



# Type 2 diabetes mellitus in older adults: clinical considerations and management

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**Abstract** | The past 50 years have seen a growing ageing population with an increasing prevalence of type 2 diabetes mellitus (T2DM); now, nearly half of all individuals with diabetes mellitus are older adults (aged  $\geq 65$  years). Older adults with T2DM present particularly difficult challenges. For example, the accentuated heterogeneity of these patients, the potential presence of multiple comorbidities, the increased susceptibility to hypoglycaemia, the increased dependence on care and the effect of frailty all add to the complexity of managing diabetes mellitus in this age group. In this Review, we offer an update on the key pathophysiological mechanisms associated with T2DM in older people. We then evaluate new evidence relating particularly to the effects of frailty and sarcopenia, the clinical difficulties of age-associated comorbidities, and the implications for existing guidelines and therapeutic options. Our conclusions will focus on the effect of T2DM on an ageing society.

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The rising burden of type 2 diabetes mellitus (T2DM) is a substantial concern for health-care systems worldwide, with 1 in 11 people globally currently diagnosed with diabetes mellitus, ~90% of whom have T2DM<sup>1</sup>. A strong association exists between increasing age and T2DM, such that older adults (defined as those aged  $>65$  years) now constitute nearly half of all adults diagnosed with diabetes mellitus<sup>2</sup>. Notably, older adults show greater diversity in physical and cognitive abilities than younger adults. Furthermore, the presence of comorbidities, the increased predisposition to hypoglycaemic events, individual care needs and a lack of resilience that can lead to an increased risk of frailty further add to the complexity of disease management in older adults<sup>3</sup>.

This Review offers a current commentary on the key epidemiological, pathophysiological and clinical issues associated with T2DM in older adults. We evaluate emerging evidence of the effect of frailty and sarcopenia on T2DM, the clinical dilemmas posed by multiple morbidities, the implications for existing guidelines and the therapeutic options available. Focus is placed on the effect of T2DM in an ageing society.

## Epidemiology of T2DM in older adults

The number of older adults with T2DM is rapidly increasing worldwide; this change is primarily attributed to increased life expectancy with long-term prior exposure to cardiometabolic risk factors, especially excess adiposity, skeletal muscle shrinkage and reduced levels of physical activity<sup>4–7</sup>. Between 2017 and 2045, the global

population of adults aged  $\geq 65$  years with diabetes mellitus is projected to grow from 122 million to 253 million, in parallel with an estimated increase in the number of adults aged 65–99 years from 652 million to 1.42 billion<sup>8</sup>.

The prevalence of diabetes mellitus levels off in older adults, which probably reflects the balance between increased incidence in this age group and increased mortality amongst those diagnosed with T2DM earlier in life<sup>9</sup>. In the USA, the annual rate of newly diagnosed diabetes mellitus amongst older adults is of ~9.4 per 1,000 persons and the prevalence in this age group is of 21.4%<sup>9</sup>. Taking into account the trends of diabetes mellitus prevalence by age compared with World Bank income categories, high-income and middle-income countries show the highest prevalence (on average 22% and 19%, respectively) for adults aged  $\geq 60$  years<sup>8</sup>. Currently, the countries with the highest numbers of older adults diagnosed with diabetes mellitus are China (34.1 million, ~20% of all older adults), USA (11.5 million, ~21% of all older adults), India (11.0 million, ~17% of all older adults), Germany (4.9 million, ~27% of all older adults) and Brazil (4.3 million, ~22% of all older adults)<sup>4</sup>.

Prediabetes (defined as HbA<sub>1c</sub> levels of 5.7–6.4%) is present in almost half (48% or 26 million people) of older adults in the USA. Moreover,  $>2$  million older adults are estimated to have undiagnosed diabetes mellitus in the USA<sup>9</sup>. Indeed, older adults might dismiss non-specific symptoms, such as fatigue, nocturia, weight loss and blurred vision, as normal ageing. Furthermore,

**Key points**

- Older adults ( $\geq 65$  years of age) with type 2 diabetes mellitus (T2DM) account for nearly half of all individuals with diabetes mellitus.
- T2DM in older adults is highly heterogeneous but is generally associated with various degrees of underlying insulin resistance, excess adiposity,  $\beta$ -cell dysfunction and sarcopenia.
- The management of T2DM in older adults is complicated by the frequent occurrence of multimorbidity, necessitating highly individualized approaches.
- The presence of frailty, cognitive decline and functional impairments in older adults with T2DM highlights the importance of liaison with carers and social support.
- Targets for glycaemic control in older adults with T2DM are often less stringent than in younger adults to avoid hypoglycaemia and minimize unbeneficial interventions.

certain anaemias present in older adults (high red blood cell turnover, haemoglobinopathies or anaemia of renal disease) can distort HbA<sub>1c</sub> levels, leading to an underdiagnosis of T2DM<sup>10,11</sup>. Although T2DM comprises  $>90\%$  of all occurrences of diabetes mellitus in older adults (either newly diagnosed or long-standing diabetes), the number of patients with type 1 diabetes mellitus who are living into old age is also increasing. Of note, newly diagnosed diabetes mellitus in older adults could also rarely be a very late-emerging form of autoimmune diabetes<sup>2,12,13</sup>.

**Pathogenesis of T2DM in older adults**

T2DM is characterized by hyperglycaemia, which results from a progressive deterioration of insulin secretory  $\beta$ -cell function, typically combined with varying degrees of insulin resistance. These two key pathogenetic mechanisms are usually accompanied by other glucoregulatory disturbances such as inappropriate hyperglucagonaemia and an impaired incretin response (FIG. 1)<sup>14,15</sup>. Insulin resistance alone is seldom sufficient to trigger the development of T2DM as the pancreas can initially compensate by proportionally increasing insulin secretion. However, long-term hyperinsulinaemia incurs a stress on  $\beta$ -cells that disrupts the acute (first phase) insulin secretory response to a glycaemic stimulus and eventually impairs the later (second phase) insulin response<sup>14,15</sup>. Hence, inadequate insulin secretion is an essential pathogenetic component for most patients with T2DM<sup>14,15</sup>. Ageing contributes to the pathogenesis of T2DM both directly through the decreased  $\beta$ -cell function that accentuates the lack of insulin secretion and indirectly by increasing insulin resistance through obesity and other risk factors (FIG. 1)<sup>16,17</sup>. For example,  $\beta$ -cell senescence and reduced  $\beta$ -cell sensitivity to glucose during ageing increase the susceptibility to T2DM through inadequate compensation for insulin resistance<sup>18,19</sup>.

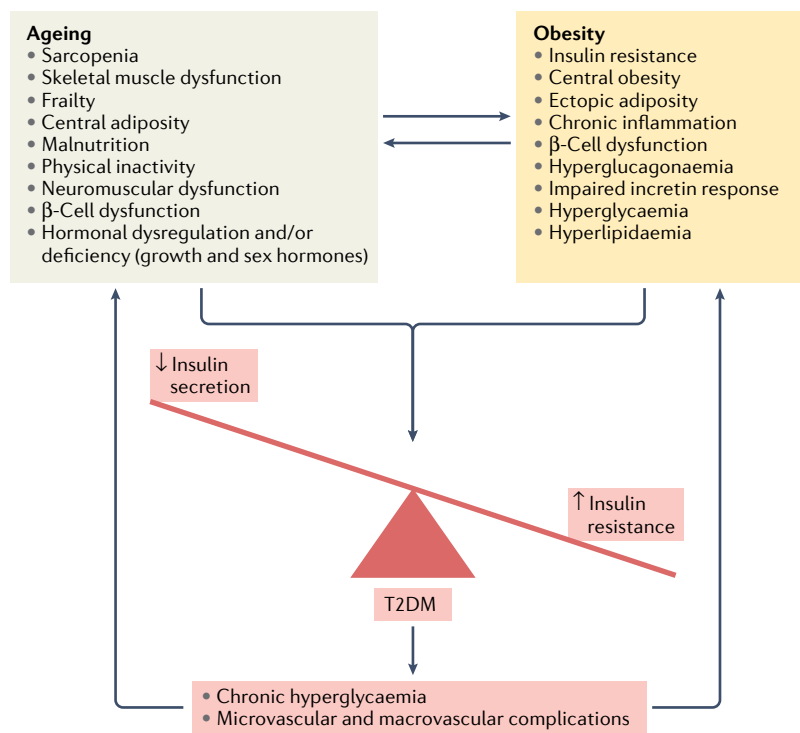
The detrimental effects of ageing on cellular pathways of insulin action and glucose metabolism are modest when age-related changes in body composition are considered<sup>20,21</sup>. For example, the effects of ageing that lead to increased insulin resistance are primarily associated with the excess adiposity and decreased muscle mass and function (sarcopenia) that are common in older adults, which can be worsened by a sedentary lifestyle (FIG. 1)<sup>17,22,23</sup>. Excess adiposity in older adults typically comprises an absolute or relative increase in visceral adipose tissue depots compared with subcutaneous

adipose tissue, which is often reduced<sup>24,25</sup>. Moreover, ageing is associated with ectopic deposition of lipids in the liver as well as with intracellular lipids and extra adipose tissue in cardiac and skeletal muscles<sup>25,26</sup>. These changes further increase the risk of insulin resistance, with intramuscular adipose tissue being a key factor contributing to insulin resistance in lean older people<sup>23,26</sup>. In addition, unfavourable age-related changes in body composition can be aggravated by physical inactivity and poor dietary habits as well as by the effects of comorbidities and their medications<sup>27,28</sup>.

Excess visceral and ectopic (intramuscular and hepatic) adiposity decreases insulin sensitivity by producing the adipokines and cytokines that impede the pathways of insulin action downstream of the insulin receptor, such as tumour necrosis factor, and low-grade inflammatory factors such as C-reactive protein<sup>29</sup>. Furthermore, both ageing and obesity are associated with the increased production of pro-inflammatory cytokines from adipose tissue<sup>30</sup>. In addition, both ageing and obesity are associated with an increased population of macrophages within adipose tissue, a decreased number of regulatory T cells and a reduced self-renewal of mesenchymal progenitor stem cells, thereby promoting metabolic dysregulation and inflammation<sup>31</sup>. Impaired nutrient metabolism and an age-related decline in mitochondrial function also link ageing and insulin resistance, although the mechanistic details remain to be clarified<sup>16,29,32</sup> (BOX 1).

Age-associated blunting of insulin-mediated glucose uptake is linked with the progressive deterioration of the structure and function of skeletal muscles. Specific age-related changes include a reduced skeletal muscle mass with smaller and fewer type II fibres as well as a decreased density of capillaries in skeletal muscle<sup>33,34</sup>. Underlying mechanisms include mitochondrial dysfunction, increased low-grade inflammation, intramyocellular lipid accumulation and oxidative stress as well as the accumulation of senescent cells and decreases in autophagic capacity and enzymatic activity<sup>23,35–37</sup>. During skeletal muscle ageing, pro-inflammatory pathways become activated. Furthermore, the number of mitochondria is reduced and their oxidative capacity is decreased due to the reduced activity of antioxidant enzymes, which leads to the intracellular accumulation of reactive oxygen species and increased levels of oxidative stress in skeletal muscle<sup>23,35</sup>. Although the complete spectrum of the underlying mechanisms has not been fully clarified, all of the processes that characterize skeletal muscle ageing induce insulin resistance and, accordingly, increase the risk of T2DM<sup>23,35</sup>.

Evidence suggests that a relationship exists between ageing and T2DM at a biological level: a number of studies in humans have shown that both diabetes mellitus and ageing shorten telomere length<sup>38</sup> (BOX 1) and that T2DM induces premature cellular senescence<sup>39</sup>. However, the nature of this relationship requires further study to understand if the biological processes involved in ageing drive T2DM pathology or if diabetes increases the rate of biological ageing. Ageing can indirectly increase insulin resistance and precipitate T2DM through several comorbidities that are prevalent among



**Fig. 1 | Pathophysiological links between ageing, obesity and T2DM.** Type 2 diabetes mellitus (T2DM) with overt chronic hyperglycaemia typically represents the outcome of an imbalance between increased insulin resistance and the deterioration of insulin secretory function. A combination of potential contributing factors due to both ageing and obesity can directly lead to this imbalance, which results in the development and progressive worsening of T2DM. In addition, obesity-related factors and hyperglycaemia can also contribute to premature or accelerated biological ageing. Furthermore, ageing via cellular senescence and dysfunction in various organs or tissues (for example, adipose tissue, skeletal muscles and pancreas) might heighten and/or accelerate the pathophysiological consequences of increased adiposity, particularly of ectopic adiposity and central obesity. Increasing insulin resistance and the activation of pro-inflammatory pathways in both adipose tissue and skeletal muscles, skeletal muscle loss (sarcopenia) and dysfunction (for example, mitochondrial dysfunction, accumulation of reactive oxygen species and increased oxidative stress levels in skeletal muscles), and pancreatic  $\beta$ -cell dysfunction (for example, decreased insulin secretion due to glucotoxicity, lipotoxicity and/or  $\beta$ -cell senescence) are key parameters in the pathophysiology of this vicious cycle. As T2DM progresses over time, an increasing disease burden in older adults from chronic hyperglycaemia, macrovascular and/or microvascular complications, and co-morbidity can further promote the adverse effects of the risk factors related to ageing and/or obesity.

older adults, notably vascular diseases, chronic stress and poor psychological health<sup>16,27,40</sup>.

### Clinical considerations

The heterogeneity of T2DM among older adults reflects many factors<sup>41</sup>. For example, clinical differences exist between late-onset T2DM and long-standing T2DM that a patient has had since middle age that affect the presentation and severity of the disease. Furthermore, older adults show considerable differences in functional status, in the ability to care for themselves and in the burden of comorbidities, all of which further add to the observed heterogeneity<sup>3,42</sup>. For purposes of common goal setting and treatment recommendations, this heterogeneity can be captured in three main groups. The first group comprises individuals in good health with little or no cognitive or functional impairment and a long life expectancy (for example, >10–15 years). The second group contains

those who have some comorbidities and mild disabilities. Finally, the third group includes those who have a high number of comorbidities and/or disabilities and a shorter life expectancy (for example, <5 years)<sup>43</sup>. These factors can modify the disease process compared to that in younger adults and therefore affect the management of both T2DM and any comorbidities<sup>44</sup>. Several common clinical aspects are considered here, namely the specific care needs relating to frailty and sarcopenia, multimorbidity, and the susceptibility to hypoglycaemia.

### Frailty

Frailty is a geriatric syndrome characterized by declining physiological reserves and impaired responses to stressors<sup>45,46</sup>. Several definitions of frailty are available; however, two are most commonly used. First, are the criteria proposed by Fried et al. that include a loss of body mass and grip strength, reduced walking speed, physical inactivity, and exhaustion; the presence of three or more of these factors fulfil the criteria for frailty<sup>46</sup>. The second commonly used definition is the deficit accumulation model proposed by Rockwood and Mitnitski, which is known as the frailty index or clinical frailty scale and assesses the level of dependency of an individual on care providers<sup>47</sup>. The prevalence of frailty in community-dwelling older adults is mostly estimated at 10–14% but rates as high as 40% have been reported in some studies<sup>48</sup>. This prevalence increases linearly with age, from ~7% in community-dwelling adults aged 65–69 years to up to 25% in those aged >80 years. Of note, frailty is more common and occurs earlier amongst those with diabetes mellitus than in those without, affecting about one-quarter of all individuals with diabetes mellitus aged >65 years<sup>49</sup>.

Diabetes mellitus in combination with frailty is associated with an increased risk of complications, hospitalization and a faster functional decline than in those without frailty. Indeed, frailty is a better prognostic marker of risk of death in older adults with T2DM than T2DM alone or T2DM with comorbidities<sup>50,51</sup>. Clinical trials in older adults with diabetes mellitus and frailty are scarce. However, observational studies involving older adults with frailty suggest that the degree of glycaemia has little effect on functional outcomes, provided that hyperglycaemia is not severe<sup>52–54</sup>. Instead, the evidence now suggests that a multifactorial intervention, rather than those singularly targeting glucose control, could be effective in delaying the progression of frailty. For example, the MIDFRAIL study evaluated the effectiveness of a multimodal intervention (compared with usual care) comprising a 16 week individualized and progressive resistance exercise programme, structured diabetes and nutritional education, and optimized diabetes care in pre-frail adults (Fried score 1–2) with T2DM and in older adults with T2DM and frailty. At 12 months of follow-up, patients in the intervention group showed clinically relevant improvements in measures of physical and cognitive function and reduced episodes of hypoglycaemia and hospital admissions compared with the group that received usual care. This improvement equated to an average annual health-care cost saving per patient of 428 euros (2016 costings)<sup>55</sup>.

## Box 1 | Research gaps

The escalating prevalence of type 2 diabetes mellitus (T2DM) and its debilitating comorbidities in older adults (aged  $\geq 65$  years) impair quality of life for individuals, add inordinate costs for health care and present formidable challenges for research. Although the effects of long-term poor glycaemic control are well appreciated (but often under-served), insulin resistance and chronic inflammation are underlying and connecting factors that deserve greater attention.

T2DM, sarcopenia, premature frailty and dementia are each associated with decreased insulin sensitivity and long-term activation of pro-inflammatory pathways, which are frequently exacerbated by earlier obesity, non-diabetic hyperglycaemia (prediabetes), and undiagnosed and/or poorly controlled T2DM<sup>76</sup>. Recognizing these causes of prediabetes in order to improve screening selection warrants greater consideration as a prelude to more effective disease prevention.

Another area of knowledge deficit is that several features of T2DM are suggestive of accelerated and accentuated ageing. For example, the metabolic dyscrasias are similar, some chromosomal changes are the same (such as shortened telomeres), genetic disturbances that confer reduced longevity often induce T2DM, and the morbidity profiles are similar but emerge earlier and progress faster with T2DM<sup>3</sup>. A more detailed understanding of the cellular determinants of ageing could benefit our appreciation of T2DM and vice versa.

From a practical perspective, a larger evidence base is required for older adults to inform the therapeutic advantages and limitations when confronted with the typical multimorbidity of T2DM in this age group. Further research should look into clarifying ideal glycaemic targets in relation to functional status.

Older adults represent a highly heterogeneous group and most of this heterogeneity still remains to be defined. Management pathways that consider social support and the availability of institutional care need to be elaborated on, assessed and implemented in accordance with local resources to optimize the broader remit of T2DM care for older adults with frailty.

Considerable uncertainty exists regarding the ideal targets for glycaemic control in older adults with frailty and how these should be tailored to functional status<sup>56,57</sup> (TABLE 1). Nevertheless, there is a growing consensus for a less intensive approach in these individuals<sup>42,58</sup>. This approach (for example, aiming for HbA<sub>1c</sub> levels of 7.5–8.5% (58–69 mmol/mol)) in older adults with frailty is based on evidence that 8–9 years of intensive glycaemic control (HbA<sub>1c</sub> levels of 6.5–7% (48–53 mmol/mol)) are required to achieve measurable reductions in microvascular complications<sup>59</sup>. In patients with a short life expectancy, such intensive control increases the risk of hypoglycaemia and lifestyle restrictions might compromise quality of life without providing tangible benefits<sup>59</sup>. Clinical guidelines have now been published that advocate the assessment of frailty as an essential part of the management of older adults with diabetes mellitus, thereby recognizing the importance of frailty and the potentially limited long-term benefits of intensive glycaemic control in older adults with frailty<sup>6,60,61</sup>. Of note, frailty assessment can inform functional status; therefore, it has been proposed as a useful measure to guide individualized treatment targets and therapeutic decisions. Thus, although an HbA<sub>1c</sub> target level of  $<7.5\%$  (58 mmol/mol) might be appropriate for those who are fit and have fewer comorbidities, a less stringent HbA<sub>1c</sub> target level of 8.0–8.5% (64–69 mmol/mol) has been considered reasonable in those who are frail or have a limited life expectancy<sup>14</sup>.

### Sarcopenia

Sarcopenia is defined as the progressive loss of muscle strength and mass associated with ageing<sup>60</sup> and is an important component of the frailty phenotype<sup>61,62</sup>.

The decline in muscle strength and mass observed in sarcopenia can give rise to an increased risk of falls, hypoglycaemia, disability, hospitalization and mortality<sup>63,64</sup>.

Sarcopenia and T2DM share a relationship, with each condition exaggerating the effects of the other, leading to functional decline and disability<sup>65</sup>. The gradual loss of muscle mass with ageing<sup>66,67</sup> occurs at a rate of 1–2% per year from the age of 50 years, increasing to around 3% per year after the age of 60 years and considerably faster after the age of 75 years<sup>61</sup>. The mechanisms by which age-related sarcopenia leads to insulin resistance and contributes to the development of T2DM were described earlier. Of note, the rate of loss of skeletal muscle mass is typically 10–20% faster in men and 100% faster in women with T2DM than in healthy older adults. This rate of loss varies between muscle groups but invariably reduces muscle function<sup>68,69</sup>. A number of longitudinal cohort studies have shown that the loss of both muscle strength and mass is accelerated in people with T2DM<sup>70,71</sup>. For example, in the US Health, Aging and Body Composition Study, which observed 1,840 community-dwelling adults aged 70–79 years, the decline in maximal strength of leg muscles was one-third greater in those with T2DM over a 3-year period than in those without diabetes<sup>71</sup>. Furthermore, in the CHIANTI study, those with T2DM had statistically significantly lower muscle density, knee and ankle strength, less muscle power, and reduced muscle quality compared with those without T2DM<sup>72</sup>. In Korean and Indian populations, strong associations have been noted between prediabetes, T2DM and sarcopenia, especially in those over 60 years of age<sup>73,74</sup>.

The mechanisms by which T2DM accelerates the age-related loss of muscle mass and function involve nutritional, endocrine, inflammatory and neurological pathways<sup>75</sup>. All these mechanisms can disrupt signalling downstream of the insulin receptor, which impairs the normal actions of insulin in muscle and thereby disrupts protein synthesis and increases protein catabolism<sup>76</sup>. In addition, poor glycaemic control and oxidative stress over time as well as the presence of complications (particularly neuropathy) impede muscle energetics and contribute to the further loss of muscle quantity and function leading to the increased risk of frailty<sup>77</sup>.

### Hypoglycaemia

Although hypoglycaemia is generally recognized as being more common in older than in younger people with T2DM<sup>78</sup>, true frequencies of hypoglycaemia in older adults with T2DM are not well established<sup>79</sup>. Studies involving people with T2DM of all age groups have estimated that rates of symptomatic hypoglycaemia are between 5 and 16 episodes per patient per year, with severe hypoglycaemia rates between 0.10 and 0.44 episodes per patient per year<sup>79</sup>. These broad ranges can be attributed to differences in the applied definitions of hypoglycaemia and in the cohorts studied. Of note, the frequency of reported hypoglycaemia also varies depending on the type of glucose-lowering agent used, with rates being greater in patients who are treated with insulin compared with those treated

Table 1 | Glycaemic, lipid and blood pressure goals in older adults<sup>a</sup> with T2DM

Patient subgroups	Recommended targets for glycaemia and treatment considerations	Recommended target lipid levels and treatment considerations	Recommended blood pressure targets and treatment considerations
<b>AACE guidelines<sup>140</sup></b>			
Without concurrent serious illness and with a low risk of hypoglycaemia	HbA <sub>1c</sub> <6.5% (48 mmol/mol)	Achieve LDL-C thresholds according to the following patient levels of cardiovascular risk: excessive risk <55 mg/dl; very high risk <70 mg/dl; high risk <100 mg/dl; moderate risk <100 mg/dl; low risk <130 mg/dl	<130/80 mmHg
With concurrent serious illness and a high risk of hypoglycaemia	HbA <sub>1c</sub> >6.5% (48 mmol/mol)		
<b>ADA guidelines<sup>14</sup></b>			
Healthy: few coexisting chronic illnesses, intact cognitive and functional status	HbA <sub>1c</sub> <7.5% (58 mmol/mol); fasting glucose 90–130 mg/dl (5.0–7.2 mmol/l); bedtime glucose 90–150 mg/dl (5.0–8.3 mmol/l)	Offer statin treatment unless contraindicated	<140/90 mmHg
Complex or intermediate: multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment	HbA <sub>1c</sub> <8% (64 mmol/mol); fasting glucose 90–150 mg/dl (5.0–8.3 mmol/l); bedtime glucose 100–180 mg/dl (5.6–10 mmol/l)	Offer statin treatment unless contraindicated	<140/90 mmHg
Very complex or poor health: long-term care or end-stage chronic illness or moderate-to-severe cognitive impairment or 2+ ADL dependencies	HbA <sub>1c</sub> <8.5% (69 mmol/mol); fasting glucose 100–180 mg/dl (5.6–10.0 mmol/l); bedtime glucose 110–200 mg/dl (6.1–11.1 mmol/l)	Consider statin treatment in those with established cardiovascular disease	<150/90 mmHg
<b>IDF guidelines<sup>6</sup></b>			
Category 1: functionally independent	HbA <sub>1c</sub> 7–7.5% (53–58 mmol/mol)	LDL-C <80 mg/dl	<140/90 mmHg
Category 2: functionally dependent	HbA <sub>1c</sub> 7–8% (53–64 mmol/mol)	Considering relaxation of targets	<150/90 mmHg
Frailty	HbA <sub>1c</sub> up to 8.5% (69 mmol/mol)	Considering relaxation of targets	<140/90 mmHg
Dementia	HbA <sub>1c</sub> up to 8.5% (69 mmol/mol)	Considering relaxation of targets	Assess individual circumstances and consider withdrawing treatment
Category 3: end of life	Avoid symptomatic hyperglycaemia	Treatment not necessary	Assess individual circumstances and consider withdrawing treatment
<b>EDWPOP guidelines<sup>138</sup></b>			
No comorbidities or single system disease	HbA <sub>1c</sub> 7–7.5% (53–58 mmol/mol)	Primary prevention (those with no previous CVD): offer statin therapy for those with 10-year CVD risk >15%. Secondary prevention (those with established CVD): offer statin therapy as first-line and consider adding fibrate therapy if triglyceride levels are elevated after 6 months of statin treatment	140–145/90 mmHg
Frail	HbA <sub>1c</sub> 7.6–8.5% (60–69 mmol/mol) or fasting blood glucose 137–162 mg/dl (7.6–9.0 mmol)		150/90 mmHg
<b>Endocrine Society guidelines<sup>157</sup></b>			
Good health: no comorbidities or 1–2 non-diabetes chronic illnesses and no ADL impairments and <1 IADL impairment	Fasting glucose 90–130 mg/dl (5.0–7.2 mmol); bedtime glucose 90–150 mg/dl (5.0–7.2 mmol); HbA <sub>1c</sub> 7.0–7.5% (53–58 mmol/mol)	Offer statin treatment and annual lipid profile; relaxed goals in those aged >80 years	140/90 mmHg; lower target (130/80 mmHg) in those with previous stroke or progressive chronic kidney disease
Intermediate health: 3 or more non-diabetes chronic illnesses and/or any one of the following: mild cognitive impairment or early dementia and/or >2 IADL impairments	Fasting glucose: 90–150 mg/dl (5.0–7.2 mmol); bedtime glucose: 100–180 mg/dl (5.6–10.0 mmol); HbA <sub>1c</sub> <8% (64 mmol/mol)		140/90 mmHg; lower target (130/80 mmHg) in those with previous stroke or progressive chronic kidney disease
Poor health: any one of the following: end-stage medical condition; moderate-to-severe dementia; >2 ADL impairments; residence in a long-term nursing facility	Fasting glucose 100–180 mg/dl (5.6–10.0 mmol); bedtime glucose 110–200 mg/dl (6.1–11.1 mmol); HbA <sub>1c</sub> <8.5% (69 mmol/mol)		145–160/90 mmHg

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; ADL, activities of daily living; CVD, cardiovascular disease; EDWPOP, European Diabetes Working Party for Older People; IADL, instruments of activities of daily living; IDF, International Diabetes Federation; LDL-C, LDL-cholesterol; T2DM, type 2 diabetes mellitus. <sup>a</sup>Older adults, aged ≥65 years.

with other glucose-lowering agents<sup>80</sup>. In the United Kingdom Prospective Diabetes Study, the frequency of severe hypoglycaemia in individuals of all age groups with T2DM treated with a sulfonylurea or insulin was 0.44 episodes per patient per year<sup>81</sup>. However, a large (33,048 person-years) population-based study in Tennessee, USA, of older adults with T2DM treated with insulin or a sulfonylurea reported severe hypoglycaemia rates of 1.23 episodes per 100 person-years with sulfonylureas and of 2.76 episodes per 100 person-years with insulin<sup>82</sup>. In the Freemantle Diabetes study involving 616 community-dwelling adults in Western Australia with a mean age of 67 years, 8.4% of participants experienced hypoglycaemia, with the incidence of severe hypoglycaemia reaching 1.7 per 100 person-years<sup>83</sup>. In this study, the duration of insulin treatment, a glomerular filtration rate (GFR) below 60 ml/min, the presence of neuropathy, educational attainment above primary level and previous severe hypoglycaemia were all notable factors predicting hypoglycaemia risk.

Physiological changes associated with ageing substantially alter both the awareness of and responses to hypoglycaemia in older adults. For example, studies of individuals without diabetes mellitus have shown that older adults recognize the symptoms of hypoglycaemia at lower blood levels of glucose than younger adults, with a statistically significant attenuation of autonomic responses and longer recovery times in older adults<sup>84,85</sup>. As these studies involved adults without diabetes, differences are probably due to ageing rather than the level of glycaemia. In older adults with T2DM, factors associated with ageing, such as a decline in renal function, altered drug pharmacokinetics and the presence of other comorbidities (for example, cognitive decline), can further exaggerate the risk of hypoglycaemia<sup>86</sup>. Of note, the presentation of older adults with hypoglycaemia is often atypical, presenting as falls, transient ischaemia, nausea or unsteadiness, thus obscuring and delaying the diagnosis<sup>87</sup>.

Hypoglycaemia in older adults can have severe clinical consequences and an increased risk of death. For example, in older adults with T2DM, a strong association between hypoglycaemia and fatal cardiovascular disease events has been noted in cardiovascular outcome studies<sup>88–90</sup>. In the ACCORD study of intensive glucose control, the older subgroup with T2DM showed no effect of the intervention on cardiovascular mortality, whereas the intensive arm of the younger subgroup showed an increased risk of cardiovascular mortality (older HR 0.97; younger HR 1.71;  $P=0.03$ ). Regardless of the intervention arm, the older subgroup experienced higher annualized rates of severe hypoglycaemia (4.45% intensive and 1.36% standard) than the younger subgroup (2.45% intensive and 0.80% standard)<sup>91</sup>. Of note, in the ACCORD study, symptomatic hypoglycaemia was associated with an increased risk of death (mainly from cardiovascular events); for example, in the intensive treatment arm, a mortality of 2.8% was observed in those with one or more episodes of symptomatic hypoglycaemia versus a mortality of 1.2% in those with no episodes<sup>88</sup>. The ADVANCE study of intensive glycaemic control in patients with T2DM reported similar findings, with a mortality of 19.5% in those who experienced

a severe hypoglycaemic event versus 9% in those who did not<sup>89</sup>. In the post hoc analysis of the VADT trial of intensive glucose control in military veterans (mean age 60.4 years), severe hypoglycaemia within the previous 3 months was associated with an increased risk of cardiovascular death and increased all-cause mortality compared with those who did not experience recent hypoglycaemia (HR 3.7 for cardiovascular death and 2.4 for all-cause mortality)<sup>90</sup>. Thus, in older adults who are potentially frail, the increased risk of any hypoglycaemia, and especially of severe hypoglycaemia, poses a very considerable mortality risk. In addition to the excess risk of death, severe hypoglycaemia in older adults is also associated with the increased risk of falls and injuries<sup>92</sup>.

### Cognitive impairment

T2DM is now recognized as a notable risk factor for the development of cognitive impairment and dementia (including Alzheimer disease) in older adults, particularly in association with insulin resistance and vascular disease<sup>93</sup>. Indeed, diabetes mellitus in midlife is associated with a 19% greater cognitive decline over 20 years compared with individuals without diabetes<sup>94</sup> as well as a 1.5–2.5-fold increased risk of dementia and Alzheimer disease in older adults<sup>95–97</sup>. Preliminary evidence shows an association between poor glycaemic control and increased risk of dementia in type 1 diabetes mellitus; however, a definitive link has yet to be established and T2DM seems to account for most of the overall association between diabetes mellitus and dementia<sup>98</sup>.

In addition to the overall risk of developing dementia, T2DM is associated with deficits across multiple domains of cognitive function in older adults<sup>98,99</sup>. A bell-shaped association between HbA<sub>1c</sub> levels and cognitive function was reported in a 2019 study amongst those aged >70 years; in this study, worse test scores for cognitive ability coincided with the lowest and highest HbA<sub>1c</sub> levels and women were more vulnerable than men to poor cognitive ability with increased HbA<sub>1c</sub> levels<sup>100</sup>. This study and others suggest a non-linear link between poor glycaemic control and an increased risk of cognitive decline in older adults with diabetes mellitus<sup>98,101–105</sup>. Furthermore, underlying chronic insulin resistance and absolute insulin deficiency are also recognized as underlying factors that are strongly detrimental to cognitive functions<sup>106</sup>. In addition, excess body mass<sup>107</sup>, impaired renal function<sup>108,109</sup>, hypotension<sup>110</sup> and comorbid depression<sup>111,112</sup> are all reported as factors associated with an increased risk of dementia in older adults with T2DM.

The onset of dementia in older adults with T2DM is typically accompanied by a loss of executive function and delayed recall, which are cognitive domains that influence glycaemic control; these changes are associated with an increased risk of falls<sup>113</sup>. Moreover, cognitive impairment can adversely affect adherence to treatment regimens<sup>114</sup>, making the management of older adults with cognitive decline even more challenging<sup>115</sup>. However, interventions exist that can potentially mitigate cognitive decline in older adults with diabetes mellitus. For example, even very modest exercise can moderate some of the cognitive decline observed in older adults with diabetes mellitus<sup>116</sup> and reduce the risk of developing dementia.

### Multimorbidity

Multimorbidity is defined as the coexistence of two or more chronic diseases<sup>117</sup>. Importantly, multimorbidity is well recognized to increase the risk of death<sup>118</sup> and constitutes a growing issue for older adults<sup>119</sup>. Indeed, multimorbidity has been estimated to affect 55–98% of older adults, depending on the definitions applied and the age groups included<sup>120</sup>. Increased disability, a reduced quality of life and an increased uptake of health-care services are closely associated with multimorbidity, further highlighting the impact of this problem<sup>120</sup>. Evidence suggests that frailty can contribute to the risk of older adults with diabetes mellitus developing multimorbidity<sup>120</sup>. Adults of all ages with multimorbidity have an increased risk of death but the mortality risk of frailty itself can often outweigh that of multimorbidity when frailty and multimorbidity coexist<sup>121</sup>. Frailty and multimorbidity evidently share a complex association, which requires further investigation (BOX 1).

An increased prevalence of multimorbidity in older adults with diabetes mellitus is attributed in part to advances in T2DM treatments<sup>122</sup> and cardiovascular disease management<sup>123</sup>, which have prolonged life expectancy but allowed other chronic conditions to manifest<sup>124</sup>. Up to 40% of older adults with diabetes mellitus have four or more comorbid diseases<sup>125</sup>. The most common co-morbidity clusters include diabetes mellitus–hypertension, diabetes mellitus–arthritis–hypertension and diabetes mellitus–arthritis–hypertension–heart disease<sup>126</sup>. Conditions associated with old age, including frailty, incontinence, chronic pain and falls, are also highly prevalent in older adults with diabetes mellitus and decrease the quality of life<sup>127</sup>.

Multimorbidity increases the complexity of T2DM management of older adults and requires a more personalized approach to ensure adequate glycaemic control alongside coexisting and competing treatment targets. The self-management of diabetes by older adults becomes more difficult with comorbidities. In addition, the development of comorbid conditions, such as heart failure and/or dementia, can render desirable treatment targets impossible or risky to achieve. Indeed, the analysis of a health database in the USA involving 23,430 adults with diabetes mellitus suggested that 16 of 17 investigated comorbid conditions hamper the management of hyperglycaemia<sup>128</sup>. The perceived treatment priorities might differ between clinicians faced with managing diabetes mellitus in older adults with multimorbidity. For example, fewer than 40% of patient–clinician partnerships agree that taking medication is one of the most important treatment strategies<sup>129</sup>.

### Prevention and management

#### Prevention

Several large prospective studies have confirmed that the identification of prediabetes (defined as impaired glucose tolerance and/or impaired fasting glucose) provides an opportunity to delay or prevent progression to T2DM<sup>111</sup>. Screening individuals at high risk of T2DM who are selected by questionnaire (for example, Finnish Diabetes Risk Score) or the screening of people attending outpatient clinics for cardiometabolic conditions

(for example, metabolic syndrome, hypertension or cardiovascular disease) yields a high proportion of individuals with HbA<sub>1c</sub> levels approaching 6.5% (48 mmol/mol). Of note, prediabetes is variously defined as HbA<sub>1c</sub> levels of 5.7–6.4% or 6.0–6.4% (39–47 mmol/mol or 42–47 mmol/mol, respectively). Screening can also help identify previously undiagnosed diabetes mellitus and is particularly relevant in those moving to or living in institutionalized care settings.

Both lifestyle and pharmacological interventions have been shown to delay progression from prediabetes to T2DM<sup>130</sup>. Indeed, intensive lifestyle interventions can more than halve the rate of progression from prediabetes to T2DM across a range of ages (as seen in the Da Qing study, Finnish Diabetes Prevention Study and American Diabetes Prevention Program)<sup>131–133</sup> and are generally more effective than pharmacological interventions. Although the proportion of older adults (here defined as those aged >60 years) was small in these studies, age-based subgroup analyses indicate that lifestyle changes are more effective in older age groups compared with younger adults<sup>134</sup>. The implementation of these interventions at a population level has also yielded encouraging findings. For example, initial results from the National Health Service Diabetes Prevention Programme in the UK show higher levels of participation by older adults (including those aged ≥75 years) in lifestyle interventions, with superior reductions in body weight and HbA<sub>1c</sub> levels compared with younger counterparts<sup>135</sup>. Of the pharmacological interventions, metformin can also delay the progression of prediabetes in younger individuals and those with obesity; however, its efficacy is limited in older adults with prediabetes<sup>135</sup>. Thiazolidinediones and acarbose have also been shown to reduce the progression from prediabetes to T2DM, including in older adults, but they are not currently approved for this indication<sup>136</sup>.

#### Guidelines and treatment goals

Guidelines for the treatment of hyperglycaemia in older adults with T2DM take into account the frequently associated cardiorenal challenges seen in this group and reiterate the need to minimize the risk of hypoglycaemia while providing flexibility to adjust treatment goals for frail individuals with comorbidities<sup>137,138–140</sup>. Given the diverse phenotypes amongst older adults with T2DM, it is appropriate to adopt a highly individualized approach that incorporates functional goals alongside risk factor control.

Adequate glycaemic control can defer the onset and reduce the severity of microvascular complications at any age. However, as noted earlier, intensive treatment strategies might be less beneficial and/or less practicable in older adults with frailty and T2DM, especially if such strategies will predispose patients to hypoglycaemia, to which this age group is particularly vulnerable<sup>141</sup>. Furthermore, the benefits of intensive glycaemic control tend to accrue over a long period of time and might be less relevant in those with limited life expectancy<sup>59</sup>. Intensive strategies can also be more difficult to implement in the presence of comorbidities that restrict therapeutic options.

Currently, the criteria for individualization and treatment intensification in T2DM suggest less stringent glycaemic target levels in older patients with long-standing diabetes, noting the higher susceptibility to hypoglycaemia and other adverse events that accompany advancing age<sup>14</sup>. Patient motivation and self-empowerment are less dependent on age; however, local factors that affect resource allocation and clinical inertia (delayed treatment escalation) might have an age-related aspect<sup>142</sup>. HbA<sub>1c</sub> target levels of <6.5% or <7% (<48 mmol/mol or <53 mmol/mol, respectively) are usually advocated for newly diagnosed younger and fitter individuals with T2DM and might also be appropriate for fit and healthy older patients. However, clinical guidelines increasingly propose less stringent control (for example, HbA<sub>1c</sub> level of <8%; <64 mmol/mol) in older adults who are less fit, with a long duration of diabetes. Furthermore, HbA<sub>1c</sub> levels of up to 8.5% (69 mmol/mol) have been suggested as acceptable in older patients with complex needs and frailty and/or multimorbidity, provided that symptoms are relieved and that microvascular and macrovascular risks are addressed appropriately<sup>137,138</sup>. Given the benefits of glycaemic control, older patients should still expect individualized glycaemia management to be as rigorous as is safely and practically reasonable, consistent with patient preferences and quality of life.

Less stringent glucose target levels, which are focused on symptomatic control and minimization of the risk of hypoglycaemia, are a reasonable approach in older adults with advanced disability and those living in institutionalized care settings. As many of these individuals have complex needs and might not be able to self-manage, family members, caregivers and diabetes educators might need to be involved to ensure care plans are clearly communicated and implemented<sup>143</sup>.

Concurrent attention to non-glycaemic cardiovascular disease risk factors, notably blood pressure and LDL-cholesterol, remains integral to the management of T2DM at all ages. The notion of setting less rigorous targets for older adults than for younger individuals remains in contention. Most guidelines suggest blood pressure target goals of ≤140/85 mmHg in older adults but lower targets (for example, <130/80 mmHg) in patients with microvascular or cardiovascular disease; LDL-cholesterol targets are usually <2.6 mmol/l (100 mg/dl) in all adults but, ideally, lower targets (for example, <1.8 mmol/l; 70 mg/dl) are set in patients with cardiovascular disease or a very high cardiovascular risk at all ages<sup>14</sup>. The recommendations of various guidelines for the management of glycaemia, lipids and blood pressure in older adults are summarized in TABLE 1.

### Health education

Health education for patients and care providers remains a foundational component of diabetes management and should be appropriately nuanced to meet the needs of older adults. For example, selected key messages about a healthy diet, physical activity, medication and the importance of glucose testing can pay dividends and will benefit from periodic reinforcement<sup>144,145</sup>.

### Lifestyle

Recommendations for a balanced healthy diet apply to all age groups with T2DM, particularly noting a low intake of saturated fats, simple sugars and salt, and the need to adjust portion size and total daily caloric intake in accordance with desired weight control<sup>14</sup>. However, over-zealous dieting by older adults can detrimentally accelerate the loss of muscle mass. Furthermore, rapid weight loss (intentional or unintentional) might also disguise β-cell failure and worsening T2DM<sup>146</sup>. Therefore, care should be taken by older adults when dieting to ensure that adequate nutrition is achieved. If poor nutrition is suspected, vitamin supplements to restore normal circulating levels can be useful for general health. By contrast, amino acid supplements to counter sarcopenia have limited effect<sup>14,147</sup>.

The benefits of even very modest physical activity are well recognized. In older adults with the limiting factors of reduced mobility and comorbidities, bespoke exercises such as ‘chair-based exercises’ that include resistance and/or aerobic components can improve muscle mass and strength and assist glycaemic control and mental wellbeing<sup>137,148,149</sup>. A meta-analysis of eight cohort studies with older adults noted that the use of resistance exercises for ≥3 months typically decreased HbA<sub>1c</sub> levels by up to an average of 0.5%; however, no consistent association was observed with exercise intensity, frequency or duration of each session<sup>149</sup>. Although functional benefits are also observed with moderate-intensity aerobic exercise in older adults, reductions in HbA<sub>1c</sub> levels have generally been less compared with resistance exercises<sup>150,151</sup>. The benefits of resistance exercise in pre-frail and frail older patients with T2DM have been demonstrated in studies applying multimodal interventions with a mix of exercise and dietary interventions<sup>55,152</sup>.

The value of exercise, especially to reduce metabolic deterioration, assist weight control, counter sarcopenia and defer frailty, is not in dispute. However, controversy continues for older adults with T2DM over the optimal type of exercise, its frequency and intensity, the duration of sessions, and the need for supervision. Furthermore, the possible long-term vascular benefits remain unclear<sup>153,154</sup>. The heterogeneity of T2DM and its comorbidities in this age group precludes prescriptive detail herein for exercise regimens; clinical judgement must be applied on an individual basis. However, general advice remains to start gently and increase gradually but sufficiently to gain benefit and to comfortably maintain the exercise while avoiding over-exertion.

The high prevalence of prediabetes amongst older adults (noted in the epidemiology section), with an up to 10% annual progression to T2DM in some regions, has focussed attention on the value of asymptomatic screening and interventions for this group<sup>4,9,14,155</sup>. Dietary and exercise interventions have reduced rates of progression to T2DM and of the emergence of comorbidities for groups into the seventh decade of life; however, evidence for the use of these interventions in the eighth decade is unclear<sup>155,156</sup>. Controversy exists concerning cost and whether to refine screening based on risk factors such as age, family and personal medical history, BMI, and ethnicity. Of note, with advancing age, the increased



all-cause mortality reduces population-based rates of progression from prediabetes to T2DM<sup>3</sup>. Furthermore, older adults might show slower disease advancement and have less time for the development of complications than younger age groups<sup>3</sup>.

### Therapeutic choices

Although individualized non-pharmacological interventions provide a continuing foundation for the treatment of T2DM in older adults, the majority of these patients will also require pharmacotherapy<sup>157</sup>. Selecting appropriate glucose-lowering therapies for older adults with T2DM is complicated by many factors<sup>42</sup>. Ideally, therapies will provide substantial and durable glucose-lowering action, avoid hypoglycaemia and unwanted weight gain, and be convenient and well tolerated with a strong safety profile. In view of the high prevalence of cardiorenal conditions in older individuals, agents that offer protection or are suitable for use with these common comorbidities are favoured. Other comorbidities that are also common to older age groups and might shape the choice of glucose-lowering agents include depression, cognitive impairment, sarcopenia, liver impairment, osteoporosis, risk of falls and fractures, frailty, and the use of multiple medications. Notably, strong evidence for the use of several glucose-lowering agents in older adults is scarce and patients aged over 75 years are under-represented in most prospective trials of new agents<sup>158</sup>. Although many of the available therapies can still be considered in fit older adults, the choice of suitable glucose-lowering agents for older patients with frailty is limited (TABLE 2). Careful attention must also be given when a combination of glucose-lowering agents is required to achieve the recommended target. Wherever possible, combinations with a minimal risk of hypoglycaemia must be considered.

**Metformin.** When lifestyle interventions are unable to achieve or sustain adequate glycaemic control in T2DM, metformin is usually preferred at any age as a first-line pharmaceutical therapy as it counters insulin resistance, it offers glucose-lowering efficacy with a low risk of hypoglycaemia, weight neutrality and cardiovascular protective properties, and has been in use for decades<sup>159</sup>. Data from studies in older adults with T2DM treated with metformin have confirmed that this medication is efficacious, has a favourable safety profile and is associated with a reduced risk of age-related comorbidities and frailty<sup>160,161</sup>. However, the chronic use of metformin in older patients brings the risk of weight loss and associated functional deficits, which should be appreciated<sup>162</sup>. Additionally, possible long-term reductions in levels of vitamin B12 and folate are associated with metformin treatment; although these reductions are not usually clinically important, they have been associated with cognitive impairment in older patients<sup>163,164</sup>. Sufficient renal function is required for metformin clearance, so the dosage might need to be down-titrated (for example, to  $\leq 1,000$  g per day) if the estimated GFR (eGFR) declines substantially below 60 ml/min and stopped if eGFR falls below 30 ml/min (REF.<sup>165</sup>). Thus, the monitoring of renal function is essential. Metformin-related lactic acidosis is

a rare adverse event, usually occurring with drug accumulation due to unrecognized renal impairment. Metformin should be stopped if a serious potentially hypoxaemic condition occurs. In addition, gastrointestinal disturbances can occur in older adults (particularly those aged >80 years) treated with metformin and can be minimized through gradual dose escalation (taken with meals); however, a small minority might not tolerate any dose<sup>165</sup>.

**Sulfonylureas.** Sulfonylureas continue to be extensively used in patients with T2DM as a low-cost option to add to metformin. They can be effective in the short term in controlling hyperglycaemia in individuals who retain substantial  $\beta$ -cell function; however, their durability of effectiveness is often poor, probably reflecting the diminishing  $\beta$ -cell secretory responsiveness<sup>159</sup>. The insulin-releasing action of sulfonylureas can continue at low glucose concentrations, which accounts for their high risk of hypoglycaemia, making these drugs an undesirable choice for older adults with frailty<sup>79</sup>. The risk of hypoglycaemia varies between different sulfonylurea preparations: short-acting sulfonylureas with inactive metabolites are associated with lower rates of hypoglycaemia than longer-acting preparations. Among second-generation sulfonylureas, gliclazide is associated with a low risk of hypoglycaemia: affecting  $\sim 1.4\%$  of all patients annually with glucose levels of  $\leq 56$  mg/dl (3.1 mmol/l) and 0.1% of patients with severe hypoglycaemia requiring third-party assistance<sup>166,167</sup>. Shorter-acting sulfonylureas are therefore preferred in older adults. The introduction of a sulfonylurea requires a gradual dose titration with glucose monitoring and extra caution if glucose levels are approaching euglycaemia or if hypoglycaemia unawareness is suspected, especially in older patients with a long duration of T2DM. The cardiovascular safety of sulfonylureas has been in contention for several decades but trials published in 2018 involving the third-generation sulfonylurea glimepiride in patients of all ages have not identified a cardiovascular risk if used in adults without frailty who have a good awareness of hypoglycaemia<sup>168</sup>.

**Meglitinides.** Meglitinides, like sulfonylureas, stimulate insulin secretion from pancreatic  $\beta$ -cells in a non-glucose-dependent manner. The faster onset and shorter duration of action of the insulinotropic effect of meglitinides could offer advantages compared with sulfonylureas for patients at risk of inter-prandial and nocturnal hypoglycaemia<sup>159</sup>. The predominantly hepatic route of elimination of repaglinide enables its use in individuals with impaired renal function. In addition, the meal-related dosing schedule can be useful in those with irregular feeding habits; however, meal-related versus once-daily administration can lead to adherence issues. Of note, information regarding the cardiovascular effects of meglitinides is limited.

**Dipeptidyl peptidase 4 inhibitors.** Acting to increase the plasma concentrations of incretins, dipeptidyl peptidase 4 (DPP4) inhibitors impede the degradation of endogenous glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic peptide and thereby increase their actions<sup>159</sup>. GLP1 is the main incretin,

Table 2 | Blood glucose-lowering agents used in the treatment of T2DM

Drugs and dose ranges <sup>a,b</sup>	Clinical effects	Main modes of action and additional clinical benefits	Limitations and special considerations in older adults
<b>Oral</b>			
Biguanide: for example, metformin (IR, SR/XR formulations) 500–3,000	High efficacy; low hypoglycaemia risk; weight neutral	Counter insulin resistance; ↓ hepatic glucose output; ↑ glucose uptake and cycling; potential CV benefits	Monitor renal function; do not start if GFR <45 ml/min; stop if eGFR <30 ml/min; use ≤1,000 mg/dl if GFR <45 ml/min; interrupt if using contrast media; avoid if significant liver impairment, any hypoxaemia or history of lactic acidosis; might reduce vitamin B12 levels; rare risk of lactic acidosis if renal function is inadequate
Sulfonylureas: for example, glibenclamide 2.5–20; gliclazide 40–320; gliclazide MR 30–100; glimepiride 1–6; glipizide 2.5–20; tolbutamide 500–3,000	High efficacy; moderate hypoglycaemia risk; weight gain	↑ Insulin secretion (even at low glucose concentration); duration of action varies with agent and dose; tolbutamide short-acting ~6 hours; glibenclamide long-acting ~24 hours; others effective for ~6–24 hours	Initial efficacy might diminish by 6–12 months; titrate dose slowly, monitor glucose; avoid in liver and/or renal impairment depending on agent; risk of hypoglycaemia, especially glibenclamide; discuss meal frequency and driving; check glucose
Meglitinides: for example, nateglinide 60–540; repaglinide 0.5–16.0	Intermediate efficacy; moderate hypoglycaemia risk; weight gain	↑ Insulin secretion (even at low glucose concentration); more rapid onset and shorter duration (<6 hours) of action than sulfonylureas	Avoid in liver impairment; take with main meals; useful in patients with irregular meals; repaglinide might be helpful in mild-to-moderate renal impairment; risk of hypoglycaemia
DPP4 inhibitors: for example, alogliptin 6.25–25.00; linagliptin 5; saxagliptin 2.5–5.0; sitagliptin 25–100; vildagliptin 50–100	Intermediate–high efficacy; low hypoglycaemia risk; weight neutral	Prolong circulating half-lives of some incretin hormones such as GLP1, ↑ prandial insulin release, ↓ prandial glucagon release	Risk of pancreatitis: avoid if there is a history of pancreatitis and discontinue in acute pancreatitis; dose adjustment in renal impairment, except linagliptin. Caution: possible increased risk of heart failure
Thiazolidinedione: for example, pioglitazone 15–45	High efficacy; low hypoglycaemia risk; weight gain	↑ Insulin sensitivity mainly via the activation of PPAR $\gamma$ ; might lower risk of stroke	Slow onset of action, risk of oedema; increased risk of heart failure and bone fractures; check liver enzymes
SGLT2 inhibitors: for example, canagliflozin 100–300; dapagliflozin 5–10; empagliflozin 10–25; ertugliflozin 5–15	Intermediate–high efficacy; low hypoglycaemia risk; weight reduction	↓ Glucose reabsorption from renal filtrate causing the elimination of glucose in urine; ↓ blood pressure; reduce risk of heart failure; evidence of renal protection (↓ decline in GFR, ↓ albuminuria)	Monitor renal function and hydration; caution if GFR <60 ml/min; if GFR falls below 45 ml/min label varies for individual agents; glucosuric effect associated with risk of genital and urinary infections. Caution: equivocal evidence for risk to lower limbs in patients with peripheral vascular disease
Alpha-glucosidase inhibitors: for example, acarbose 50–600	Intermediate efficacy; low hypoglycaemia risk; weight neutral	↓ Rate of carbohydrate digestion by competitive inhibition of intestinal glucosidases	Efficacy depends on a diet rich in complex carbohydrates; avoid if gastrointestinal disorders; adverse effect of flatulence
<b>Subcutaneous injection</b>			
GLP1 receptor agonists: for example, dulaglutide 0.75–1.50 QW; exenatide 5–10 $\mu$ g BD; exenatide QW2 or QW; liraglutide 0.6–1.8 OD; lixisenatide 10–20 $\mu$ g OD; semaglutide 0.5–1.0 QW	High efficacy; low hypoglycaemia risk; weight reduction	Activate GLP1 receptors; ↑ prandial insulin release; ↓ prandial glucagon; delay gastric emptying; ↑ satiety effect; ↓ blood pressure; evidence of cardiorenal benefits	Risk of pancreatitis: avoid if there is a history of pancreatitis and discontinue in acute pancreatitis; initial nausea, titrate as appropriate. Caution with some GLP1 receptor agonists in severe renal impairment and avoid in end-stage renal disease
Insulin; ultra-rapid-acting, Fiasp; rapid-acting, Aspart, glulisine or lispro; short-acting, Actrapid, Humulin S or Insuman rapid; intermediate: insulatard or Humulin I; long-acting, degludec, detemir or glargine; biphasic (pre-mixed), Humalog, Humulin M3 or Novomix	Very high efficacy; high hypoglycaemia risk; weight gain	↓ hepatic glucose output; ↑ peripheral glucose uptake; ↑ glucose metabolism; ↓ lipolysis; ↑ lipogenesis; ↑ protein anabolism	Select regimen consistent with patient lifestyle and needs; necessary education and support; glucose monitoring required; appropriate lifestyle adjustments required; high risk of hypoglycaemia

↑ increase; ↓ decrease; BD, twice daily; CV, cardiovascular; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GLP1, glucagon-like peptide 1; IR, immediate release; MR, modified release; OD, once daily; PPAR $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; QW, once weekly; QW2, once every 2 weeks; SGLT2, sodium–glucose cotransporter 2; SR, slow release; T2DM, type 2 diabetes mellitus; XR, extended release. <sup>a</sup>Some agents are not available in all countries (for example, gliclazide is not available in the USA). The names and formulations of agents might differ between countries, for example, glibenclamide is available as micronized glyburide in the USA, and formulations of glipizide might vary between countries. Additional agents have indications as glucose-lowering agents outside of Europe, for example, colesevelam (bile sequestrant), bromocriptine (dopamine D2 receptor agonist) and pramlintide (amylin analogue taken as subcutaneous injections before meals) have an indication for diabetes in the USA, and additional  $\alpha$ -glucosidase inhibitors (miglitol and voglibose) are available in some countries. Rosiglitazone is available in some countries outside of Europe. Dosages may vary between countries, for example, a maximum recommended dose of metformin is 3,000 mg per day in Europe and 2,550 mg per day in the USA. Exclusions, precautions and monitoring might also vary (for example, the extent of renal impairment to contraindicate metformin or to require dose adjustment varies between countries; thiazolidinediones are excluded for New York Heart Association categories I–IV in Europe but III–IV in the USA. Fixed-dose combinations of several oral agents are widely available, for example, single-tablet combinations of metformin with a DPP4 inhibitor or SGLT2 inhibitor. Fixed-ratio combinations of a GLP1 receptor agonist with insulin have been introduced. Pre-mixed insulins are identified with the proportion of the shorter-acting component first in Europe but second in the USA. Prescribers are encouraged to check national and local formulary directives. <sup>b</sup>Dose range mg/day (unless stated). Data from TABLE 2 are updated from REF.<sup>159</sup>.

potentiating nutrient-induced insulin secretion without causing hypoglycaemia or weight gain and suppressing excess glucagon secretion from  $\alpha$ -cells. Most DPP4 inhibitors are eliminated in urine and require a dose reduction in renal impairment, except linagliptin, which is eliminated via the liver. Although limited trial evidence exists regarding the use of DPP4 inhibitors in older adults, the safety profiles of these agents have been reassuring<sup>169–171</sup>. The rates of major adverse cardiac events were not affected by the use of DPP4 inhibitors in large prospective studies, although some lingering concerns about a small increased risk of hospitalization for heart failure suggest that these agents should be used with caution in older patients with heart failure<sup>172–174</sup>. The low risk of hypoglycaemia, good tolerability profiles and once-daily oral administration (of most DPP4 inhibitors) have led to the increased use of these agents in older adults.

**Sodium–glucose cotransporter 2 inhibitors.** To decrease blood concentrations of glucose through a glucosuric effect, sodium–glucose cotransporter 2 (SGLT2) inhibitors act by reducing glucose reabsorption from the renal filtrate. The effect is self-limiting, as glucosuria diminishes when blood levels of glucose decline, thereby preventing hypoglycaemia<sup>159</sup>. Glucosuria also provides caloric loss, which assists weight loss, and an osmotic diuresis associated with glucosuria contributes to reduced blood pressure. Indeed, large outcome trials in patients with T2DM have indicated cardioprotective and renoprotective effects, notably with reductions in heart failure hospitalization and albuminuria, and a slower age-related decline in GFR<sup>175–177</sup>. Over 40% of participants recruited to the EMPA-REG (empagliflozin) and CANVAS (canagliflozin) trials were aged >65 years and had similar cardiovascular benefits to younger participants<sup>176,178,179</sup>. No differences between age groups were noted for the risk of genital infections or for the putative rare adverse events of fractures or lower limb amputations<sup>179</sup>. The glucosuric effect of SGLT2 inhibitors requires adequate renal function and an eGFR of  $\geq 60$  ml/min is generally recommended for the best glucose-lowering effect. However, dapagliflozin, empagliflozin and ertugliflozin can be continued while GFR is  $>45$  ml/min/1.73 m<sup>2</sup>. Furthermore, an appreciation of the potential renoprotective effects of SGLT2 inhibitors now permits canagliflozin to be started at a low dose if GFR is  $>30$  ml/min/1.73 m<sup>2</sup> and continued until end-stage renal disease occurs. Nevertheless, declining GFR presents caution for the use of SGLT2 inhibitors in many older people with frailty who will be susceptible to the effects of volume depletion, which can occur with the concurrent use of SGLT2 inhibitors and loop diuretics<sup>179,180</sup>. In addition, potential links to lower limb ischaemia and amputation risk with SGLT2 inhibitors are being investigated<sup>180</sup>; therefore, older patients with poor peripheral circulation might not be good candidates for this therapy.

**GLP1 receptor agonists.** The glucose-lowering effect of GLP1 receptor agonists (GLP1RAs) involves the potentiation of nutrient-stimulated insulin release and

the suppression of glucagon release (with both of these effects being glucose dependent), thus avoiding hypoglycaemia. In addition, GLP1RAs delay gastric emptying and exert a satiety effect that facilitates weight loss<sup>159</sup>. A limited number of studies evaluating GLP1RA in older adults with T2DM have shown good efficacy and tolerance<sup>181–183</sup>. Post hoc analyses of large cardiovascular outcome trials with GLP1RAs also indicate that the cardiovascular benefits extend to all age groups, including those aged over 75 years<sup>183</sup>. Available as daily or once weekly subcutaneous injections, GLP1RAs are prone to cause initial (but usually transient) nausea and other gastrointestinal symptoms. These agents are mostly degraded in the circulation and can be used with dose adjustment (if necessary) in patients with renal impairment. Although initial concerns were raised regarding the excess risk of acute pancreatitis, the long-term safety profile of GLP1RAs has been reassuring as evidenced from large cardiovascular outcome trials<sup>184</sup>.

**Thiazolidinediones.** By activating the peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ), thiazolidinediones improve insulin sensitivity in newly differentiated adipocytes and skeletal muscle and reduce hepatic glucose production<sup>159</sup>. Thiazolidinediones have a slow onset of action; however, the durability of their glucose-lowering efficacy is generally longer than with sulfonylureas and they do not increase the risk of hypoglycaemia. Pioglitazone is available in most countries but rosiglitazone is not available in Europe and is use-restricted in many countries. Weight gain is an adverse effect of thiazolidinediones; however, pioglitazone exerts some PPAR $\alpha$ -mediated activity, which can benefit blood lipid control. Pioglitazone has similar efficacy across all age groups<sup>185</sup> and has a more favourable cardiovascular safety profile than rosiglitazone<sup>186,187</sup>. Pioglitazone has been reported to protect against the development of some cardiovascular disease events, including stroke, and it can be used in patients with mild renal impairment<sup>186</sup>. Of note, thiazolidinediones might cause fluid retention and risk of oedema, which could precipitate or exacerbate heart failure; as such, the use of a thiazolidinedione is contraindicated in Europe at any stage of cardiac failure (New York Heart Association stages I–IV). Furthermore, possible links of pioglitazone with an increased risk of bladder cancer remain uncertain. In addition, pioglitazone is associated with an increased risk of bone fractures, which is a usual risk in patients with frailty and detracts from their use in patients with osteoporosis or osteopenia<sup>159,165</sup>.

**$\alpha$ -Glucosidase inhibitors.** By impeding the final steps of carbohydrate digestion,  $\alpha$ -glucosidase inhibitors, such as acarbose, delay the absorption of simple sugars from meals rich in complex carbohydrates.  $\alpha$ -Glucosidase inhibitors do not cause hypoglycaemia or weight gain and can usefully reduce inter-prandial hypoglycaemia in insulin-treated patients by prolonging the prandial absorption time<sup>188</sup>. In older adults with T2DM, studies investigating the use of acarbose are limited; however, efficacy seems to be similar to that seen in younger

individuals<sup>189</sup>. The abdominal adverse effects of bloating, flatulence and diarrhoea can reduce adherence and any gastrointestinal disease in older adults is a major caution against its use<sup>159,165</sup>.

**Insulin.** Patients who are very old (>75 years) and/or living with frailty should only start insulin therapy or intensify it to multiple daily injections when other options for glucose control have been exhausted. As insulin therapy is associated with the risk of hypoglycaemia, caution should be taken while initiating insulin especially for those living alone, dependent on carers or with serious co-morbidity. Nevertheless, basal insulin can effectively address a rapid escalation of symptomatic hyperglycaemia that is uncontrolled by other agents. Combination treatments, including the addition of basal insulin to oral therapies (for example, adding once-daily basal insulin to one or more oral glucose-lowering agent) can be considered before the initiation of more complex insulin regimens, but requires special consideration of hypoglycaemia risk<sup>146</sup>. The weight gain observed with insulin therapy might be useful in older adults with sarcopenia and/or frailty and insulin is often the only realistic option in those with advanced renal or liver disease. A suitably cautious starting dose and titration schedule and a straightforward regimen are required that are consistent with the comorbidities and cognitive function of the patient as well as with carer resource availability.

**Other glucose-lowering agents.** In the USA and some other regions, bromocriptine, colesevelam and pramlintide have indications for use to decrease blood concentrations of glucose in T2DM; however, these drugs are not often used in patients with T2DM and are not generally used in older patients or in those with disabilities<sup>159</sup>.

**Conclusions**

The increasing prevalence of T2DM in older adults reflects an increase in risk factors (such as prior obesity and inactivity) as well as improvements in general health care that have extended life expectancy. The disparate phenotypes of T2DM in older adults, who might be living with frailty, necessitate highly individualized management and different comorbidities can restrict the treatment options and require particular attention to drug contraindications (BOX 1). Older-onset T2DM tends to progress more slowly than early-onset T2DM. Furthermore, treatment targets are often less stringent compared with those in younger patients to avoid hypoglycaemia and to minimize lifestyle changes that are unlikely to yield tangible benefits within the anticipated life expectancy. The presence of frailty with sarcopenia, severe life-limiting morbidities, cognitive decline and functional impairments also strongly influence the management strategies and emphasize the importance of liaison with carers and social support.

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#### Review criteria

Literature searches were conducted using Google Scholar, MEDLINE and Embase with the following terms: 'elderly', 'frail', 'older people' and 'aged' combined with 'diabetes', 'type 2 diabetes', 'prediabetes' and 'glucose control'. The selection was made by at least two of the present authors and was limited to English language articles from 2000 to 2020 and relevant references cited in the publications selected. Priority was given to prospective randomized studies and meta-analyses, though these were scarce, and observational and descriptive studies, guidelines, and policy documents were also consulted.

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