpone the emergence of sarcopenia[39]. Glitazones, through insulin-sensitizing effects, and dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists, through improvement of muscular blood supply, may have beneficial effects on reducing the loss of lean muscle in older people with diabetes[40,41]. Sulfonylureas, especially glibenclamide, and glinides have been shown to induce muscle atrophy in humans[42]. In rat experiments, glimepiride, among sulfonylureas and repaglinide among glinides were the most potent atrophic agents[42]. Insulin increases protein synthesis in young adults, but not in older people, and to date there are no data on whether the new class of sodium-glucose co-transporter-2 inhibitors has any effects on muscle function[43].

Frail persons

Nutrition and exercise

Once frailty is established, the goals are to achieve relaxed metabolic targets, maintain function, and prevent deterioration into disability. These patients are

likely to be living in the community with some care assistance. Adequate nutrition and exercise intervention still have a positive role in this group of patients. Protein supplementation for frail older people in addition to reasonably tolerated resistance exercise training resulted in muscle hypertrophy, increase in muscle strength, muscle mass, and performance[44].

Glycemic control

For frail older people, a safer target of HbA1c around 59-69 mmol/mol (7.5-8.5%) is appropriate. The presence of multiple comorbidities is a potential competitor for the benefit of tighter glycemic control in this population. In a decision analysis to assess the effects of comorbid conditions and functional impairment, the expected benefits of tight glycemic control of HbA1c 53 vs. 63 mmol/mol (7.0 vs. 7.9%) declined steadily as the level of comorbidities and functional impairment increased[45]. De-intensification and simplification of hypoglycemic medications, especially switching multiple-dose insulin regimens to once-daily insulin with or without noninsulin agents, is appropriate without gross deterioration in glycemic control to reduce the risk of hypoglycemia[46].

Disabled persons

Nutrition and exercise

Once disability is established, the goals are to relieve symptoms and to maintain quality of life. These patients are likely to be fully dependent, resident in care homes, and have limited life expectancy. However, maintenance of adequate nutrition and exercise as tolerated is still beneficial. It has been shown that exercise appears feasible in care homes for residents between the age of 80 and 89 years and resulted in significant improvements in muscle strength and functional performance outcomes such as chair-to-stand time, stair climbing, gait speed, balance, and functional capacity[47] Adequate nutrition combined with exercise also has similar positive functional outcomes in care home residents[48].

Glycemic control

A target HbA1c of 69-75 mmol/mol (8.5-9.0%) is appropriate for this group of patients. Lower targets may be harmful by increasing the risk of hypoglycemia and reducing quality of life with no clear benefit. Also, higher HbA1c > 75 mmol/mol (> 9.0%) has been shown to be associated with increased mortality[49]. Targets in this population should focus on short-term day-to-day blood glucose levels to maintain a random blood glucose > 4 but < 15 mmol/l as values outside this range is likely to result in cognitive changes rather than a long-term HbA1c[50]. This is to avoid both hyperglycemia, which may lead to lethargy, dehydration, visual impairment, incontinence, and infections and hypoglycemia, which may lead to falls and confusion. De-intensification or even complete withdrawal of hypoglycemic medications should be considered, especially in those patients with significant weight loss, tight glycemic control, and recurrent hypoglycemia[51,52].

CONCLUSION

Diabetes increases the risk of disability that seems to be not fully explained by the diabetes-related complications or coexisting morbidities. Sarcopenia and frailty are emerging as new diabetes-related complications that are likely to play a key role in the pathway to disability. A multimodal intervention that includes nutrition, exercise, and glycemic control may help delay the progression to disability. An individualized approach for intervention that is based on the patient's functional level is recommended.

Key points

- Disability associated with diabetes is not fully explained by diabetes-related complications or coexisting morbidities.
- Diabetes promotes the pathogenesis of sarcopenia and frailty, which is likely to be the final mediator in the pathway to disability.
- An individualized multimodal intervention according to the patient's functional level is needed to prevent disability and to maintain function and quality of life.

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Management of type 2 diabetes in the elderly patient

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Abstract

Type 2 diabetes is a rising global problem; elderly patients have the highest prevalence and their management is complicated by the presence of comorbidities and age-related changes. When establishing a treatment regime for elderly individuals, concerns in terms of functional status, living arrangements, the presence of frailty, cognitive impairment, and risk of hypoglycemia must be considered before selecting specific treatments. Geriatric assessment must be sought to maximize the potential benefit of treatment. Glycemic targets must take into consideration the presence of comorbidities, life expectancy, and the risks associated with tight glycemic control. In general, HbA1c goals between 7.5-8.0% are regarded as appropriate for elderly individuals. Regardless, goals must be adjusted in relation to treatment response and expected complications. Diet therapy and physical activity are the cornerstone of treatments to improve glycemic control and maintain an adequate functional status; pharmacological first-line therapy includes the use of metformin, which carries a low risk of hypoglycemia and has been associated with improved outcomes. Consideration of combined therapy must be weighed against hypoglycemia and cardiovascular risk, expected adverse reactions, and potential benefits from more intensive treatment regimes. Cardiovascular risk management must be focused on hypertension management and lifestyle changes such as cessation of smoking and moderate weight loss; statin use must be individualized considering life expectancy, cognitive status, and the presence of frailty to improve benefits. (J Lat Am Geriat Med. 2017;3:26-36)

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CHALLENGES OF TYPE 2 DIABETES MELLITUS MANAGEMENT IN THE ELDERLY PATIENT

Type 2 diabetes mellitus (T2D) is a chronic, degenerative disease that represents a significant health burden worldwide, being especially relevant in elderly patients and affecting up to 20% of the population. The elderly patient with T2D belongs to a rather heterogeneous spectrum of disease presentation. This age group may include cases with early onset T2D patients that have long disease exposure and high susceptibility for the development of chronic complications, which increases the chance of dependence and complex management[1]. But also, T2D patients diagnosed at an older age, usually ≥ 70 years, have a low prevalence of microvascular complications and can reach glycemic targets with one or two antidiabetic agents. The complexity of management is increased by the interaction of T2D with comorbidities and geriatric syndromes, which increases the likelihood of poor management, additional diabetes-related complications, and preventable mortality[2]. Recent evidence suggests that the combination of geriatric syndromes

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and cardio metabolic conditions significantly impact functional and cognitive capacity, especially in elderly women[3]. The demonstration of the interaction of geriatric syndromes and T2D for the development of comorbidity, frailty, functional and cognitive dysfunction has not been extensively studied.

Even though the prevalence of frailty in elderly patients might be up to 25%, the inclusion of this population in randomized clinical trials has been inconsistent, making the availability of reliable clinical data rather scarce[4] on the development of geriatric complications such as urinary incontinence, falls, frailty, cognitive impairment, dementia, and functional dependence[5]. Furthermore, diabetes has been associated to an increased risk of disability in mobility, activities of daily living (ADL) and instrumented activities of daily living (IADL)[6]. The International Diabetes Federation (IDF) recommends initiating T2D management in elderly individuals considering functional status in three categories: functionally independent, functionally dependent, and end-of-life care. They further categorize functional dependence per the presence of frailty and/or dementia[7]. The recommended assessment requires a multidisciplinary approach to assess functional capabilities as well as medical and psychosocial comorbidities for the designation of treatment and rehabilitation plans, management of comorbidities, and requirements for long-term and end-of-life care[8]. Table 1 summarizes the primary evaluations and procedures required for a simplified assessment before initiating treatment.

Living arrangements and psychosocial support are important determinants of success in T2D management[4]; this is especially true for patients living in long-term care facilities. Functional dependence modifies self-care responsibilities and requirements for disease management in this population. Recommendations by the American Diabetes Association (ADA) suggest that this population receive more simplified treatment regimes, liberal diet plans, implementation of physical activity and exercise, and avoidance of sliding scale insulin regimes. Specific comments on these strategies will be discussed in later sections.

Elderly patients with T2D and hypoglycemic medications are at a higher risk of developing complications that are implicit to this treatment[9]. Older patients with frailty are at an increased risk of falls and disability, and this is especially true for individuals with comorbid T2D[9] in whom sarcopenia or muscle mass loss occurs at higher rates because of increased catabolism. A higher rate of falls in T2D patients has been associated to the occurrence of frailty, cognitive impairment and, most importantly, to the rate of hypoglycemia in elderly individuals[10]. Further, the occurrence of chronic diseases associated with protein malnutrition, muscle wasting, and frailty have directed to resolution of hyperglycemia and normalization of HbA1c levels, leading to the coining of the term "burnt-out diabetes"; frailty has also been associated to increased insulin resistance in obese frail individuals[11]. The effect of frailty must be considered when establishing a plan for T2D management in elderly populations[8,11].

Hypoglycemia risk is an important challenge that must be addressed in elderly individuals with T2D for management implementation[7,8]. Hypoglycemia increases the risk of morbidity, mortality, frailty, and disability, leading to impaired quality of life in elderly individuals with T2D[9]. In the elderly, autonomic dysfunction may lead to decreased recognition of hypoglycemic events, thus increasing the risk of severe hypoglycemic episodes that require hospitalization, which might lead to increased cognitive and physical dysfunction[11,12]. The interplay between hypoglycemia, polypharmacy, frailty, and dementia in elderly individuals further complicates management; frail patients with tight glycemic control as indicated by decreased HbA1c levels or with medications that increase hypoglycemia risk (long-acting sulfonylureas and complex insulin regimes) tend to have an increased risk of hypoglycemic events, especially at the onset of consistent weight loss[13]. Furthermore, the rate of occurrence of hypoglycemic events has been linked to an increased risk of developing dementia, falls, and frailty[10-14]. The consideration of treatment goals and minimizing exposure to hypoglycemia-inducing medications is an important consideration for control and prognosis of T2D individuals and must be individualized for every patient.

TREATMENT GOALS

Elderly patients with T2D have a higher rate of vascular complications, including heart failure and coronary artery disease[15]. In patients with long disease exposure (> 10 years) the rate of microvascular complications exceeds the rate of cerebrovascular disease, especially in the case of diabetic eye disorders[9]. The role of glycemic control has been extensively studied for young adults, and large trials have been conducted comparing standard versus intensive glycemic targets. Nevertheless, evidence from the largest trials, including the UK Prospective Diabetes Study (UKPDS), the Action to Control Cardiovascular Risk in Diabetes

Table 1. Interventions and procedures for geriatric assessment before treatment initiation

Assessment	Tools and procedures	Relevance
Physical performance	SPPB and IDOP 3-step package	Assessment of balance and gait speed (both), as well as gait power (SPPB) which is impaired in frail patients
IADL	Lawton index, Barthel IADL index	Diabetes increases risk of disability and IADL impairment
ADL	Katz index, Barthel ADL index	Screening methods for assessment of complex regime implementation
Cognition	Mini-Mental State Examination, Montreal Cognitive Assessment, MiniCog	MiniCog is more specific for elderly with T2D, all are screening and non-diagnostic
Depressive symptoms	Geriatric Depression Scale - GDS	Depression is a common comorbidity in T2D patients and increases the risk of cognitive impairment
Frailty	Fried Frailty Phenotype	Diabetes increases the risk of frailty and the development of complications and premature mortality
Nutrition	Mini-Nutritional Assessment - MNA	Designing nutritional interventions and identifying patients at risk of malnourishment
Quality of Life (QoL)	Audit of Diabetes Dependent Quality of Life Senior - ADDQoL Senior, SF-36 questionnaire	Validated for older people with diabetes Validated in nursing homes; SF-36 evaluates quality of life in 8 domains
Cardiovascular risk assessment	Globorisk score[1]	Cardiovascular risk assessment might be relevant for prevention of complications and further functional impairment

ADL: activities of daily living; IADL: instrumented activities of daily living; SPPB: Short Physical Performance Battery.
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(ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) have included a low proportion of elderly patients with ages ranging from 53 to 66 years, with most including less than 2% of adults aged ≥ 80 years[16]. Most trials have excluded elderly populations due to the high rate of hypoglycemia with intensive glycemic targets (HbA1c < 7%), which makes the application of major trial results a challenge.

In setting a target goal for T2D management in elderly patients, an estimation of benefits in terms of hyperglycemia management and prevention of micro and macrovascular complications must be contrasted to the risk of treatment complications[8]. In terms of available data, there is no evidence for increased protection against major cardiovascular events for intensive glycemic control in the first 10 years of treatment[17,18]; additionally, the ACCORD trial showed increased mortality in the group of intensive glycemic control[19]. Reduction of microvascular complications have mostly been reported for the UKPDS trial, which included a younger population and showed benefits mostly after 8-15 years of intensive glycemic control[20]. However, harms of intensive glycemic control have been reported in all four major studies, showing an increased risk of hypoglycemia and an associated increase of decline in cognitive function[21]; age, longer disease exposure, polypharmacy, and cognitive impairment put elderly individuals at a higher risk of hypoglycemic episodes.

Glycemic goals for elderly individuals have not shown benefits for HbA1c levels ≤ 7.5%. Nevertheless, consensus data[22] show that HbA1c levels > 9% lead

to increasing rates of polyuria, fatigue, and cognitive impairment. Therefore, HbA1c range levels for optimal treatment are between 7.5-8.0% and must be adjusted based on perceived patient preferences[10], including burden of treatment (especially insulin injections), continuous glucose monitoring, life expectancy, and associated complications associated to disease exposure. When exploring factors that influence glycemic target decisions, one study showed that more intensive control targets were associated with higher baseline HbA1c levels, weight, and male physicians; glycemic target goals had an average HbA1c of 7.0%[23]. In general, disease duration, age, and polypharmacy did not affect glycemic target decisions; once the HbA1c targets have been reached, treatment de-intensification must be considered per patient's preferences and clinical assessment[24].

TREATMENT CHOICE

Diet and exercise

Elderly patients with T2D are at an increased risk of developing malnutrition[25]. In older patients, both community-dwelling and those living in long-term care facilities, a body mass index (BMI) level in the underweight category has been associated with increased mortality[26]. However, changes in body composition with aging modify the predictor capacity of frailty in elderly patients[27]. In addition, malnutrition has been associated to adverse outcomes, including pressure ulcers, delirium, depression, decreased bone mineral density, and frailty[28]. Therefore, evaluation of patients at higher risk using screening tools and biochemical assessment might be necessary before establishing a dietary lifestyle intervention[8]. Weight reduction must be gradual, especially because weight loss in overweight and obese patients can result in nutritional deficits and decreased mineral bone density. A combined approach of physical activity adjusted for functional status along with nutritional therapy with consistent carbohydrate amounts to prevent hypoglycemia and protein intake adapted to frailty status must be individualized per patient's needs[8,28]. This intervention improves functional status, psychological and cognitive function, and glycemic control[8].

SPECIFIC ANTIDIABETIC AGENTS

Pharmacological therapy in the elderly patient with diabetes must be managed in accordance with the presence of comorbidity; pharmacokinetic modifications associated with ageing and the presence of polypharmacy must be considered when prescribing for this age group. In general, high quality evidence studies that evaluate glycemic treatment in older adults, especially those over 80 years of age, are lacking. Therefore, most data are based on small-scale sub-analyses of patients included in larger studies within the required age range.

Metformin is regarded as the first-line therapy for the management of elderly patients with T2D[8,29]. However, when HbA1c levels are not achieved, the second-line agent is not well-established. Table 2 outlines the main pharmacological options for the management of T2D in older adults.

Metformin

Most guidelines recommend metformin as first-line therapy for the treatment of T2D in elderly patients[4,7,29]. When compared to other oral glucose-lowering agents, metformin has a low risk for hypoglycemia and generally has a favorable safety profile; the concomitant use of sulfonylureas and metformin[30] might lead to an increased risk of hypoglycemia compared to monotherapy, and this has also been shown for other medications. The use of metformin as monotherapy leads to a decrease in 0.5-1.0% of HbA1c levels and increases insulin sensitivity whilst promoting weight loss[10].

Two randomized clinical trials (RCT), the ADOPT[31] (A Diabetes Outcome Progression Trial) and the SPREAD-DIMCAD[32] (Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease) trials showed a reduction in cardiovascular mortality associated with metformin use in comparison to sulfonylureas, which has also been observed in a few observational studies[29]. However, follow-up in these studies has been short and the reduction in cardiovascular outcomes has been modest; furthermore, meta-analyses have shown inconsistent results[33]. Thus, results on the effect of metformin on cardiovascular mortality must be interpreted with caution.

A relevant safety concern for the use of metformin in elderly patients is its use in patients with impaired kidney function. The safety concern was based on early pharmacokinetic studies, which showed that patients with severely impaired kidney function had an increased risk of lactic acidosis. In elderly patients, estimation of renal function based on serum creatinine measurements might be incorrect and result in overestimation of kidney

Table 2. Pharmacological options for management of type-2 diabetes in the elderly

Medication group	Glycemic control	Adverse effects and safety concerns	Potential benefits
Biguanide (metformin)	1-2% reduction in HbA1c	Risk of lactic acidosis eGFR must be measured for all patients taking this medication Consider dose adjustment for patients < 45 ml/min/1.73 m^2; do not use for eGFR < 30 ml/min/1.73 m^2 or in decompensated heart failure Functional and frailty status must be considered because of unintentional weight loss Gastrointestinal adverse effects	Reduced cardiovascular events and mortality Not associated with weight gain or hypoglycemia First-line therapy for patients without impaired renal function
Sulfonylureas (glipizide, gliclazide)	1-2% reduction in HbA1c	Risk of hypoglycemia and weight gain; combination with metformin increased hypoglycemia risk Avoid long-acting sulfonylureas due to increased risk of hypoglycemia (glyburide)	Cardiovascular benefit has not been consistently shown
Glinides (repaglinide, nateglinide)	0.4-0.9% reduction in HbA1c	Risk of hypoglycemia and associated weight gain Nateglinide must be avoided in patients with renal failure	Shorter half-life when compared to sulfonylureas Might be useful in patients with bad eating habits with frailty or dementia
Thiazolidinediones (pioglitazone)	1-2% reduction in HbA1c	Fluid retention, weight gain, increased risk of heart failure Increased fracture risk	Increased risk of heart failure and myocardial infarction (the latter for rosiglitazone)
A-glucosidase inhibitors (acarbose)	0.4-0.9% reduction in HbA1c	Gastrointestinal adverse events	Reduction of cardiovascular events in patients with carbohydrate intolerance Reduction of postprandial hyperglycemia
GLP-1 agonists (exenatide, liraglutide)	1% reduction in HbA1c	Gastrointestinal adverse events (can be minimized with gradual dose increase), unintentional weight loss (should be avoided in frail patients)	Low risk of hypoglycemia; reduces fasting and postprandial hypoglycemia Uncertain risk of acute pancreatitis
DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin)	0.5-0.8% reduction in HbA1c	Uncertain risk of acute pancreatitis and joint pain	Neutral effects on major cardiovascular events, risk of heart failure still not clear
SGLT2 inhibitors	0.5-0.7%	Weight loss, blood pressure lowering, vulvovaginal candidiasis and urinary tract infection Avoid for eGFR < 60 ml/min/1.73 m^2 Risk of euglycemic diabetic ketoacidosis	Reduction in rates or cardiovascular events and mortality Ameliorates progression of kidney disease
Insulin	Variable	Risk of hypoglycemia and weight gain Requires self-monitoring, especially prandial insulin regimes Might not be the best choice for patients with frailty or dementia	Long-acting insulin can be a safer choice in combination with oral glucose-lowering agents

DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; SGLT2: sodium-glucose co-transporter type 2.

Adapted from: Sinclair A, Dunning T, Colagiuri S. Managing older people with type 2 diabetes: global guideline. International Diabetes Federation 2013. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the Aging Patient: A Review of Glycemic Control in Older Adults With Type 2 Diabetes. JAMA. 2016;315:1034-45. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med. 2016;164:740-51.

dysfunction. Instead, the use of estimated glomerular filtration rate (eGFR) must be encouraged for decision making[34]. Current guidelines recommend caution and frequent monitoring when implementing metformin treatment in patients with eGFR < 60 ml/min/1.73 m^2 and it is contraindicated for eGFR < 30 ml/min/1.73 m^2. Nevertheless, evaluation of kidney function must be sought in every elderly patient prior to metformin initiation and must be evaluated in every consult, given the possibility of decreased kidney function in this population[7]. Furthermore, recent observational data has suggested that historical contraindications of metformin use, such as chronic kidney disease (CKD), congestive heart failure (CHF), and chronic liver disease (CLD) might benefit with the use of metformin[35] and has had changes approved by the Food and Drug Administration (FDA)[36] for CHF and CKD. Given that elderly patients usually have additional comorbidities associated with T2D, metformin use in individuals with CKD, CHF, and CLD must be individualized to maximize the potential clinical benefit.

Adverse effects of metformin use include gastrointestinal effects and unintended weight loss (usually associated with side effects). This latter effect might be significant for patients at higher risk of complications such as individuals with frailty syndrome[7,29]. Nevertheless, there has been some data regarding a possible protective effect of metformin on the development of frailty and frailty-associated complications. However, in a cohort study of 2,415 elderly individuals with T2D, metformin compared with sulfonylurea was associated with a 30% decreased risk of mortality among those without any frailty-related diagnoses, but was not significantly associated with decreased risk of mortality among those with frailty-related markers. Clinical trials evaluating the effect of metformin on pre-frail individuals and on the progression and prevention of frailty are currently ongoing and pending preliminary results[11,37,38]. Metformin has also been linked to vitamin B12 deficiency in several studies; a recent meta-analysis demonstrated that metformin use decreased vitamin B12 levels by 57 pmol/l, which might lead to a deficiency status in patients with T2D[39]. The decrease in vitamin B12 levels has been shown to be more important for at-risk populations including elderly individuals; susceptibility for vitamin B12 testing included comorbidities and chronic microvascular complications, but was not consistently done in elderly patients[40].

Sulfonylureas and glinides

Sulfonylureas and glinides are a reasonable first-line therapy when metformin use is contraindicated or if the patient cannot tolerate the adverse events from metformin use[7,29]. The risk of hypoglycemia and increased weight gain associated with the use of both pharmacological classes limits the use of these medications in elderly populations. Initial monotherapy with sulfonylureas is not supported by current evidence[41]. The American Geriatrics Society recommends against the use of long-acting sulfonylureas (glyburide) in elderly patients because of an increased risk of hypoglycemia[42]. The World Health Organization (WHO) recommended that gliclazide should be considered as the preferred sulfonylurea in elderly patients, with glimepiride and glipizide as acceptable alternatives; these recommendations were supported by the ADVANCE study, which showed no increase in weight gain and low rates of hypoglycemia for gliclazide[43].

Glinides have a shorter half-life (60-90 minutes) when compared to sulfonylureas. Both repaglinide and nateglinide should be taken before meals and can be skipped in patients with frailty and dementia and irregular eating habits; they usually have a lower rate of hypoglycemia[7]. Nateglinide should be avoided in patients with severe kidney failure[10].

Dipeptidyl peptidase-4 inhibitors

The safety profile of dipeptidyl peptidase-4 (DPP-4) inhibitors makes them a feasible and tolerable option for use in the elderly[44]. Because there is decreased incretin inactivation and its action is glucose-dependent, risk of hypoglycemia is minimized in the elderly[45]. The evidence of DPP-4 inhibitors in the elderly has mostly been shown in subgroup analyses of large clinical trials; of the approved molecules, vildagliptin and linagliptin have shown greater evidence of safety and efficacy in patients > 75 years of age[46,47]. However, comparisons have mainly been assessed against placebo and not against another approved monotherapy[48].

Safety concerns on DPP-4 inhibitors included conflicting reports on an increased fracture risk and increased risk of heart failure or hospitalization due to hear failure. Two recent meta-analyses evaluated the available evidence on the incidence of fracture risk and determined that the use of DPP-A inhibitors does not modify bone fracture risk in comparison to placebo or other antidiabetic medications[49,50]. The risk of heart

failure progression or hospitalization due to heart failure is a concern that has limited the use of these agents in high-risk patients. However, meta-analyses of this safety issue have shown mixed results with mostly marginal, non-significant increases in heart failure risk, especially with saxagliptin[51,52]. The use of DPP-4 inhibitors is attractive in the elderly, remaining an alternative treatment to metformin or as an add-on therapy to reach glycemic goals; potential neuroprotective benefits are being evaluated for its effect on cognition[53].

Alpha-glucosidase inhibitors

Acarbose is an alpha-glucosidase inhibitor that reduces intestinal absorption of glucose; it has mainly been used to treat postprandial hyperglycemia and carries a low risk of hypoglycemia in elderly populations[54]. Acarbose has recently been studied for its effect on postprandial hypotension, which is a phenomenon that increases the risk of falls, mortality, and cardiovascular adverse outcomes in elderly patients[55]. Acarbose has been shown to attenuate the decrease in postprandial systolic pressure, syncope, falls, dizziness, and weakness by reducing splanchnic gastrointestinal circulation[56]. Its safety profile has made it an adequate alternative first-line treatment for patients who do not tolerate metformin treatment or who have failed glycemic goals with metformin alone; gastrointestinal side effects might contribute to discontinuation, but this has not been consistent across trials and they are usually present at higher dosages[57]. Some studies have suggested a potential cardiovascular benefit, but mostly on combinations with other protective measures[58].

Glucagon-like peptide-1 agonists

Data on the use of glucagon-like peptide-1 (GLP-1) receptor agonists has been scarce in elderly patients, but generally showed an efficacy and safety profile similar compared to younger populations[7]. A recent study showed that lixisenatide has a pharmacokinetic, efficacy, and safety profile that suggests it is useful in elderly patients[59]. However, attention must be paid in differentiating effects of short-acting (exenatide) and long-acting GLP-1 agonists. Glycemic targets are more easily reached with long-acting GLP-1 agonists, and vomiting and nausea are less compared to short-acting agents[60,61].

Gastrointestinal side effects are significant with GLP-1 agonists[62], but are mostly seen in early use and have been shown to decrease with gradually increasing dosages[63]. The GLP-1 agonists, especially liraglutide, have been associated with moderate weight reduction and low-risk hypoglycemia[64]. However, evidence of its efficacy and safety in elderly obese individuals has not been studied; weight loss might be a cause of concern in frail individuals[7,8].

SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITORS

Inhibition of sodium-glucose co-transporter-2 (SGLT2) causes glycosuria dependent on blood glucose levels and glomerular filtration rates. It is therefore contraindicated in patients with impaired glomerular function, which may limit its use in elderly populations[65]. Data on canagliflozin suggests that there is a significant but non-sustained decrease in body weight and systolic blood pressure, which has been consistent with data found in younger populations[66]. Side effects of SGLT2 inhibitors limits their applicability in elderly patients, given reports of increased urinary frequency, vulvovaginal mycotic infections, urinary tract infections, postural hypotension, dehydration, and falls, which might discourage their prescription in this population[58].

Recent data from the EMPA-REG study suggested that empagliflozin might have cardiovascular benefits, especially in the setting of heart failure, signaling a role for its use in high-risk elderly patients[67]. In addition, a follow-up report on this study reported a decrease in the rate of progression of kidney disease in patients at high cardiovascular risk[68]. However, these studies did not include an older population and its efficacy in cardiovascular risk reduction was marginal. Outcome data for elderly populations at high risk must be evaluated in longitudinal studies to investigate the potential cardiovascular benefit of SGLT2 inhibitors.

Thiazolidinediones

Thiazolidinediones carry a low risk of hypoglycemia. However, their side effect profile makes them a poor candidate for treating T2D in elderly patients[7]. Studies showing an increased risk of fractures in women above and below 50 years and in males above 50 years have been consistently reported for both rosiglitazone and pioglitazone[69,70]. Furthermore, there is an increased risk of heart failure and risk of worsening in patients with established heart failure

reported for thiazolidinediones as well as increased cardiovascular mortality for rosiglitazone, which limits their prescription for high-risk patients[71,72]. Besides additional side effects, including weight gain, fluid retention and edema, the ACCORD-MIND trial suggested a potential effect of thiazolidinediones on cognitive decline, which might be detrimental given the increased risk of cognitive impairment in elderly individuals with diabetes[73]. Therefore, prescription of these drugs must be individualized and considered only in selected cases.

Insulin treatment

In elderly patients, management of hyperglycemia has differential benefits in terms of adequately controlled basal and postprandial glucose levels[74]. The various presentations of insulin must therefore be individualized per the patient's context. Simple regimen insulin levels have shown benefit in both glycemic control and reducing the rate of hypoglycemia; the use of rapid insulin analogs has also been a matter of concern, and they are generally less prescribed in this population in comparison to long-acting insulin, which has been related to lower hypoglycemic nighttime events[75,76]. The device used for administration has been scrutinized in some studies, suggesting that vial and syringe methods yield lower treatment persistence and decreased adherence as well as lower hypoglycemic episodes compared to pen initiators, with no difference between insulin-naive and non-naive patients[77]. Nevertheless, most trials have small sample sizes and have inadequate methodological quality, which impairs the ability to make specific recommendations.

Another issue to take into consideration when initiating insulin management in elderly patients is their functional level and dependence on IADL and ADL. For individuals in long-term care facilities, the use of oral agents or basal insulin was evaluated in one RTC, showing that there were no differences in glycemic control, rate of hypoglycemia, and number of complications, emergency room visits, and mortality[78]. For community-dwelling individuals, insulin glargine or determir as a basal insulin regime has been shown in prospective RCTs to achieve adequate glycemic control and reduced daytime hypoglycemia rates compared to thiazolidinediones, insulin lispro and normal pressure hydrocephalus and lifestyle/dietary measures[79] and in addition to concomitant oral antidiabetic drugs[80]. The comparison of adjuvant oral antidiabetic agents and insulin treatment as monotherapy has shown significant clinical improvement in glycemic control, whilst reducing insulin requirements. Combinations with sulfonylureas should be avoided, given the increase in hypoglycemic events, and combinations with metformin diminish weight gain with no increase in adverse events[81]. Therefore, insulin treatment should be considered in elderly patients as a second- or third-line treatment to achieve glycemic goals, especially in undernourished subjects. Regimes should mostly consist of basal insulin combined with metformin unless it is not well tolerated; prandial insulin results in a higher rate of hypoglycemia and prescription errors compared to long-acting basal insulin regimes[7].

CARDIOVASCULAR RISK MANAGEMENT

Cardiovascular disease is the most prevalent cause of mortality in elderly T2D patients. Smoking discontinuation and treatment with low-dose aspirin should be considered in elderly individuals according to life expectancy. These interventions have a greater benefit/risk ratio in this age group and should thus be considered for prevention of cardiovascular disease[28]. Hypertension plays a significant role in this association with cardiovascular mortality, contributing to 75% of specific complications[82]. Antihypertensive medications have been associated with a reduced cardiovascular morbidity and reduced incidence of stroke and heart failure, without a significant impact on mortality. Consensus has been reached on a target blood pressure (BP) goal of 140/90 mmHg; no significant benefit has been seen with lower blood pressure targets and there have even been reports of increased mortality for BP < 115/65 mmHg[83]. Lifestyle intervention is based on decreased sodium impact and it generally has a minimal impact on BP control. The drug of choice for elderly patients with T2D with hypertension and/or albuminuria is either an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-II receptor blocker (ARB)[84]; both have shown benefit on decreasing the risk of major cardiovascular events and reduction in the progression of kidney disease[7,85]. Add-on therapies include combinations with thiazide diuretics, beta-blockers, and calcium channel blockers; however, benefit is inferior with those therapies compared to ACEI/ARB.

The use of statins for secondary prevention of cardiovascular disease in elderly patients remains an

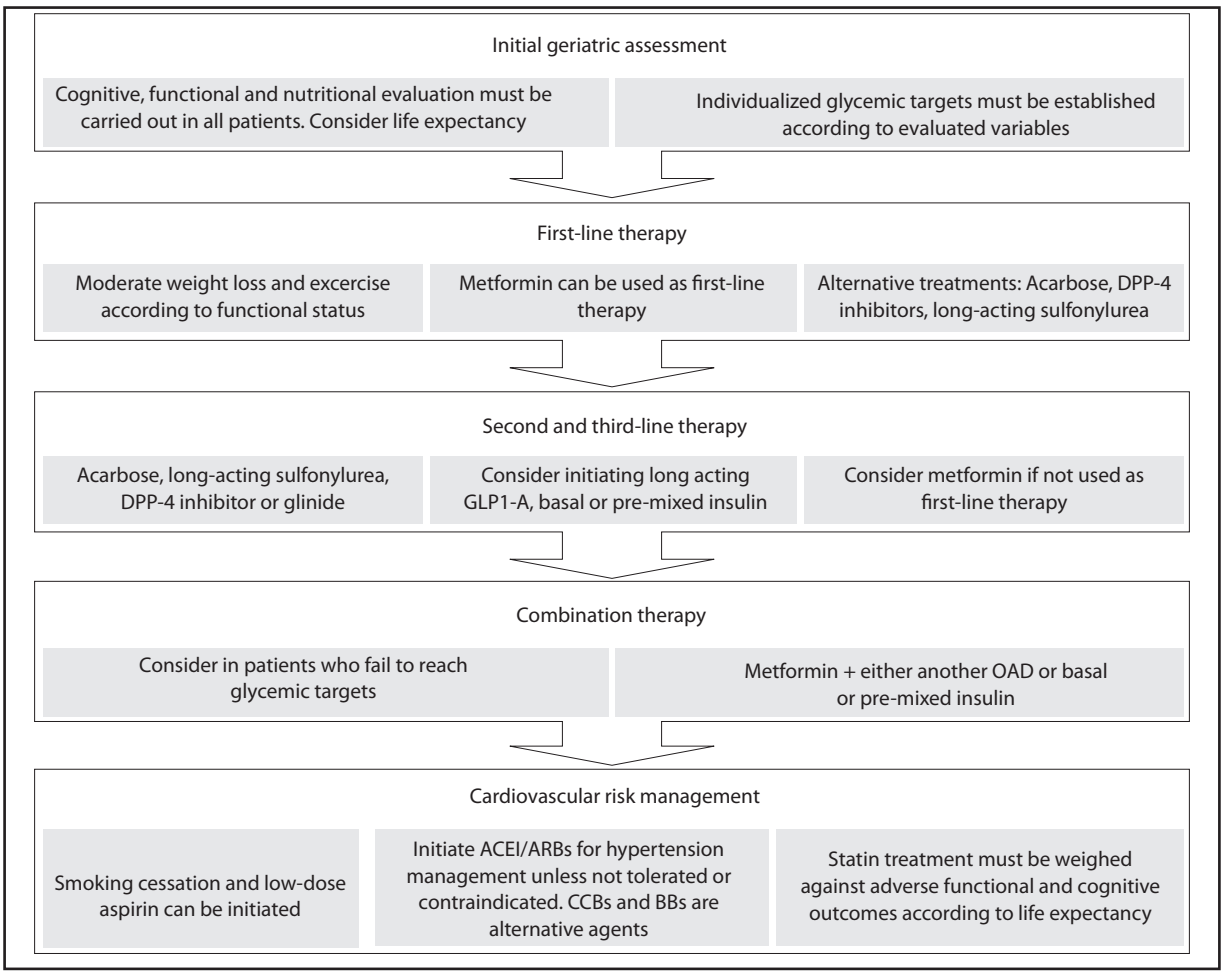

Figure 1. *Proposed algorithm for type-2 diabetes management in elderly individuals.*
ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; BB: beta blocker; CCB: calcium channel blocker; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; OAD: oral antidiabetic drug.

issue of controversy; some epidemiological data suggest that the relative risk of coronary heart disease associated with high cholesterol decreases with age[86] and that there is an inverse relationship between stroke incidence and cholesterol levels[87]. Therefore, benefits of statin treatment in individuals aged 75 and over requires clinical judgment.

High-intensity statins in the elderly carry an increased risk of adverse events, especially in individuals with frailty and sarcopenia in whom myalgia and myositis are more frequent[88]. Data on the effect of statins and cognitive outcomes has been inconsistent, with one study reporting increased cognitive improvement in patients with established dementia after statin discontinuation[89] and pooled analyses reporting no association[90]. Statin prescription should therefore weigh potential benefits and harms of therapy, and consider life expectancy, low-density lipoprotein cholesterol levels, functional and cognitive status, as well as cardiovascular risk to make informed decisions and maximize treatment benefits[7].

CONCLUSIONS AND PERSPECTIVES

Management of T2D in elderly patients is complex and requires a full evaluation of comorbidities, geriatric syndromes, and socioeconomic background to improve prescription and minimize the effect of adverse events. Glycemic goals should not be stringent and must be based on life expectancy and functional and cognitive status and must adjust to the living arrangements of elderly individuals. Intensive glucose control has been associated with adverse outcomes and should not be used routinely. Randomized controlled trials comparing oral antidiabetic medications are scarce and generally have low methodological

quality; thus, clinical judgment is required for adequate prescription.

In an elderly patient with newly diagnosed T2D it is reasonable to start with lifestyle intervention strategies along with metformin treatment as first-line therapy to reach glycemic goals. Alternatives include DPP-4 inhibitors, acarbose, and long-acting sulfonylureas of glinides, though the latter two must be evaluated in terms of independence and cognitive function. In general, most oral antidiabetic medications are well tolerated in elderly patients; however, thiazolidinediones, short-acting sulfonylureas, and SGLT2 inhibitors should not be routinely prescribed and only be used in very specific settings. Combined therapy should be considered in patients who cannot reach glycemic goals with metformin or in whom the first-line therapy was not well tolerated; insulin regimes must be simple and mostly based on basal insulin. Figure 1 resumes a proposed algorithm for T2D management in elderly individuals.

High-quality RCTs are required to analyze the efficacy and safety of oral antidiabetic medications against metformin, and combinations should be further evaluated for hypoglycemia risk and adverse event rates. Specific evaluations in patients with frailty, cognitive impairment, and comorbidities must be carried out, and long-term follow-up is especially required to evaluate the risks and benefits of cardiovascular risk management in this population. This creates an area of opportunity for future research and calls for evaluation of current practices in the management of T2D in elderly individuals.

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THE JOURNAL OF LATIN AMERICAN GERIATRIC MEDICINE REVIEW ARTICLE

Hypertension in the elderly with diabetes: Where is the evidence and what should be the targets?

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Abstract

Hypertension is frequently present in the elderly, especially in the presence of type 2 diabetes mellitus. The 2009 Canadian Hypertension Education program mentioned that the target for blood pressure control should be < 130/80 mm Hg in presence of diabetes mellitus without specifications on age limits. This paper will review the major clinical studies on treatment of hypertension in the elderly and in patients with diabetes mellitus to verify what the evidence is. Targets for blood pressure treatment will then be discussed, depending on the clinical condition of elderly patients with diabetes mellitus. (J Lat Am Geriat Med. 2017;3:37-9)

Key words: Hypertension. Elderly. Diabetes. Targets hypertension. Diabetes. Elderly.

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INTRODUCTION

Hypertension is frequent in patients with diabetes mellitus (DM), either type 1 or type 2. The pathogenesis is complex and involves genetic and environmental factors such as salt intake and low physical activity associated with endothelial dysfunction[1]. Hypertension and diabetes are associated with an increased mortality rate compared to non-hypertensive patients. In consequence, clinicians often prescribe one or more antihypertensive drugs to their elderly patients to prevent cardiovascular events. The clinical studies on the effect of hypertension treatment on cardiovascular events have shown contradictory results or have not reached the target of < 130/80 mm Hg mentioned in treatment guidelines. The 2009 Canadian Hypertension Education Program (CHEP) recommendations mention that in presence of DM, blood pressure (BP) should be < 130/80 mm Hg without age specification[2]. The 2016 CHEP guidelines also mentions a BP target of < 130/80 mm Hg, but also remarks that caution should be exercised in patients who might poorly tolerate a substantial drop in BP, as in the elderly[3]. This paper will review the major studies that influenced our approach to the treatment of hypertension in the elderly and will focus on adapted recommendations in this population.

HYPERTENSION IN THE ELDERLY: CONTRIBUTION OF HYPERTENSION IN THE VERY ELDERLY TRIAL AND SPRINT

The Hypertension in the Very Elderly Trial (HYVET) enrolled 3,645 subjects ≥ 80 years old with sustained systolic BP > 160 who were randomized to receive

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either indapamide 1.5 mg daily or matching placebo[4]. Perindopril 2 or 4 mg daily or matching placebo was added if necessary to lower BP. At two years, the average BP in the treated group decreased from 173/91 mm Hg (seated position) to 147/78 mm Hg. Active treatment was associated with a 30% decrease in fatal and nonfatal stroke, 39% reduction in the rate of death from stroke, 21% decrease in death from any cause, 23% decrease in death from cardiovascular causes, and a 64% decrease in the rate of heart failure. The study included 6.9% of diabetic subjects, which represents a lower prevalence than anticipated in the average elderly population.

More recently, the Systolic Blood Pressure Intervention Trial (SPRINT) randomly assigned 9,361 subjects with a systolic BP ≥ 130 mm Hg with increased cardiovascular risk to a BP target of < 120 mm Hg (intensive treatment) or < 140 mm Hg (standard treatment)[5]. After a median follow-up of 3.3 years, a significant decrease of primary composite cardiovascular outcome was observed in the intensive treatment group, and a significant diminution of all-cause mortality in the same group. Rates of serious adverse events (hypotension, syncope, electrolyte abnormalities, acute kidney injury or failure) were higher in the intensive group. The objective of the SPRINT studies was the enrollment of 28.2% of subjects ≥ 75 years old and clinical benefit was observed in all age groups. The SPRINT study excluded diabetic subjects, patients in institutions, and subjects with an estimated glomerular filtration rate < 20 ml/min/1.73 m^2.

The HYVET and SPRINT studies demonstrated the clinical benefit of treating hypertension in the population > 75 years old up to a systolic BP < 120 mm Hg in SPRINT, but the low prevalence or exclusion of diabetes makes the result of these studies only partly applicable to this specific population.

DIABETIC HYPERTENSION STUDIES: ADVANCE AND ACCORD

In 2008, two major blood glucose and hypertension control studies were published.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) randomly assigned 4,733 patients with type 2 DM to intensive BP lowering therapy, targeting a systolic BP < 120 mm Hg, or standard therapy, targeting a systolic BP < 140 mm Hg[6]. The mean follow-up was 4.7 years. No significant differences were observed for primary outcome (composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). A diminution in strokes (pre-specified secondary outcome) was observed in the intensive BP treatment group ($p = 0.01$). Serious adverse events attributed to antihypertensive treatment occurred more frequently in the intensive therapy group (3.3 vs. 1.3% in the standard treatment group; $p < 0.001$). The mean age of the participants at baseline was 62.2 years.

The study Action in Diabetes and Vascular disease: preterAx and Diamicron-MR Controlled Evaluation (ADVANCE) randomized 11,140 patients with type 2 DM to a fixed combination of perindopril-indapamide or placebo, regardless of their BP at entry[7]. After a mean follow up of 4.3 years, the systolic BP of patients assigned to the active treatment arm was 134.7 mm Hg and the BP in the placebo group was 140.3 mm Hg (difference of 5.6 mm Hg). The mean diastolic BP in the active treatment group was 74.8 mm Hg and in the placebo group 77.0 mm Hg (difference of 2.2 mm Hg). The relative risk of death from cardiovascular cause was reduced by 18% ($p = 0.03$). The mean age of participants at baseline was 66 years. A subsequent publication observed that benefit was present in all ages, including participants ≥ 75 years old[8].

In summary, the ACCORD and ADVANCE studies documented that a target BP around 135 mm Hg is beneficial across different age ranges in the diabetic population, but a BP target of < 120 mm Hg showed benefits only in secondary outcomes.

DIABETES AND HYPERTENSION STUDIES IN THE ELDERLY: THE SHEP AND SYST-EUR TRIALS

Two randomized studies specifically looked at hypertension in the elderly with DM.

The Systolic Hypertension in the Elderly Program (SHEP) randomized 4,736 patients ≥ 60 years old to receive an active treatment including a possible combination of diuretic, atenolol, and reserpine versus placebo. A substudy was done in the 583 patients who initially were diagnosed as having type 2 DM[9]. In the diabetic population, the active treatment group had an initial systolic BP of 170 mm Hg and a subsequent diminution of 9.8 mm Hg on five-year follow-up. The active treatment group showed a 34% diminution for major cardiovascular events compared to placebo.

The Systolic Hypertension in Europe (Syst-Eur) trial randomized 4,695 patients with systolic hypertension to receive nitrendipine or placebo. A total of 492 patients were initially diagnosed as having type 2 DM[10]. In this subgroup and after a median follow-up of two

years, the BP in the active treatment group went down from 175.3 mm Hg to 161.8 mm Hg. This group showed a significant reduction in overall mortality and mortality from cardiovascular causes compared to the placebo group.

WHAT ABOUT LOW OR DECLINING SYSTOLIC AND DIASTOLIC BLOOD PRESSURE?

In a recent study, we documented that after a mean follow up of eight years, elderly diabetic patients who initially had a creatinine ≥ 84 micromol/liter, an office systolic BP ≤ 130 mm Hg and a diastolic BP ≤ 67 mm Hg on the ambulatory blood pressure monitoring had a significantly increased risk of cardiovascular mortality[11]. Moreover, a more rapidly declining systolic or diastolic BP has been associated with an increased mortality risk in a cohort of elderly patients with type 2 DM[12]. The concept of J curve mortality has also been observed in the International Verapamil-Trandolapril Study (INVEST)[13]. When decreasing systolic BP to target levels in patients with established coronary artery disease (especially if isolated systolic hypertension is present), be cautious when the diastolic BP is < 60 mm Hg because of concerns that myocardial ischemia might be exacerbated[3]. A recent meta-analysis suggested that in a general population with type 2 diabetes, a systolic BP of < 140 mm Hg is associated with an increased cardiovascular mortality risk[14].

CONCLUSION

Hypertension is a very frequent medical condition in the elderly with type 2 DM. Target treatment for systolic BP is probably around 135-150 mm Hg. The benefits of additional BP lowering in this population are not clear, and the incidence of adverse events increases with the augmentation of antihypertensive drugs. The clinician should individualize each patient in the context of polypathologies, polymedication, and vital prognosis. Other studies will be necessary to answer this very important question.

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