Research Paper

Optimal therapy of type 2 diabetes: a controversial challenge

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Abstract: Type 2 diabetes mellitus (T2DM) is one of the most common chronic disorders in older adults and the number of elderly diabetic subjects is growing worldwide. Nonetheless, the diagnosis of T2DM in elderly population is often missed or delayed until an acute metabolic emergency occurs. Accumulating evidence suggests that both aging and environmental factors contribute to the high prevalence of diabetes in the elderly. Clinical management of T2DM in elderly subjects presents unique challenges because of the multifaceted geriatric scenario. Diabetes significantly lowers the chances of "successful" aging, notably it increases functional limitations and impairs quality of life. In this regard, older diabetic patients have a high burden of comorbidities, diabetes-related complications, physical disability, cognitive impairment and malnutrition, and they are more susceptible to the complications of dysglycemia and polypharmacy. Several national and international organizations have delivered guidelines to implement optimal therapy in older diabetic patients based on individualized treatment goals. This means appreciation of the heterogeneity of the disease as generated by life expectancy, functional reserve, social support, as well as personal preference. This paper will review current treatments for achieving glycemic targets in elderly diabetic patients, and discuss the potential role of emerging treatments in this patient population.

INTRODUCTION

The global prevalence of type 2 diabetes mellitus (T2DM) is rapidly growing as a consequence of life-style changes, urbanization and population aging [1]. The increase of life expectancy in parallel with increasing risk of developing T2DM with advancing age is a significant driver of the diabetes epidemic [2-4]. Although elderly diabetic patients are widely represented in the clinical practice, focus on diabetes care in this age group is still relatively scarce, while the momentum for more clinical trials including older patients should be encouraged. In this regard, a recent analysis showed that only 0.6% of interventional trials in diabetes specifically targeted elderly patients, 30.8% excluded patients older than 65 years and the majority excluded those aged >75 years [5]. Therefore, an important limiting factor for producing specific evidence-based clinical guidelines for older people with diabetes is the need to extrapolate evidence from data obtained from younger adults. Moreover, the general viewpoint is that people aged 60+ years are part of the older population and the terms 'elderly' and 'older people' are often interchangeable; however, this definition can be quite arbitrary and misleading. While an age thresholds could be used to identify geriatric age, the connotation of the geriatric patient comes from a more "comprehensive" definition that must include the functional status, the number and severity of comorbidities, societal and economic parameters, and overall degree of frailty [6]. Therefore, the optimal management of diabetes in the elderly population must recognize the vast heterogeneity to which disease duration, diabetes complications, functional status, comorbid illnesses, and patient's setting contribute to modulate the degree of vulnerability [7]. Elderly diabetic patients frequently have functional disabilities, cognitive decline, increased rates of bone fracture, polypharmacy, and hypoglycemic events due to comorbid illnesses. It is known that diabetic patients

with macrovascular complications are more susceptible to develop frailty, which, in turn, is associated with increased mortality [8]. Moreover, elderly patients may move in and out states of illness and functional impairment on a regular basis [9]. All these factors contribute to make the optimal therapy of T2DM in geriatric patients a controversial challenge [10] and advocate for a personalized approach [4,11]. This view is in line with the modern overall approach to T2DM management [12,13]. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) has recently suggested an individualized and tailored care for T2DM, taking into account several elements, including age, patient attitude and expected treatment efforts, risks potentially associated with hypoglycemia or other adverse events, disease duration, life expectancy, comorbidities and established vascular complications as well as resources and support system [14].

Moreover, the most recent guidelines, while emphasizing individualization of HbA1c targets, underline that age *per se* should not be an excuse for suboptimal metabolic control [4,14,15]. Indeed, although attention has rightly been paid to the risks of over treatment of hyperglycemia in older subjects exposing them to the risk of hypoglycemia, treatment burden, increased risk of mortality, the potential negative impact of untreated or undertreated hyperglycemia, must be recognized even in patients with short life expectancy as a cause for dehydration, electrolyte abnormalities, urinary incontinence, dizziness, falls and overall poor outcome [4].

Reaching the best risk-to-benefit ratio of anti-diabetic treatment in the elderly T2DM patients is, however, not a simple task as the heterogeneity of this population has not been yet fully addressed by proper clinical trials. Therefore, in this review, we will discuss pros and cons as well as limitation of information with respect to the elderly population of the available pharmacologic treatments.

METHODS

The authors collected materials for this review from a search of PubMed using as filters keywords relating to T2DM management in older people. In addition, a manual review of the references lists from retrieved articles was also performed to find further articles. Papers were reviewed for relevance by abstract, selecting only English language articles. The final list of cited references was chosen on the basis of relevance to the topic of review.

Epidemiology of diabetes in the elderly

Ageing population is a growing problem and an important risk factor for several chronic diseases such as diabetes mellitus (DM) [16,17]. The prevalence of diabetes among US adults aged ≥65 years ranges from 22% to 33%, depending on the diagnostic criteria used [18,19]. Current estimates indicate that in the US, 26.9% of people ≥65 years of age are diagnosed with diabetes [20]. The high prevalence of T2DM among the elderly has been confirmed in a prospective population-based study in The Netherlands, showing that elderly patients, aged 70 years and over, account for 50% of the type 2 diabetic population, supporting health-care planning for older people [21].

As the population ages and both overweight and obesity continue to rise, the prevalence of diabetes in the elderly is expected to further increase [18,22,23] amplifying the already high burden of disease and its related costs [24]. Already today, the prevalence of diabetes in nursing homes is particularly high and care for diabetes in this setting specific is often inappropriate or insufficient [25,26]. Moreover, diabetes in the elderly is a well-recognized cause of accelerated frailty, disability, hospitalization, institutionalization, and death, thus absorbing a growing fraction of healthcare resources [14,27,28].

Overview on pathogenesis of diabetes in the elderly

Aging is a process characterized by a multifaceted interaction of genetic, epigenetic, and environmental factors [29]. Genetic variants have been shown to impact on human longevity, showing a strict association with both unsuccessful aging and diabetes [29-31]. A strong genetic predisposition to T2DM in the elderly is apparent as well though only some candidate genes have been identified [32,33]. The pathogenesis of T2DM is characterized by two major mechanisms: impairedβ-cell function and insulin resistance [34]. The former is the main defect observed in lean older subjects, while obese older patients have relatively normal insulin secretion but marked resistance to insulin-mediated glucose disposal [35]. The Cardiovascular Health Study showed that the association between some risk factors and incident DM varied significantly depending on whether DM was preceded predominantly by insulin resistance, β-cell dysfunction, or both, thus suggesting putative subtypes of DM with biologic and clinical implications [36]. With aging, glucose-stimulated insulin response tends to decline, impaired insulin secretion pulsatility is lost, decreased sensitivity to incretins develops, andβ-cell mass is reduced [17]. Many events contribute to the age-related loss of β-cell mass and function, including

the age-associated mitochondrial dysfunction, as well as increased oxidative stress and inflammation [36-42].

Aging results in a progressive loss of muscle mass and strength called "sarcopenia" that has a complex etiology involving neuronal, hormonal, immunological, nutritional and physical activity mechanisms [43,44]. Muscle mass loss in the elderly is associated with an increased fat mass infiltration that has been shown to be associated with worsened insulin sensitivity [45]. In this regard, in a recent cross-sectional study of 301 non diabetic subjects with a mean age of 65.9 years, a strong association between insulin resistance and relative muscle mass has been described [46]. Similarly, an association between sarcopenia and insulin resistance, diabetes, and metabolic syndrome has been reported in a large Korean population, particularly in elderly participants [47]. The link between sarcopenia and insulin resistance is a complex one, most likely mediated by several factors (i.e. mitochondrial dysfunction, reactive oxygen species, subtypes of adipocytes, fat-associated inflammation and adipocytokines) as recently reviewed [48]. Anyway, though sarcopenia may be not the primary cause of skeletal muscle insulin resistance in the elderly subjects, loss of lean muscle mass can be considered a worsening determinant.

Moreover, poor dietary habits and decreased physical activity all contribute to reduce insulin sensitivity in older population [49]. Glucose metabolism in older people can also be affected by co-existing illnesses and polypharmacy [33]. Finally, autoimmune phenomena may play a role in the pathogenesis of T2DM in a subset of older patients [50].

Although understanding of the pathogenesis of type 2 diabetes has advanced rapidly, the underlying molecular mechanisms remain partially unknown even because they are multiple, complex and linked each other. There is a huge progress in aging research on the role of the nutrient sensor mammalian target of rapamycin (mTOR) in aging and age-related diseases, including insulin resistance [51]. mTOR integrates multiple signals including growth factors, hormones, and cellular energy levels to regulate protein translation and cell metabloism, and survival, thus mediating the nutrient effects on insulin resistance. The attractive link between mTOR and insulin signaling cascades suggests that mTOR could become a therapeutic target in insulin-resistant status, even if its clinical application in metablic diseases is still limited [51].

In summary, diabetes in the elderly is the result of a tangled and still incompletely understood combination of genetic and environmental factors that overlap and are magnified by the ageing process (Figure 1).

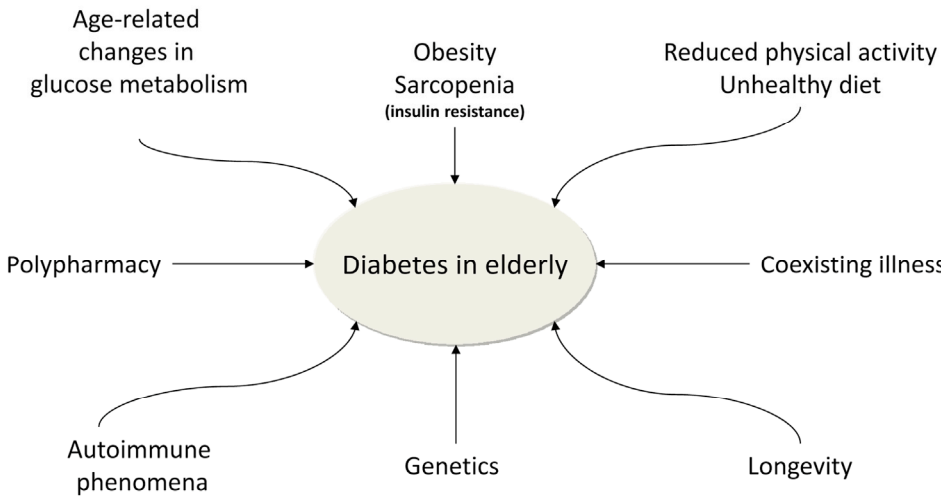

Figure 1. The figure 1 shows the main factors contributing to the high prevalence of diabetes mellitus in the elderly.

Special thoughts for elderly patients affected by type 2 diabetes mellitus

T2DM can be independently associated with various aging phenotypes collectively defined as "geriatric syndromes" [11,52-57]. These geriatric conditions should be referred to as a *third category* of diabetic complications [58] and include cognitive impairment and dementia [55,59-67], depression [68,69], reduced muscle strength and quality [70-72], disability [73-77], falls and fall-related morbidity [78,79], as well as urinary incontinence [80]. These clinical conditions are very frequent in older diabetic people, especially in the frail ones. When present they exert a negative effect on the quality of life, functional outcomes, and mortality [54,81-83]. Moreover, these impairments, in particular cognitive decline, can affect in a significant manner the (self)-management of diabetes [84,85]. The cognitive decline is likely to initiate early in the natural progression of diabetes and it correlates with overall glycemic control [86-88]. To emphasize the link between T2DM and cognitive function some authors have proposed Alzheimer's disease as a third form of diabetes [89]. The etiology of cognitive impairment in diabetic patients is multifactorial [90] with a role played by dysglycemia, microvascular disease, insulin resistance, hyper-phosphorylation of tau protein, amyloid-β deposition, inflammation and oxidative stress [91,92]. More recently a role for sirtuins has been claimed. Sirtuins belong to a family of highly conserved protein deacetylases that depend on nicotinamide adenine dinucleotide (NAD+) for their activity [93]. These proteins have been shown to influence the course of several neurodegenerative disorders by controlling transcription factor activity [94,95]. Expression of SIRT1, the best characterized member within the family of sirtuins, seems to be reduced in T2DM and in conditions of insulin resistance [96], while, its activation improves insulin sensitivity [97].

Older diabetic people may be more vulnerable also because of coexisting comorbidities and related polypharmacy. Moreover, aging may be associated with changes in several pharmacokinetic and pharmaco-dynamic parameters. These include reduction of renal and hepatic function and increased volume of distribution of lipid soluble drugs resulting in an increase of drug half-life [98-101]. Pharmacodynamic changes can cause drug accumulation in the circulation and intensified sensitivity, for instance, to sulfonylureas thus increasing the risk of hypoglycemia [98]. In this setting, aging *per se* is a strong predictor of hypoglycemia [102-104] and hypoglycemia, in turn, is a major complicating factor of antidiabetic treatment [105]. Impaired counterregulatory response and increased symptom threshold worsen the risk and outcomes of hypoglycemia in elderly diabetic patients [106-107]. The risk of such an event in the elderly can be by reduced or irregular eating pattern, intercurrent diseases and concomitant use of other drugs [108]. Patients on five or more medications, particularly if they include ACE-inhibitors and nonselective beta-adrenoceptor antagonists, are more prone to drug-induced hypoglycemia [102-103]. Altogether, the various degree of concomitance of these factors may account for the variable rate of hypoglycaemia in the elderly reported in the literature. In the ACCORD trial, each one year increment in baseline age was associated with a 3% increase in the risk for hypoglycaemia requiring medical assistance [109].

Hypoglycaemia in the elderly is associated with serious morbidity, including cardiovascular events, stroke, arrhythmias, and falls result in fractures on a background of osteoporosis [110-117]. Results of post-hoc analyses of both the ACCORD and VADT trials have shown a strong association between severe hypoglycemia and cardiovascular mortality, especially in the elderly population [118]. In the ACCORD trial, intensive glucose lowering increased the risk of cardiovascular disease and total mortality in younger participants whereas it had a neutral effect in older participants, though the older subgroup had a greater annualized rate of severe hypoglycemic episodes [119]. Prevention of hypoglycemia requires identification of risk factors [102,113], patient and family education and reassurance regarding prevention, detection, and treatment of hypoglycemic events [4]. Reducing the risk of hypoglycemia should follow, in the elderly, the paradigm "start low and go slow" [100].

However, the heterogeneity of the older diabetic population must be fully appreciated [120] if adequate glycemic control has to be provided. Optimal care should balance health and function, tapering and tailoring the pharmacological approach in order to reach invidualized goals while avoiding clinical inertia. Biological rather than chronological age of the patient should be considered in defining therapeutic strategies [121]. Assessment of psychological age and social age is also recommended as part of a comprehensive (and multidisciplinary) geriatric appraisal of older people with diabetes in order to address the role of various comorbidities and polypharmacy before selecting treatment plans [122].

Diabetes treatment guidelines for the elderly

Optimizing drug therapy is essential in the care of an older person. In line with the Quality Use of Medicines Framework, three key steps should be considered in drug prescription: 1) to identify the best treatment

(considering non-pharmacological measures whenever possible); 2) to select medicines cleverly (considering the possibility of serious adverse effects or drug-to-drug interactions); and 3) to use medicines based on the strongest clinical evidences [123]. Likewise, three subgroups of older patients should be considered: 1) those who are relatively healthy; 2) those with complex medical histories in whom self-care may be difficult, and 3) those with a significant comorbidities and functional impairment [124,125]. Therefore, clinicians caring for older diabetic patients have to solve a therapeutic puzzle: balancing the patient's needs while taking into consideration health profile and glycemic goals and avoiding adverse effects.

Past guidelines have often not been able to provide specific recommendation for older diabetic patients. The California Healthcare Foundation/American Geriatrics Society in collaboration with other medical organizations suggested that a reasonable HbA1c goal for "relatively" healthy elderly with good functional status should be ≤53 mmol/mol (<7%). On the contrary, for frail adults or with life expectancy <5 years, and when the risks of intensive glycemic control appear to overcome the benefits, a target HbA1c of 64 mmol/mol (8%) is suggested [54,126,127]. The U.S. Department of Veterans Affairs and the U.S. Department of Defense (VA/DOD) diabetes guidelines were updated few years ago. The VA/DOD guidelines do not distinguish by age-group, but stratify glycemic goals based on comorbidity and life expectancy [128]. The more recent ADA-EASD position statement suggests that the goals of treatment for older T2DM patients who are cognitively intact and have long life expectancy should be the same as those for younger subjects, while less stringent goals are suggested for those with limited life expectancy, advanced diabetes complications, or extensive comorbid conditions [14]. Recently, the International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People, and the International Task Force of Experts in Diabetes recommended a target HbA1c range of 53-58 mmol/mol (7-7.5%) should be aimed for (DCCT aligned) for older T2DM patients with a single system involvement (Evidence level 1+, Grade of recommendation A), while for frailer (dependent; multisystem disease; care home residency including those with dementia) patients at high risk of hypoglycaemia in whom symptom control and avoidance of metabolic decompensation is paramount, target HbA1c range should range between 60-69 mmol/mol (7.6-8.5%) (Evidence level 1+, Grade of recommendation A) [15]. In the attempt to provide a less dictated approach a pragmatic strategy based on four variables has been recently proposed: (A)ge, (B)ody weight, (C)omplications and (D)uration of disease (ABCD) [121]. In short, in younger patients the goal is minimizing the risk of long-term complications while in older patients, especially in the frail ones the goal is to minimize shorter-term geriatric syndrome and maximize quality of life [127].

Determinants of glycemic control in elderly patients affected by T2DM are summarized in Figure 2.

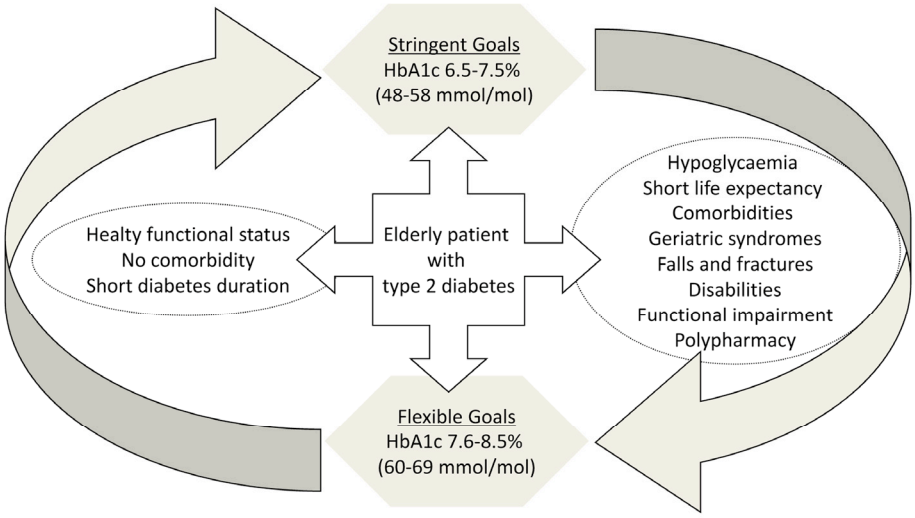

Figure 2. The figure 2 reports determinants of glycemic control in elderly patients affected by type 2 diabetes mellitus.

Treatment options

Mechanisms of action, advantages, disadvantages, concerns and novel aspects are summarized in the table.

Table. The table summarizes properties of currently available glucose lowering agents in elderly patients affected by type 2 diabetes mellitus

Sulfonylureas (1st generation: glibenclamide 2nd generation: glipizide, glimepiride, gliclazide)	Increased release of insulin by glucose independent closure of the ATP-sensitive K-channels	Proven glucose lowering efficacy Long term clinical experience Relatively low cost	Risk of hypoglycaemia Weight gain	Caution in renal impairment, hepatic dysfunction, concomitant insulin therapy, recent hospitalization, poor nutrition, cognitive decline and polypharmacy Cardiovascular profile is an important concern	
Glinides (repaglinide)	Increased release of insulin with a mechanism partially glucose dependent	Rapid onset of action and short duration Improved post-prandial hyperglycaemia	Risk of hypoglycaemia Weight gain Frequent dosing schedule Relatively high cost	Caution in hepatic dysfunction, concomitant insulin therapy, recent hospitalization, poor nutrition, cognitive decline and polypharmacy Cardiovascular profile is an important concern	
Dipeptidyl peptidase-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin)	Stimulation of insulin secretion Suppression of glucagon secretion	Low risk of hypoglycaemia	Increased respiratory infections Angio-edema Relatively high cost	Limited long term data Pancreatitis (?)	Potential cardio-protective and neuro-protective effects
Glucagon-like peptide 1 analogues (exenatide, liraglutide, lixisenatide)	Stimulation of insulin secretion Suppression of glucagon secretion Slow gastric emptying	Low risk of hypoglycaemia Weight loss	Gastro-intestinal effects (nausea/vomiting) Injectable Relatively high cost	Limited data on elderly patients Pancreatitis (?)	Potential cardio-protective and neuro-protective effects

Sodium-glucose cotransporter 2 inhibitors (canaglifozin)	Target Inhibition of renal reabsorption of glucose	Low risk of hypoglycaemia Systolic blood pressure reduction	Genitourinary infections, especially in women Pollakiuria Unintended weight loss	Cancer risk (?) Dose adjustment may be recommended in the elderly on loop diuretics and in those with an estimated GFR<60 mL/min or suffering from orthostatic hypotension	
Insulin **Fast-acting: insulin lispro** **Insulin aspart** **Insulin glulisine** **Long acting:** **Insulin glargine** **Insulin detemir** **Ultra long acting: insulin degludec**	Replacement of endogenous insulin	Mimics physiology Rapidly effective Theoretically unlimited efficacy	Risk of hypoglycaemia Injectable Weight gain	Require patient's ability or caregiver involvement Glucose monitoring and dose adjustment	

Metformin

Metformin acts primarily through insulin sensitization of the liver, thus reducing hepatic glucose output and, secondarily, improving peripheral insulin resistance [129]. The recent ADA/EASD position statement and the AACE/ACE guidelines recommend metformin as first line treatment drug, due to its effectiveness and low risk of hypoglycemia [14,130]. In line with these recommendations, EDWPOP clinical guidelines stated that "age per se is not a contraindication to metformin" (Evidence level 2++; grade of recommendation B) [15] with some reduction in all-cause and cardiovascular mortality as compared to sulfonylurea monotherapy [131]. Metformin can cause gastrointestinal side effects (i.e. nausea, diarrhea, vomiting, abdominal pain), usually related to rapid titration and high dose initiation [132]. These adverse effects, although transient, may be undesirable in older, frail, anorexic and underweight patients [133], and may represent a dose-limiting barrier [134]. Metformin can also result in poor vitamin B12 status [135-137], which might accelerate cognitive dysfunction [138]. However, the main concern with respect to the use of metformin in the older adult with diabetes relates to the frequent existence of impaired renal function that should be regularly monitored in all patients on the drug [14,15,139]. EDWPOP guidelines recommend avoiding metformin "in patients with renal impairment and severe coronary, cerebrovascular or peripheral vascular disease" (Evidence level 2++; grade of recommendation B) [15] because of the risk of lactic acidosis. However, the observed association between metformin and lactic acidosis may be coincidental rather than causal [140], and there is no evidence from prospective comparative trials or from observational cohort studies that the risk of lactic acidosis and lactate levels differ appreciably in patients taking metformin as compared to other glucose-lowering treatments [141]. In a recent cross sectional analysis, it has been demonstrated that in elderly diabetic patients with moderate to severe renal impairment, the prescription of oral anti-hyperglycemic treatments is frequent, although inappropriate or not recommended. Nonetheless, metformin was associated with lower cardiovascular event rates [142]. The dose of metformin should be reduced (by 50% or to half-maximal dose) in patients with a GFR 30 to 45 mL/min per 1.73 m^2, and monitored at 3-month interval and the drug stopped for an eGFR <30 ml/min per 1.73 m^2 [143,144].

Metformin continues to gain attention for potential anti-cancer properties and neuro-protective effects, thus emerging as a novel therapeutic agent in aging-related diseases [132].

Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome proliferation activated receptor-gamma (PPAR-gamma) agonists that improve peripheral insulin sensitivity by increasing peripheral adipose tissue lipogenesis and reducing hepatic fat content and hepatic glucose production [145]. TZDs could be an appealing strategy in the geriatric practice because of the low risk of

hypoglycemia in comparison with sulfonylureas [146]. However, the real use of TZDs in the elderly is limited by their potential side effects. As suggested by two large observational studies, women taking TZDs have an increased risk of fractures as compared to those treated with other oral anti-diabetic drugs [147,148]. Similarly, TZDs have been associated with a questionable risk of bladder cancer [149-151]. Finally an increased prevalence of congestive hearth failure has been reported in patients on TZDs [152]. More debated remain the association between TZD use and cardiovascular events. In a case-control study of a cohort of 159,026 patients aged ≥ 66 years, TZD therapy (primarily rosiglitazone) was reported to be associated with increased risk of congestive hearth failure, acute myocardial infarction and death as compared to other oral hypoglycemic agents [153]. These results have not been confirmed in other studies [154] while an observational study suggested that TZDs were not associated with increased mortality for cardiac events and congestive heart failure in older patients [155]. The PROACTIVE prospective study showed a modest reduction of cardiovascular end points associated with pioglitazone [156] especially in patients with no peripheral artery disease [157].

In a 6-month randomized, open-controlled trial, it was reported that treatment with pioglitazone in diabetic patients affected by Alzheimer disease was associated with improvement in both cognition and regional cerebral blood flow, suggesting that PPAR-gamma agonists may offer a novel strategy for treating cognitive dysfunction [158].

Anyway, TZDs should not be considered a first-line approach and should be avoided in patients at high risk of weight gain, peripheral edema, heart failure, and bone loss and in those with history of osteoporosis or bladder cancer.

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs) specifically target postprandial hyperglycemia by reducing carbohydrate digestion and absorption [159]. The hypoglycemic effect of AGIs is non as powerful, lowering HbA(1c) by 0.5-1%, but the risk of hypoglycemia, when they are used in monotherapy, is low, making these agents of interest in the elderly [35]. In older diabetic patients inadequately controlled on diet alone, acarbose has been associated with a significant reduction in HbA1c (-0.6%) as well as in the incremental post-prandial glucose values (-2.1 mmol/L) and mean fasting plasma glucose (-0.7 mmol/L) as compared to placebo [160]. In patients on prandial insulin, a mismatch between peak serum glucose level and peak prandial insulin levels may occur, with a possible increased risk of hypoglycemia [98], but a randomized, open-label study comparing the efficacy and safety of preprandial insulin in combination with acarbose in elderly patients (≥60 years) showed that addition of acarbose allows insulin adjustment from 30 min to immediately before meals, without affecting glycemic control, along with a low incidence of hypoglycemia [161]. However, the gastrointestinal adverse effects (i.e. abdominal bloating, flatulence, and diarrhea), frequent dosing, and relatively high costs [58] represent a limitation for the use of AGIs in geriatric patients

Insulin secretagogues

Insulin secretagogue therapy (sulfonylureas, SUs and glitinides) is commonly used in clinical practice. These agents may be utilized as first, second-line or adjunct therapy behind metformin for treatment of T2DM. SUs cause glucose independent closure of the ATP-sensitive K-channels and release of insulin by binding to the SUR1 receptor on pancreatic beta cells [162,163]. Meglitinides, including repaglinide, have a similar mechanism but are partially glucose dependent and characterized by a rapid onset time and shorter duration of action [164,165]. EDWPOP guidelines for T2DM suggest adding an insulin secretagogue when glycemic targets have not been achieved or maintained (evidence level 1+; grade of recommendation B), avoiding glibenclamide in elderly persons (>70 years) with newly diagnosed T2DM because of marked risk of hypoglycaemia (evidence level 1+; grade of recommendation A) [15]. Renal impairment, hepatic dysfunction, concomitant insulin therapy, recent hospitalization, advanced age, poor nutrition, cognitive decline and polypharmacy are the main risk factors of hypoglycemia [102,166]. However, difference in such a risk exists among SUs with gliclazide being associated with lowest rate of hypoglycemia. Therefore, gliclazide, glipizide and third generation SUs (i.e. glimepiride) have been suggested as preferred agents in the elderly [102,166,167]. Accordingly, the American Geriatric Society clinical guidelines suggest short acting anti-diabetic agents to be preferred to longer-acting SUs [15,54].

A 24-week, randomized, open label, crossover trial, in elderly patients aged ≥65 years and in a subgroup of 37 patients aged≥75 years showed that treatment with repaglinide was associated with fewer hypoglycemic events as compared with those treated with gliben-clamide [168]. Nonetheless, the risk of hypoglycemia associated with the use of meglitinides is not trivial [169].

Finally, cardiovascular profile of SUs is an important concern because of their possible effects on ischemic

preconditioning [170], though the true relevance of this phenomenon has not yet been fully demonstrated and it is largely based in animal studies. Nonetheless, in a retrospective analysis, an increase in overall mortality risk has been reported for sulfonylureas as compared to metformin [171]. To summarize, SUs should not be seen as first-line treatment choice in the elderly. Were a sulfonylurea introduced, it should be prescribed with caution, usually starting at half the usual dose and to be titrated gradually while providing the person with diabetes and his/her relatives adequate education with respect to the risk of hypoglycemia.

Incretins

Dipeptidyl peptidase-4 inhibitors (DPP4-I), usually referred as gliptins, are a relatively novel class of oral anti-hyperglycemic agents that stimulate insulin secretion and suppress glucagon secretion in a glucose-dependent manner [172,173]. Due to their efficacy, low risk of hypoglycemia and good tolerability, gliptin-based therapy plays a novel role in the management of diabetes and appears a fitting and intriguing choice for older adults [152,174]. According to the DWPOP guidelines, DPP4-I should be considered as an add-on therapy to metformin when the use of a SU poses an unacceptable risk of hypoglycemia (evidence level 1+; grade of recommendation A) [15]. The potential benefits of DPP-4 in the elderly have been discussed in a number of reviews [2,58,169,175-177]. However, *ad hoc* studies to establish clinical efficacy of DPP4-I in elderly T2DM patients have been only recently performed. These trials confirm in these individuals as well significant reduction of HbA1c with no hypoglycemia, body weight gain or other side effects [178-186]. Trials have been also performed in patients with moderate and severe renal impairment. With appropriate dosage adjustment with the exception of linagliptin, which has no renal excretion, these studies too have confirmed a good benefit-to-risk ratio with no further loss in renal function nor increased rate of hypoglycemia [187-192]. In the recent INTERVAL study, a multinational, double-blind, 24 week trial, drug naïve or inadequately controlled diabetic patients aged ≥70 years were randomly assigned to vildagliptin (patient mean age 75.1 yrs) or placebo (patient mean age 74.4 yrs)_while setting individualized treatment targets on the basis of age, baseline HbA1c, comorbidities and frailty status [193]. Vildagliptin-treated patients achieved targets in 52.6% of the cases versus 27% of placebo-treated group, with a significant, relevant reduction of HbA1c values and no emergence of new safety signals [193]. Vildagliptin is metabolized mainly in the liver so liver function monitoring should be recommended, even if a recent meta-analysis indicated that vildagliptin is not associated with increased risk of hepatic events [194]. In diabetic patients aged up to 80 years, linagliptin had significant glucose lowering effects, showing a well-tolerated profile, which may result particularly useful in the elderly [195-199]. In a recent randomized, double blind, parallel-group, multinational phase 3 study, including patients aged 70 years or older (mean age 74·9 yrs), linagliptin was effective in lowering glucose, with a safety profile similar to placebo [186]. Data on the safety and efficacy of saxagliptin in the elderly are limited. Karyekar *et al* performed a post hoc analysis of pooled data from five 24-week phase 3 trials including older patients aged ≥65 years [185]. Results showed that saxagliptin was effective and well tolerated either when used as monotherapy, as add-on therapy, or initial combination therapy with other anti-diabetes drugs. Hypoglycemia, not requiring medical intervention, was reported in 3.0% to 9.4% of patients taking saxaglipitn (0%-8.0% for comparators) while confirmed hypoglycemia occurred in 0% to 0.7% (0% to 0.7% for comparators) [185]. Similar results have been reported for aloglipitn (as monotherapy and co-administration with other anti-diabetic agents) in a pooled analysis of six randomized, double blind, placebo-controlled studies, comparing the efficacy and safety of alogliptin in elderly (mean age 70 yrs) and younger (mean age 51.8 yrs) patients with type 2 diabetes mellitus [179]. The efficacy and tolerability of sitagliptin have been evaluated in a randomized, double blind, placebo-controlled, parallel-group study in diabetic patients aged ≥65 years (mean age 72 yrs). Although a relatively small number of subjects has been included, the study demonstrated that sitagliptin significantly improved glycemic parameters, with no hypoglycemia [184].

Over the last years more information on the potential of this class of oral agents have been gathered to further enhance the interest with respect to their use in elderly patients. Recent data suggest that gliptins may have pleiotropic, additional non-glycemic properties, including cardio- [200] and neuro-protective effects [201-204]. Cardiovascular (CV) safety of gliptins is a field of growing interest. In the SAVOR-TIMI trial while no effect on overall CV morbidity and mortality was reported, an excess of hospitalization for heart failure was observed [205]. This finding will require further assessment as absolute number of events was limited and an imbalance in the pro-BNP levels was present in the sitagliptin vs the control group with increased hospitalization occurred in the patients in the top pro-BNP quartile. Results from EXAMINE showed that among diabetic patients who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not different between patients on alogliptin as compared with those on

placebo [206]. Taken together, these data confirm a neutral cardiovascular safety profile in high CV risk patients, as often are older T2DM individuals.

Glucagon-like peptide 1 (GLP-1) analogues include exenatide, liraglutide, and lixisenatide. These compounds may have a slightly greater effect on HbA1c as compared to DPP4-I, low risk of hypoglycemia and cause a moderate loss in body weight [207]. According to the DWPOP guidelines GLP-1 agonist may be considered as 3th line add-on therapy to metformin and SU (evidence level 2++, grade of recommendation B) in very obese older patients up to an age of 75 years) [15]. Data on these agents above this age, especially the *frail patient*, are scanty [98,208]. In a placebo-controlled, patient-blind, crossover study compared elderly patients (mean age 78 ± 3 yrs) to controls (mean age 57 ± 6 yrs) with T2DM, exenatide was tolerated in all age groups, and dosage adjustment was requested according to patient's renal function [209]. A pooled analysis of 6 randomized, placebo-controlled, multinational trials included data from 3967 patients aged 18 to 80 years has shown that liraglutide provides effective glycemic control and is well tolerated in patients aged ≥65 years [210], although its use can be limited by concomitant impairment of the kidney function. Lixisenatide is the most recently approved GLP-1 receptor agonist [211,212], but less information, particularly in older T2DM patients, are available. Though preliminary data may suggest a potential neuro-protective effect [213,214], results of intervention trials are awaited. Importantly, clinical trials of the effects of GLP-1 agonists in patients with neurodegenerative diseases have been started, and clinical trials in patients with mild cognitive impairment or early-phase Alzheimer disease are on their way.

Although GLP-1 analogs are characterized by a favorable benefit-to-risk ratio, their use in the elderly should consider potential impairment of kidney function as well as gastric side effects. These compounds, though with some difference within the class, can cause nausea and vomiting and, therefore, may not be indicated in those elderly patients with erratic nutrition habits nor they may be recommended in those with lower body weight or progressive loss of body weight.

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent a novel approach to treat T2DM. The mechanism of action is unique and does not hinge upon beta-cell function or tissue insulin sensitivity [215,216]. Through SGLT2 inhibition, reabsorption of tubular glucose is reduced and urinary glucose excretion increased [217] with very low risk of hypoglycemia. Moreover, loss of glucose causes mild but persistent reduction in body weight and concomitant fluid loss can reduce blood pressure. In a randomized, double-blind, placebo controlled phase 3 study, the efficacy and safety of canagliflozin, at different dosage, have been evaluated in older diabetic patients, aged 55 to 80 years (mean, 63.6 years), which were inadequately controlled on their usual treatment regimen [218]. The study demonstrated good tolerability and significant amelioration of glycemic control, along with a reduction of body weight and systolic blood pressure [218]. The most common side effects of these drugs include genitourinary infections and pollakiuria while, effects potentially dangerous for the geriatric age, such as dehydration, is uncommon. To note that concomitant prostate hypertrophy has not been so far identified as a limitation for the use of these agents [219,220]. Dose adjustment may be recommended in the elderly, those on loop diuretics, and those with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m(2) if there are concerns or symptoms of volume-related side effects [221]. The efficacy of SGTL-2 inhibitors is likely to be self-limited in the presence of reduced GFR as this will be consensually associated with reduced tubular load and therefore reduced glucose excretion. Nonetheless, in a randomized, double-blind, placebo-controlled, phase 3 trial, canagliflozin improved glycaemic control and was generally well tolerated in subjects with T2DM and stage 3 chronic kidney disease [222]. Though SGLT2 inhibitors appear to be an emerging, appealing treatment option in diabetes, the safety issue remains the most important parameter determining the future of these drugs and more studies are needed before specific suggestions for elderly patients can be made.

Insulin

The natural history of T2DM is characterized by a progressive decline in β-cell mass and function [223]. As a consequence, insulin therapy may be needed in older diabetic patients [98], also own to the anabolic effect the hormone. However, use of insulin requires special considerations in elderly patients. Comorbidities, cognitive dysfunction, vision loss, neuropathies, disabilities, and poor manual dexterity can all affect the patient's ability to self-management of insulin and may be limiting factors to insulin use in some cases or require caregiver assistance. Indeed, clinicians should evaluate the social network of patients who may have difficulty administering insulin – including family, friends, and caregivers – and should also determine whether the patient is socially isolated and/or living alone [224]. On the other hand, data show that insulin initiation in poorly controlled diabetic patients can improve quality of life [225]. Insulin

initiation should be performed with caution and with defined targets to prevent worrisome adverse events, in particular hypoglycemia. As already stated, it is advisable to "start low and go slowly", taking particular attention to insulin dose titration. Insulin requirements may be variable in elderly patients due to habits and pathophysiologic factors as well. While renal dysfunction may reduce renal insulin clearance and result in insulin accumulation with increased risk of hypoglycemia, concomitant use of other drugs can result in an increased insulin demand as it may occur with steroids. When oral agents fail to lower glucose levels adequately, insulin can be used either as monotherapy or in combination with a SUs or metformin (Evidence level 1+, grade of recommendation) [15]. Short acting insulin analogs (i.e insulin lispro, aspart, and glulisine) can help in the case of unpredictable eating habits or in those patients unable to adhere to dietary recommendations. Insulin dose can be titrated by carbohydrate intake also after meal when amount of carbohydrate ingested is erratic [224]. The long-acting basal insulin analogs (insulin detemir and glargine) represent by and large the most common choice for basal insulin therapy in elderly patients [14,15]. These analogs offer several advantages, including a more physiologic pharmacologic profile and they carry a reduced risk of hypoglycemia, particularly of nocturnal hypoglycaemia [226-228]. Focusing on elderly subjects, a pooled analysis of data from five randomized controlled trials showed that addition of insulin glargine to oral antidiabetic drugs in older adults (aged ≥65 years) with poor glycemic control was associated with greater reductions in HbA1c and fasting blood glucose and lower risk of nocturnal hypoglycemia as compared to NPH insulin [229]. Moreover, in a planned subgroup analysis of the original study, addition of once-daily morning glargine emerged as a simple regimen to initiate insulin therapy in elderly patients (aged 65 and older), restoring glycemic control more effectively and with less hypoglycemia than twice-daily 70/30 alone [230]. The new basal insulin analog, insulin degludec, has showed peculiar characteristics, including stable pharmacokinetic and pharmacodynamic profiles, true 24-hour duration of action in all patients, low within-person variability in absorption and glucose-lowering action, more flexible dose timing, and low occurrence of hypoglycemia [231]. In a recent pre-planned meta-analysis in elderly patients (≥ 65 years), the rate of confirmed and nocturnal hypoglycemia was significantly lower with insulin degludec as compared to insulin glargine [232]. Insulin premix formulations, in some elderly patients and in special settings, may provide added convenience [233]. Insulin pen devices may facilitate insulin injection and dosing and help patients maintaining their independence [224].

In summary, insulin remains the most effective and flexible form of treatment and as such it remains a valuable treatment opportunity in the elderly diabetic person, although insulin therapy in this group of subjects has not been adequately investigated. Moreover, the limited data comparing different insulin treatment schemes do not allow an evidence-based choice of insulin regimens in the elderly [234]. As repeatedly stated, careful individualization of insulin therapy as well is needed. While fast-acting insulin may be preferred to control post-prandial glucose, a carefully adjustment of dose on the basis of carbohydrate consumption is needed. Long-acting insulin can be easier to use though their long duration must be carefully taken into account as they may expose the elderly patient to the risk of late hypoglycemia. Careful education must be provided to the patient, his/her family and any person that may assist him/her. Finally, insulin may be necessary in concomitance with any intercurrent acute event, such as an infection, trauma, or surgical operation.

Emerging drugs

Recent observations showing that a family of enzymes called sirtuins can significantly extend life in various organisms has led researchers to believe that they may also be capable to control age-related metabolic disorders, including obesity and type 2 diabetes in humans. It is well known that Sirtuin-1 (SIRT1) may have anti-diabetic effects, modulating insulin secretion and improving insulin resistance through several mechanisms [235]. Therefore, identification of therapeutic agents capable of modulating the expression and/or activity of sirtuins is expected to provide promising strategies for optimizing diabetes care [235]. In this regard, in vitro and animal studies have demonstrated that synthetic compounds, which have potent SIRT1-activating power, may improve insulin sensitivity in peripheral tissues (skeletal muscle and liver), reduce plasma glucose, and increase mitochondrial capacity [236,237]. Because of the sirtuin family's role in aging and age-associated pathologies, elderly subjects may represent the target populations for the treatment with this new class of compounds. Recently, elderly volunteers (mean age 67.1 yrs; range 61-77 yrs) were treated with SRT2104, a selective small molecule activator of SIRT1 or placebo once daily for 28 days, exploring multiple pharmacodynamic endpoints [238]. In this trial, although any significant changes in OGTT were observed, it has been demonstrated a trend toward a slower increase in insulin

and C-peptide in the treated group [238]. The new molecule was generally safe and well tolerated and this observation supports further development of sirtuin activators to be used in future clinical trials in elderly patients.

CONCLUSIONS

In spite of the fact that elderly diabetic patients account for a great majority of the diabetic population, limited attention has been paid in clinical trials thus limiting the clinical evidence on which treatment guidelines may find ground. Indeed, randomized trials generally have excluded older diabetic patients, in particular the *frail* ones, and clinical guidance has been largely based on data obtained in younger (adult) populations, thus making the optimal therapy of T2DM in geriatric patients controversial. Older people with diabetes represent quite a heterogeneous population that is more likely to have comorbidities and geriatric syndromes, in addition to cardiovascular complications and hypoglycemia. A more appropriate treatment of the elderly T2DM patients would require accurate definition of the geriatric patient not only based on clinical needs but also encompassing healthy, social, economic parameters. Clinicians must be fully aware of this heterogeneity in setting the therapeutic goals and in choosing the therapeutic strategy, which, invariably, should be centered on the patient's features, in line with the recent ADA/EASD position statement and in particular the ADA/AGS consensus document on diabetes in older adults [14,239]. These documents advocate a personalized and tailored care based on several elements, including patient's attitude and expected treatment efforts, risks potentially associated with hypoglycemia or other adverse events, disease duration, life expectancy, comorbidities and established vascular complications as well as resources and social and familial support. What must be always appreciate, however, is that age *per se* should not be an excuse for "clinical inertia" because the risk generated by inappropriate hyperglycemia has to be considered in all patients also in those with short life-expectancy. The complexity of interactions between comorbidity, polypharmacy, aging and settings where the older T2DM adult may be living must suggest caution as reflected by the classic adage "start low + go slow". Yet, the targets and overall aim of the treatment should be always made clear.

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