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THERAPIES AND NEW TECHNOLOGIES IN THE TREATMENT OF DIABETES (M PIETROPAOLO, SECTION EDITOR)

Diabetes Treatment in the Elderly: Incorporating Geriatrics, Technology, and Functional Medicine

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Abstract

Purpose of Review The current approach to diabetes in the elderly incorporates components from the comprehensive geriatric approach. The most updated guidelines from the American Diabetes Association reflect influence from the consensus made in 2012 with the American Geriatrics Society. Notably, the framework included the evaluation for geriatric syndromes (falls and urinary incontinence), functional and cognitive abilities. The goal for this review is to provide an updated summary of treatment strategies for community-dwelling older adults. We identified the need to expand our approach by addressing innovative approaches and scientific concepts from telemedicine, functional medicine, and geriatrics.

Recent Findings Findings on cardiovascular protection with sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and some glucagon-like peptide 1 receptor agonists (GLP-1RA) support their use for older patients with diabetes. However, careful consideration for agent selection must incorporate the presence of geriatric issues, such as geriatric syndromes, or functional and cognitive decline, as they could increase the risk and impact adverse reactions. Telemedicine interventions can improve communication and connection between older patients and their providers, and improve glycemic control. Functional medicine concepts can offer additional adjuvant strategies to support the therapeutic interventions and management of diabetes in the elderly.

Summary A systematic review confirmed the efficacy and safety of metformin as first-line therapy of type 2 diabetes in the older adult, but multiple reports highlighted the risk for vitamin B12 deficiency. Randomized controlled trials showed the efficacy and safety of antihyperglycemic agents in the elderly, including some with longer duration and lesser risk for hypoglycemia. Randomized clinical trials showed cardiovascular protection with SGLT-2i (empagliflozin, canagliflozin) and GLP-1RA (liraglutide, semaglutide). The most current guidelines recommend addressing for geriatric syndromes, physical and cognitive function in the elderly, in order to individualize targets and therapeutic strategies. Clinicians managing diabetes in the elderly can play a major role for the early detection and evaluation of geriatric issues in their patients. Telemedicine interventions improve glycemic control, and certain functional medicine strategies could be adjuvant interventions to reduce inflammation and stress, but more studies focused on the elderly population are needed.

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Introduction

The aging of the world's population and the ongoing diabetes and obesity epidemics are impacting healthcare worldwide. By 2050, there will be 2 billion adults aged 60 and older, at least one out of four will have diabetes [1, 2] with overweight or obesity [3, 4, 5•]. Diabetes is chronic and progressive, and its prevalence increases with aging [6]. Younger adults usually endure less multimorbidity or risk for physical or cognitive dysfunction, albeit some present with complex clinical scenarios. However, their older counterparts usually face more challenges beyond traditional diabetes-related issues, due to the overlap with the aging process and age-related or age-dependent diseases [7]. The elderly present the highest rates of diabetes-related major lower-extremity amputation, myocardial infarction, visual impairment, and end-stage renal disease [8], cognitive dysfunction, falls, fractures [9•], dementia [10], cardiovascular (CV) events [11], malignancies [12], depression [13], physical disability, sarcopenia [14, 15], and frailty, which is associated with increased mortality [16, 17, 18•]. Furthermore, implementing standard pharmacologic interventions to coexistent multimorbidity might inevitably result in polypharmacy, with increased costs and risk for non-adherence and medication-related complications [19]. Consequently, the approach to treating diabetes in older adults must encompass all the abovementioned factors, as they can hinder the ability to perform diabetes self-management and increase treatment errors, hypoglycemia, and poor glycemic control [20–22].

We also briefly summarized the rapidly expanding telemedicine interventions for diabetes which are aligned with essential elements of the chronic disease model. Strategies include telephone calls and short message services, websites, mobile health apps, remote monitoring devices, and sophisticated artificial intelligence systems, linking patients and healthcare providers. Transmitted data include patient-measured (e.g., blood glucose levels, symptoms, lifestyle choices, etc.) and systems-delivered (e.g. diabetes educational materials, questions and feedback, etc.) information, which can be tailored to individual needs. Electronic systems collect, store, and process the data, establishing trends and gathering case-specific information over time, often in real-time. Prior studies have shown benefits in reducing hemoglobin A1c (HbA1c) in gestational diabetes [23] and diabetic retinopathy [24]. Concerns for widespread implementation include limitations in availability, usability, and engagement in older adults [25]. However, older adults can be trained and effectively engaged and learn how to use most telemedicine devices [26].

Finally, we address functional medicine, consistent with its approach to complex, chronic diseases. It integrates the interactions between various biological systems to address the disease in an individualized, patient-centered way (https://www.ifm.org/functional-medicine/what-is-functional-medicine/). Among these, immune dysregulation, xenobiotics exposure, nutrient deficiency, gut microbiome, and stress affect metabolism and insulin resistance. We summarized the past 5 years of evidence addressing concepts and strategies related to glycemic metabolism, obesity, and aging, supporting the future integration with our standard approaches to the management of complex diabetes cases in the elderly.

Therapeutic Interventions

Lifestyle modifications (healthy diet, physical activity, and exercise) are feasible to implement, and older adults can still benefit from modest intentional weight loss [27•, 28]. The Montana Cardiovascular Disease and Diabetes Prevention Program showed older adults had higher lifestyle participation and self-monitoring rates than younger subjects [29]. A recent study randomly allocated 160 mildly-to-moderately frail, sedentary, older adults with obesity, to aerobic, resistance or combined training [30]. While this RCT did not focus on diabetes alone, intentional weight loss plus combined aerobic and resistance exercise were the most effective interventions for improving functional status. We recommend future review of two ongoing RCTs that will evaluate dietary protein [31] and multi-modal interventions for frailty [32] in older patients with type 2 diabetes (T2D).

Pharmacologic therapies for chronic diseases involve long-term safety and tolerability, especially in the elderly, with aging- and disease-related changes in pharmacokinetics and pharmacodynamics. While we did not see the introduction of a new antihyperglycemic medication class, there is greater focus on understanding CV benefits (or risks) from these medications. We present recent relevant reports for each of the most commonly used agents, and then reports focusing on CV outcomes.

Metformin

Metformin remains the first-line therapy for T2D. A recent systematic review identified 4 interventional and 11 observational studies, most subjects aged ≥ 65 [33]. The efficacy and safety of metformin was better than alternatives, albeit more studies are needed in people ≥ 80 years. A cohort study in US Veterans aged 65–89 compared the mortality between metformin and sulfonylurea users [34]. Metformin was associated with a 30% decreased mortality risk among those without any frailty-related diagnoses. An ongoing RCT is testing metformin as a novel intervention for frailty prevention [35].

While there have been last reports, the last 5 years showed a regained interest in vitamin B12 (B12) deficiency with metformin use. A 2014 systematic review (6 RCTs included) reported lower B12 levels in patients treated with metformin, compared to subjects on placebo or rosiglitazone [36]. Reductions were greater in subjects receiving ≥ 2 g/day. A 2015 meta-analysis (19 studies) also reported greater B12 deficiency with metformin (OR 2.45, 95% CI 1.74–3.44, $P < 0.0001$) [37]. A retrospective cohort study of 13,258 US Veterans showed B12 deficiency (< 170 pg/dL) in 7% of people with diabetes on metformin, compared to 3% of people without diabetes or metformin use ($P = 0.0001$) [38]. The current standard practice incorporates B12 monitoring and treatment.

Sulfonylureas

A 2015 systematic review and meta-analysis of 18 studies using sulfonylureas found greater CV-related mortality with glibenclamide, lower with gliclazide and glimepiride [39]. There is no evidence to support CV mortality as a drug class. We strongly recommend against the use of glyburide, but still endorse the use of glimepiride and glipizide for certain patients. These agents are still effective in the older population, with additional benefits due to low cost and access, but we recommend special caution in cases with hypoglycemia risk or uncontrolled obesity.

Sodium Glucose Co-transporter 2 Inhibitors (SGLT-2i)

Subjects with uncontrolled T2D on basal insulin were randomized to 0, 10, or 25 mg of empagliflozin [40]. Respectively, the rates of urinary tract infection (9, 15, and 12%) and genital infection (2, 8, and 5%) were not directly proportional to increasing dosages. However, other studies had similar adverse events [41, 42], especially volume depletion-related, which were greater with increasing age [43]. When randomized to non-canagliflozin, 100 or 300 mg of canagliflozin, subjects < 75 years presented events in 1.4%, 2.2%, and 3.1% respectively, and when ≥ 75 years, 2.6%, 4.9%, and 8.7%, respectively. Others highlighted that canagliflozin was found to double the risk of amputations [44], albeit these events are rare.

Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RA)

Combining GLP-1RA with insulin can reduce HbA1c and weight, without greater hypoglycemia [45]. A meta-analysis evaluated lixisenatide use in 500 older subjects with uncontrolled T2D [46]. Hypoglycemia occurred more in the intervention versus the placebo group (8.6 and 3.6%, $P = 0.03$), with no reported severe events. A pooled analysis showed lixisenatide was similarly tolerated in those age ≥ 75 years as in those ≥ 65 years [47]. Later, the GetGoal-O randomized 350 older adults (age ≥ 70) to lixisenatide versus placebo [48]. The adverse events were similar to those reported in younger counterparts. Notably, patients with impaired nutrition or cognitive dysfunction were excluded. A more recent report indicated that adding lixisenatide to basal insulin improved glycemic control, albeit increasing hypoglycemia risk [49]. An analysis of 4442 subjects who used liraglutide in the UK showed that older age was associated with more significant gastrointestinal side effects and discontinuation of the medication [50].

A systematic review compared the efficacy and safety of once-weekly versus daily or twice per day GLP1-RAs [51]. Adverse events were similar across most medications, except exenatide, with lesser risk in the long- compared with the short-acting form (RR 0.67, 95% CI 0.52–0.87; $P < 0.01$; $I2 = 0\%$).

Dipeptidyl Peptidase 4 Inhibitors (DPP4i)

A 2013 RCT in 241 community-dwelling older adults (age ≥ 70 years) found linagliptin was effective and safe [52]. Researchers used data from 2 RCTs, where subjects with age ≥ 70 years received linagliptin or placebo [53]. Adding linagliptin to basal insulin offered less hypoglycemia risk than placebo (HR 0.61, 95% CI 0.39–0.97 versus HR 0.59, 95% CI 0.37–0.94, $P < 0.05$). Also, hypoglycemia was lower in those with kidney disease (HR 0.45, 95% CI 0.27–0.76) and in those treated with ≥ 35.6 insulin units/day (HR 0.46, 95% CI 0.23–0.91).

A 2014 study of 205 older adults (mean age 69 years) showed that saxagliptin was well-tolerated (2.1-year follow-up) [54]. The following year, a larger study (8561 older subjects, 2330 ≥ 75 years) of similar duration reported an increased risk for hospitalization due to heart failure in subjects treated with saxagliptin [55]. This finding has not been reported with other agents within this class.

A pooled analysis of 25 studies (encompassing 2446 older subjects randomized to sitagliptin 100 mg or placebo) described effective glucose reduction and less hypoglycemic events with sitagliptin (7.0 vs. 14.3 per 100 patient-years; difference − 7.6, 95% CI − 11.2 to − 4.3) [56]. The researchers suggested this was due to a lesser need to use other agents with greater risk (e.g., sulfonylureas).

A more recent review of 33 publications using DPP-4i in older adults (including 1 meta-analysis and 17 RCTs)

concluded there was evidence for lesser hypoglycemia risk, but a lack of consistent data for long-term benefits [57].

Insulin Formulations

The DURABLE trial was a 30-month multicenter RCT, where 258 patients were assigned to insulin lispro mix 75/25 (intermediate- and short-acting) and 222 patients to glargine insulin. After 24 weeks, the group in lispro mix presented slightly better HbA1c levels and slightly higher percentages of patients achieving target HbA1c < 7.0%, more weight gain, and higher rates of overall hypoglycemia, but lower rates of nocturnal hypoglycemia [58].

Newer long-acting formulations of basal insulin, glargine 300 units/mL [59, 60], and degludec 100 units/mL and 200 units/mL [61, 62] are at least as effective, and with less risk for hypoglycemia. These formulations could be considered when hypoglycemia persists despite clinical efforts to minimize the risk. Notably, one suggested the long-acting formulations could be beneficial for patients having issues with insulin self-injection [62].

Cardiovascular Outcomes

Positive Effects

The multicenter Empagliflozin, cardiovascular outcomes, and mortality in T2D trial (EMPA-REG) randomized 7020 participants to daily empagliflozin 10 or 25 mg or placebo [63]. Empagliflozin had 38% relative risk reduction (RRR) in CV mortality, 35% RRR in heart failure hospitalization, and 32% RRR in any-cause mortality. A post hoc analysis of phase III studies with empagliflozin found blood pressure (BP) reduction and improved arterial stiffness and vascular resistance [64].

The multicenter Canagliflozin Cardiovascular Assessment Study (CANVAS) randomly assigned 10,142 subjects to canagliflozin or placebo [65]. Canagliflozin reduced CV mortality, nonfatal myocardial infarction, or nonfatal stroke. Other studies with canagliflozin showed prevention of CV events [66] and heart failure [67]. Six hundred and sixty-six subjects with T2D and heart failure risk were randomized to canagliflozin (100 or 300 mg) or placebo, to evaluate CV biomarkers during 2 years [68]. At 26, 52, and 104 weeks, canagliflozin delayed the rise of N-terminal pro-B-type natriuretic peptide (− 15.0%, − 16.1%, and − 26.8%) and high-sensitivity troponin I (− 8.3%, − 11.9%, and − 10.0%), all with $P < 0.05$. A phase 3b RCT will evaluate if dapagliflozin may reduce major CV events [69].

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial found lower CV and all-cause mortality rates with liraglutide compared to placebo [70]. Semaglutide showed a lower composite rate of CV mortality, nonfatal myocardial infarction, or nonfatal stroke when compared to placebo, but no significant difference in all-cause mortality [71].

A recent meta-analysis showed that SGLT-2i and GLP-1RA were associated with lower all-cause mortality than DPP-4i or placebo [72••]. On the other hand, an analysis of the BARI 2D study, which recruited 2368 subjects with diabetes and stable heart disease, showed greater CV (16 vs 11%, $P = 0.04$) and all-cause-mortality (HR 1.89, 95% CI 1.1–3.2, $P = 0.02$) in subjects aged ≥ 75 years who received exogenous insulin or insulin secretagogues instead of insulin-sensitizing therapies, whereas younger subjects did not show mortality differences between these approaches [73].

Neutral Effect

Studies on other GLP-1RAs did not show similar results, suggesting that the benefits may not be a class effect. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial did not find a reduction of major CV events or death with the addition of lixisenatide [74]. Similar neutral findings were observed in studies with once-weekly dulaglutide [75] and exenatide [76].

Studies addressing the potential role for DPP-4 inhibitors did not find evidence to support that this class of medications would offer similar benefits. These include studies with sitagliptin [77, 78].

Geriatric Considerations: Geriatric Syndromes and Physical and Cognitive Functions

The clinical presentation of an older adult with diabetes is widely heterogeneous, even for subjects of the same age and similar comorbidities [8, 20, 79]. Individuals are impacted differently by diabetes, age-related diseases, geriatric syndromes, and aging itself, showing a range of physical and mental resilience [80, 81]. Geriatric syndromes (polypharmacy, urinary incontinence, impaired mobility, falls, frailty, persistent pain, cognitive impairment, and depression) increase the clinical complexity [82], not only impacting the targets, but also the ability to care for oneself and implement diabetes self-management. Providers can uncover these limitations by assessing the physical and cognitive functions, economic, family, and social support, and the geriatric syndromes [83••]. The American Diabetes Association (ADA) guidelines recognize the need to incorporate geriatrics components into the assessment and management of diabetes [84], and its chapter focused on the older adult reflects the consensus the ADA made with the American Geriatrics Society [8]. The framework for HbA1c-target individualization includes functional and cognitive status, falls, and urinary incontinence. For patients with well-preserved physical and cognitive functions, absent life-

threatening diseases, longevity in the family, or expected long life-expectancy, the HbA1c-target category is 6.5–7.5%, similar to younger adults. The inability to complete ≥2 Instrumental Activities of Daily Living or IADLs (shopping, cooking, household cleaning/laundry, telephone use, managing medications, finances, and driving/using public transportation), supports a HbA1c-target category of 7.5–8.0%. Limitations in ≥2 Activities of Daily Living or ADLs (dressing, toileting, bathing, grooming, eating, and getting around the home) are consistent with the highest case complexity, with HbA1c-target category of 8.0–8.5%.

The GERODIAB, a multicenter, prospective, observational study in 987 adults aged ≥70 years with diabetes, addressed the morbidity and mortality associated with glycemic control during a 5-year follow-up [85]. Both macrovascular [86] and microvascular [87] complications were associated with cognitive function, nutritional risk, and self-care deficit. Informal (family/friends) and formal support (e.g., home health nurse to assist with medication management) strategies can counter some of these limitations.

Geriatric Syndromes

Older patients with diabetes, compared to counterparts without, have an increased risk for multiple geriatric syndromes, including falls, urinary incontinence, cognitive decline, and even possibly frailty syndrome. Beyond the increased falls risk due to age-related decline in posture, balance, gait, and proprioception, diabetes alone worsens this risk by 17-fold [88]. Examples include impaired gait with diabetic peripheral polyneuropathy, diabetic peripheral vascular disease, amputations, neuropathic pain, impaired vision with diabetic retinopathy, impaired judgment with diabetic cognitive decline, and dementia, polypharmacy, and hypoglycemia [89]. Moreover, the elderly with diabetes have poor bone quality and greater vulnerability for fragility fractures [90]. Falls risk is greater in those receiving insulin [91]. Screening can and should be performed at every visit, especially in those at risk for hypoglycemia or osteoporosis. While standard testing could be performed in minutes (see the website from the Centers for Disease Control, through the STEADI program, available at https://www.cdc.gov/steadi/), the providers can also detect quickly those at greatest risk by asking if they have fallen, and observing gait and balance while walking into the office. These cases will benefit from a multifactorial risk assessment (a falls clinic) [92].

Urinary incontinence is associated with poor quality of life, depression, disability, morbidity, and mortality [93], with greater prevalence in older patients with diabetes, especially in those with mobility and cognitive impairment [94]. Providers ought to recognize the need to: (1) rule out that its etiology is hyperglycemia, in which case, enhanced antihyperglycemic interventions should follow, (2) incorporate its presence in the selection of pharmacologic therapies (e.g., avoid SGLT-2i with established, unresolved urinary incontinence), and (3) facilitate communication with the primary care provider towards for a referral to the pertinent specialist.

While falls and urinary incontinence are included in the ADA guidelines, there is growing evidence that connects diabetes in the elderly with frailty syndrome, which is yet to be included. In a prospective cohort study of 1750 individuals aged ≥60 years, participants with diabetes showed an increased risk of frailty (OR 2.18, 95% CI 1.42–3.37) after adjusting for age, sex, and education [95]. Moreover, frailty seems to increase the risk for hypoglycemia and dementia [96]. Notably, a pending 3-year multicenter trial will randomize 1500 older persons with physical frailty and sarcopenia to a multicomponent intervention (long-term structured physical activity, nutritional counseling/dietary intervention, and an information and communication technology intervention) versus a healthy aging lifestyle education program designed to prevent mobility [97]. The results will offer insight to the management of frail elderly at high risk of disability. The MID-Frail study [32], another multimodal intervention trial with 1718 frail and pre-frail subjects will provide evidence on the clinical, functional, social, and economic impact of a multi-modal approach in frail and pre-frail older people with T2D.

In our clinical practice, we incorporate frailty status into the framework for defining glycemic targets and strategies for intervention.

Cognitive Impairment and Dementia

Older patients with diabetes are 50 to 100% more likely to develop dementia, worse if long-standing disease or uncontrolled, and if accompanied by vascular complications [98]. Data from a longitudinal study (median follow up 6.1 years) was used to compare changes in multiple cognitive functional tests [99]. This study included 3069 adults aged 72 to 96, from whom 9.3% had diabetes at baseline. Cases with diabetes had lower baseline executive and global cognition; their rates of decline did not differ to those seen in patients without diabetes. A recent Cochrane systematic review studied the role of antihyperglycemic therapy and the progression of cognitive decline [100]. Treatment strategies included multiple antihyperglycemic medications, and the follow-up period of 40 to 60 months. There was no evidence that any particular antihyperglycemic strategy prevented or delayed cognitive impairment. However, using data from 2 studies (12,827 subjects), they observed more episodes of severe hypoglycemia (RR 2.18, 95% CI 1.52 to 3.14) in subjects receiving intensive therapies, but did not observe differences in mortality.

In clinical practice, clinicians need to recognize that patients with cognitive dysfunction may fail to identify, report, or treat hypoglycemic episodes correctly [101]. Efforts to reduce hypoglycemia risk include engaging the family to

monitor the patient, evaluating the option for home health nurse or telemedicine monitoring, and adjusting therapeutic interventions accordingly. Furthermore, additional benefits can include an earlier recognition and pertinent referrals to the corresponding specialists. Even if this does not change the progression of the cognitive decline, it can allow more time to educate and prepare the patient and the family.

Telemedicine Strategies

Given the ubiquitous nature of mobile technology, there has been a huge surge in mobile health interventions (mHealth) based on smartphone applications (apps) directed towards health-related issues. There are thousands of app developers and thousands of health applications available for download in the iTunes App Store for iOS and Google Play for Android [102], targeting consumers and healthcare systems. Notably, the ongoing growth of these technologies offers great potential, albeit we are also concerned about their abundance and potential confusion on the public, or issues with their efficacy.

A recent systematic review of studies using mobile apps for diabetes aimed to evaluate their effectiveness [103]. Twelve trials were identified (974 subjects), but none specifically focused on the elderly. The results showed HbA1c improvements (0.48%, 95% CI 0.19–0.77%), greater if the apps included complication prevention modules (with 1.31%, 95% CI 0.66–1.96% versus without 0.38%, 95% CI 0.09–0.67%; $P = 0.01$). Interestingly, there was no additional benefit if the app included a clinical decision-making function (with 0.18%, 95% CI 0.21–0.56% versus without 0.61%, 95% CI 0.27–0.95%, $P = 0.10$).

Another systemic review aimed to evaluate the effectiveness of mobile phone and tablet apps for self-management [104]. The authors searched the period from 2005 to 2016, and found only five RCTs controlled trials assessing the effectiveness of the diabetes apps. The duration of these studies ranged from 6 weeks to 1 year, and showed that apps could improve the symptom management through self-management interventions. However, the authors also highlighted the need for more rigorous research.

A different systematic review focused on studies assessing the effect of mobile health interventions, coded as mHealth, in multiple diabetes outcomes (HbA1c, blood glucose, BP, serum lipids, and body weight) [105]. From the 2596 retrieved articles, 13 RCTs were selected, but only six had available data to implement the meta-analysis, comprising 1022 subjects. The intervention clustered as mHealth consisted of diverse strategies that included a mobile/smartphone with self-management apps, measuring devices, patient-drive uploaded data to the apps, and provider-driven data analysis followed by feedback to the patient. The duration of the intervention in the selected studies went from 3 to 12 months. The results in this study indicated that mHealth interventions decreased HbA1c (−0.40%, 95% CI −0.69 to −0.11%), but without showing any effects on BP, serum lipids, or weight.

A more comprehensive approach was included in a separate systematic review focused on high-quality articles on diabetes self-management education and support services [106]. The researchers found 25 studies, and consistently found that the most effective interventions incorporated all the components of a technology-enabled self-management feedback loop system, which connected the patients with the healthcare teams using a 2-way communication system, analyzed the patient-generated data, tailored education, and individualized feedback.

A more recent systematic review aimed to examine the features, clinical efficacy, and usability of certain apps for diabetes [107•]. The majority of subjects were younger than age 65, but its results are relevant, as the authors described positive effects (usually a reduction on HbA1c) only when apps were paired with support from a healthcare provider or study staff. Similar to the prior report, there were no improvements in quality of life, BP, or weight.

With regard to the use of personal health records and secure messaging, another review assessed the clinical evidence for secure messaging in self-management of diabetes [108]. There were 11 identified studies, from which 7 showed statistically significant albeit narrow improvements in HbA1c. However, similar to the results observed with mobile apps, there were absent or inconsistent improvements in the participants' secondary outcomes, such as BP and cholesterol.

Our team has implemented clinical programs utilizing the available resources in our healthcare system (US Department of Veterans Affairs). We used secure messaging to send patients weekly diabetes education and monitor their blood sugars along with working closely with pharmacy for all patients with abnormal HbA1c. Our intervention showed a significant reduction in patients' HbA1c, and high satisfaction.

Another newer technology tool is the availability of video technology for clinical purposes. Based on some pilot data, it is likely that in the future some outpatient visits will be replaced by video conferencing with the primary or specialty provider. This has the potential of improving access especially for older patients living in rural areas, or when they endure transportation challenges [109].

For any telemedicine intervention to be effective, data gathering alone does not suffice. It needs to be processed, analyzed, interpreted, and feedback provided to the patient in a timely manner. Further work must implement new technologies in geriatric patients, with detailed protocols and procedures, to determine efficient and effective use of available telemonitoring tools to improve patient outcomes. Despite some promising results, such innovative solutions are not widely adopted by health systems worldwide. Lack of supportive policy and legislation, unsustainable reimbursement, inefficient business models, and concerns regarding the security and privacy of health data are among the most problematic barriers, which need be addressed [110].

Integrative and Functional Medicine

Functional medicine applies a systems biology approach and expands the attention to contributing factors that affect metabolism and insulin resistance. Some of the factors that have been studied in the last 5 years are immune dysregulation, xenobiotics exposure, nutrient deficiency, and gut microbiome.

Immune Dysregulation

Chronic inflammation in visceral adiposity creates a pro-inflammatory environment, with elevated expression pro-inflammatory immune cells and molecules (tumor necrosis factor-alpha and interleukin-6) [111]. The obesity-induced inflammation promotes insulin resistance and dysregulation of glucose and lipid metabolism [112]. Plant-derived lectins can act as exogenous "danger signal" that can promote inflammatory diseases via the NLRP3 inflammasome. These proteins have been associated with the pathogenesis of rheumatoid arthritis, diabetes, and celiac disease [113]. In addition, wheat germ agglutinin increased the binding of insulin by adipocytes, apparently by increasing the binding affinity of the insulin receptor. While we did not find any large RCT in older adults, we recommend trials of dietary modifications removing some of these foods, as a low-risk intervention to reduce inflammation and hopefully improve metabolism, weight, and diabetes control. However, we emphasize the need to adhere to standard lifestyle interventions, with control of macronutrients and caloric intake.

Xenobiotics

These are exogenous, potentially toxic substances. Bisphenol A (BPA) and phthalates (both widely disseminated in plastics) have been associated with increased risk of diabetes and obesity [111]. A European expert panel identified a 40 to 69% probability of phthalate exposure causing 20,500 new-onset cases of diabetes in older women with €607 million in associated costs [114]. The National Institute of Environmental Health Sciences at the NIH provides information to the public, available at https://www.niehs.nih.gov/health/topics/agents/sya-bpa/index.cfm.

Micronutrients: Minerals and Vitamins

Magnesium

Magnesium is a cofactor in metabolic pathways and insulin secretion. A systematic review (12 studies) described that magnesium deficiency was associated with hyperglycemia, hyperinsulinemia and insulin resistance, and an increase processed food diet will decrease the intake of magnesium-rich foods [115]. Subanalysis of these studies showed that magnesium supplementation had a beneficial effect on the serum fasting glucose concentrations and fasting insulin levels in patients with hypomagnesemia and insulin resistance. There is no consensus about the recommended magnesium type or dose, but practitioners could start with identifying deficiency on their diabetes patients and replacing deficiencies.

Vitamin B12

We have previously discussed the issue of B12 deficiency with metformin use. Here we highlight two things: (1) B12 deficiency also causes neuropathy, which should not be confused with diabetic neuropathy, and (2) aging can increase the loss of gastric parietal cells producing intrinsic factor, and hypochlorhydria could worsen the risk for B12 deficiency, which in elderly patients can be associated with cognitive dysfunction. The evaluation of vitamin B12 levels in this population and correcting its deficit should be part of the regular care of these patients.

Chromium and Cinnamon

Both agents have been proposed to improve insulin metabolism. A randomized double-blind, placebo controlled pilot (62 subjects with prediabetes) evaluated the effect of a four-month treatment with a dietary supplement containing cinnamon, chromium, and carnosine [116]. Fasting plasma glucose and fat-free mass percentage improved, HbA1c levels did not.

Active Agents

Berberine

The plant-based product berberine can stimulate glucose uptake in muscle, liver, and adipocyte, inhibit liver gluconeogenesis, and decrease inflammatory signals [117]. A 2015 meta-analysis identified 27 RCTs where berberine was used to treat T2D [118]. When comparing berberine with lifestyle to placebo (five studies, 331 subjects), the results favored the intervention group (HbA1c − 0.71%, 95% CI − 0.94 to − 0.49, $P < 0.00001$). When comparing berberine against antihyperglycemic agents (seven studies, 504 subjects) there was no difference in HbA1c reduction (− 0.1%, 95% CI − 0.33–0.14%, $P = 0.41$). When adding berberine to antihyperglycemic agents versus these agents alone (seven studies, 469 subjects), there was greater HbA1c reduction (− 0.58%, 95% CI − 0.9 to − 0.21%, $P = 0.002$).

Alpha-Lipoic Acid (ALA)

This is a potent lipophilic antioxidant and a co-factor for several mitochondrial and cytosolic enzymes, which has been previously studied and used (mostly in Germany) for the treatment of diabetic neuropathy [119]. Considering its potential use for obesity in diabetes, two meta-analyses were conducted but found no significant weight reduction with ALA [120, 121]. Findings from a recent animal model study showed that ALA reduced changes in redistribution of muscle fibers and prevented atrophy in slow and fast diabetic muscle [122]. Considering the epidemic of diabetes in obesity and sarcopenic obesity, and its connection with frailty syndrome, this would be to follow in the future.

Microbiome

The intestinal microbiome contributes to differences in body weight, fat distribution, insulin sensitivity, and glucose and lipid metabolism [123]. Thus, it would be reasonable to avoid any factors that may negatively affect the microbiota. Interestingly, a recent multicenter RCT in treatment-naïve adults (average age 53.5 ± 7 years) receiving acarbose or glipizide identified drug-dependent changes (acarbose increased the relative abundances of *Lactobacillus* and *Bifidobacterium* in the gut microbiota and depletes *Bacteroides*) which favored glycemic control [124]. While this study was done in younger adults, the other negative consideration is that a three-times-per-day formulation is not ideal for older patients, unless there were no other suitable alternatives. Nevertheless, further studies are addressing microbiome changes related to different antihyperglycemic agents. More recently, a RCT with 450 subjects with T2D and hyperlipidemia compared their gut microbiota upon treatment with metformin and a Chinese herbal formula [125]. Both agents significantly increased *Blautia* spp., and only the latter increased *Faecalibacterium* spp., which are associated with glycemic improvements.

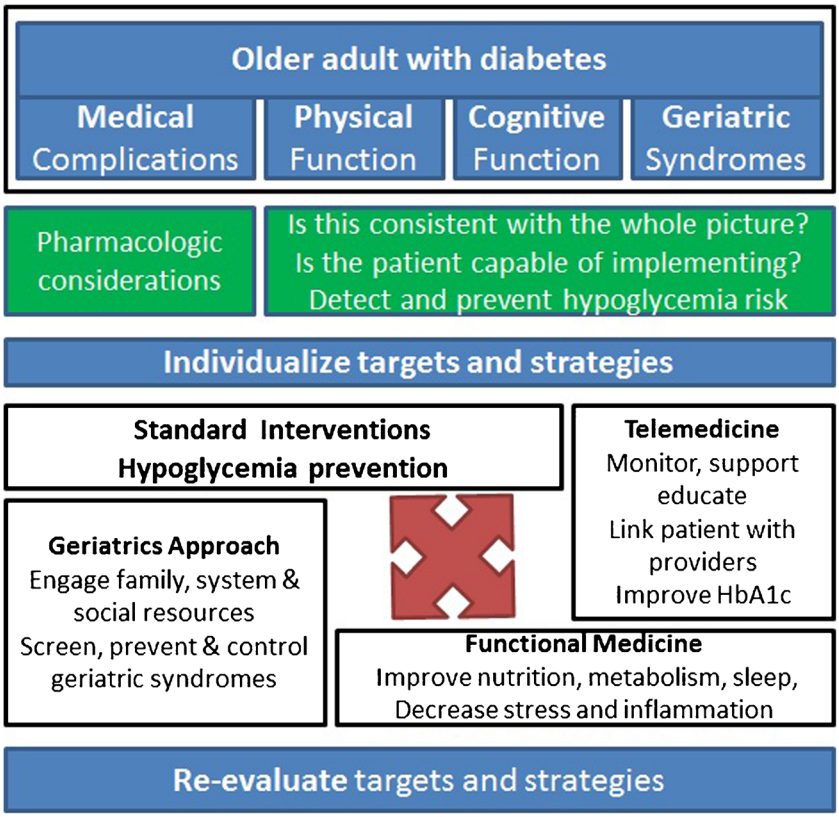

Fig. 1 Diabetes management in the elderly. The approach should be comprehensive, beyond the traditional approach to younger adults, with assessment of physical and cognitive function, and screening for geriatric syndromes. Then, when addressing the targets and strategies, ensure all factors have been considered, especially if the patient would be able to carry them. Notably, older patients who fail to respond to therapy might do so due to undetected issues in cognition or function. In addition, telemedicine strategies can be explored and they might be applicable, especially with the growing use of technology devices. Finally, concomitant interventions to reduce inflammation and control stress, improve nutrition and support established interventions, especially for patients who may show interest or may not respond to traditional therapies. Ultimately, diabetes care in this age group involves frequent reassessment, for they are at the greatest risk of developing major complications (e.g., a stroke) that can completely change their clinical picture, increasing the vulnerability for hypoglycemia and other geriatric syndromes. Henceforth, targets and strategies must be adjusted accordingly

Non-caloric artificial sweeteners have been shown to alter gut microbiota [126]. An analysis of 1454 older subjects (741 men, 713 women) from the Baltimore Longitudinal Study of Aging showed that low-calorie sweetener users had greater body mass index (0.80 kg/m^2, 95% CI 0.17–1.44), waist circumference (2.6 cm, 95% CI 0.71–4.39), and prevalence of abdominal obesity (HR 1.53; 95% CI 1.10–2.12) [127]. Notably, this was associated with a higher point estimate in the incidence of diabetes (18.4% versus 8.9%) though the difference was not statistically significant.

Conclusion

The management of elderly patients with diabetes presents unique challenges. A comprehensive evaluation and holistic approach are required to properly individualize targets and strategies in this age group. Figure 1 summarizes the concept of incorporating approaches to offer a whole health approach to the older person with diabetes.

The recommend approaches are consistent with geriatric principles:

- Start low, go slow, progressively increase towards the individualized target.
- Follow the best evidence for greater benefits and safer therapeutic profiles.
- Favor agents with the lowest hypoglycemia risk and least polypharmacy (when possible, avoid multiple times/day formulations).

Addressing geriatric syndromes, physical and cognitive status in older adults is integral to design and deliver a proper plan of care. Targets and pharmacologic strategies need to be adjusted accordingly. Noteworthy, providers taking care of older patients with diabetes should understand the risk for these complications, and their opportunity to play a role in early detection and prevention.

Telemedicine interventions improve glycemic control, but require the involvement of healthcare providers in order to be successful. There is lack of information on which apps improve diabetes-related outcomes. Telemedicine can enhance access to ongoing clinical support, which can be especially meaningful to the elderly with social isolation and lack of support and transportation challenges. The impact of telemedicine strategies on other clinical outcomes or cost-effectiveness is yet to be well clarified. Large sample size randomized controlled trials in this area are rare, and we did not come across any meta-analyses.

Endogenous (adiposity) and exogenous (chemicals, endocrine disruptors, nutrients) can affect weight, metabolism, insulin resistance, and diabetes. It seems reasonable to consider adding alternative interventions (e.g., adjust nutritional sources) especially when patients do not seem to respond to standard interventions.

Compliance with Ethical Standards

Conflict of Interest Willy Marcos Valencia, Diana Botros, Maria Vera Nunez, and Stuti Dang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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