Avoiding hypoglycaemia: a new target of care for elderly diabetic patients

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ABSTRACT

Optimising glycaemic control to prevent diabetes-associated complications has received much attention. The associated risk of iatrogenic hypoglycaemia, however, is inevitable and can have a significant impact on health. The prevalence of iatrogenic hypoglycaemia tends to increase with advancing age. Elderly people are intrinsically prone to hypoglycaemia. Ageing attenuates the glucose counter-regulatory and symptomatic response to hypoglycaemia, particularly in the presence of a longer duration of diabetes. Multiple co-morbidities and polypharmacy correlated with advancing age also increase the hypoglycaemic risk. In addition to the acute adverse effects of hypoglycaemia, such as fall with injury, cardiovascular events and mortality, a hypoglycaemic episode can have long-term consequences. Repeated episodes may have a significant psychological impact and are also a risk factor for dementia. Because of the heterogeneous health status of the elderly, not all will benefit from optimal glycaemic control. Setting an individual glycaemic target and formulating a management plan that takes account of the patient's circumstances combined with balancing the benefit and risk of diabetes intervention to avoid hypoglycaemia is a more practical approach to the management of elderly diabetic patients.

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Introduction

Diabetes mellitus is a prevalent health problem in the elderly and contributes to significant morbidity and mortality due to its acute and long-term complications. Optimising diabetic control to prevent or delay microvascular complications is well-established and it may also reduce macrovascular events. However, it takes time for good diabetic control to come into effect. Given the heterogeneous health status of elderly people, diabetes intervention strategies designed for long-term benefit may not be appropriate for all elderly patients, especially those who are frail or who have a limited life expectancy. Furthermore, hypoglycaemia is an inevitable complication of good diabetic control and elderly people are particularly vulnerable, with both acute and long-term detrimental effects. Thus, avoidance of hypoglycaemia is important. This review will discuss the risk factors for hypoglycaemia in the elderly, the impact of hypoglycaemia, and whether the elderly can benefit from stringent glycaemic control. The recently promoted patient-centred approach to diabetes management in older people will also be reviewed.

In this article, hypoglycaemia refers to treatment-induced or iatrogenic hypoglycaemia in patients with diabetes. It is defined as any episode of an abnormally low plasma glucose level that exposes the individual to potential harm,[1,2] confirmed by the documentation of Whipple's triad: symptoms and signs consistent with hypoglycaemia, a low blood glucose level, and resolution of symptoms and signs after blood glucose concentration is raised.[3] There is no definitive blood glucose level to define hypoglycaemia as the glycaemic threshold for activation of the physiological defences against hypoglycaemia and the hypoglycaemic symptom response are dynamic. It may be shifted to a higher or lower value depending on the degree of diabetic control and the prior hypoglycaemic episode.[1] The American Diabetes Association recommends that diabetic patients with a plasma glucose level of 3.9 mmol/L (70 mg/dL) should be alert to the possibility of developing hypoglycaemia.[1,2,4,5] This value (3.9 mmol/L, 70 mg/dL) approximates the glycaemic threshold for activation of physiological glucose counter-regulatory mechanisms[6,7] and is the upper limit of plasma glucose level to blunt the counter-regulatory response to subsequent hypoglycaemia[8]; it is also suggested as the cutoff value in the classification of hypoglycaemia in diabetes.[1] Severe hypoglycaemia is usually defined as episode requiring external assistance, while a mild episode can be self-treated.

避免低血糖發生：老年糖尿病患者治療的新方向

王哲慧

近來，有關控制血糖至理想水平來預防糖尿病相關併發症的觀念已備受重視，然而相關的醫源性低血糖風險卻不能避免，而低血糖症會嚴重影響健康。醫源性低血糖症的發生率會隨着年齡增加。老年人本身已較易有低血糖的情況。老齡化會改變身體的葡萄糖反調節機制和對低血糖症狀的反應，尤其是較長糖尿病史的患者更易發生。因高齡而患有多種疾病並服用多種藥物也會增加低血糖的風險。低血糖除了引起急性不良反應，如跌倒而受傷、心血管事件和死亡，也會對患者的健康造成長遠影響。病情復發更會嚴重影響患者的心理，並會增加認知障礙的風險。由於老年人身體狀況參差，並非所有患者都受惠於理想的血糖控制。為老年糖尿病患者度身訂造健康管理計劃，平衡治療的效益及風險來避免引發低血糖是一個較為實際的處理方案。

Prevalence of hypoglycaemia in type 2 diabetes

The prevalence of diabetes mellitus increases with age. A local large-scale population-based epidemiological study using 1985 World Health Organization (WHO) diagnostic criteria showed that the prevalence of type 2 diabetes was 26% in people aged 65 to 74 years, compared with approximately 10% in those aged 35 to 64 years.[9,10] Another local study of 1467 elderly subjects using a fasting plasma glucose (FPG) level of >7.8 mmol/L for diabetes screening showed a prevalence of 15% in people aged 60 to 80 years and 17% in those older than 80 years.[11] These figures would be higher if an oral glucose tolerance test was performed. Likewise, the prevalence of diabetes in these studies would be further increased if the 1999 WHO diagnostic criteria for diabetes mellitus were used, in which the cutoff value of FPG is 7 mmol/L.

A high prevalence of diabetes in the elderly and a corresponding increased consumption of anti-diabetic therapies implies that the incidence of iatrogenic hypoglycaemia increases with age. Nonetheless, the prevalence of hypoglycaemia is difficult to estimate because it is often under-recognised and under-reported in clinical practice. Severe hypoglycaemia is a dramatic event that is more likely to be reported but the recall of mild hypoglycaemia is unreliable. The wide variation in reporting of hypoglycaemia prevalence is due to the absence of a standardised definition among studies.

In general, the frequency of hypoglycaemia is substantially lower in type 2 than in type 1 diabetes.[12] Event rates for severe hypoglycaemia in type 2 diabetes range from 3 to 73 episodes per 100 patient-years compared with 62 to 320 episodes per 100 patient-years in type 1 diabetes.[4] A number of variables correlate with hypoglycaemic episodes. Risk of hypoglycaemia appears to increase with advancing age even when glycaemic control is comparable. A prospective observational registry of 3810 patients with type 2 diabetes prescribed oral anti-diabetic therapy and with comparable glycated haemoglobin (HbA1c) level (7.3%-7.6%) showed that 12.8% of those aged ≥70 years, 10.1% aged 60 to 69 years, and 9% aged <60 years experienced hypoglycaemia, of any severity, in a year.[13] Data from interventional trials showed that the incidence of hypoglycaemia was higher in the intensive treatment group. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, 2.7% and 52% of patients in the intensive treatment group experienced severe or minor hypoglycaemic episodes, respectively during 5 years of follow-up, compared with 1.5% and 37.3% of patients in the standard treatment group.[14] In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, the annual rate of hypoglycaemic episodes requiring medical assistance was 3.1% in the intensive treatment group and 1% in the standard treatment group.[15] The prevalence of hypoglycaemia also varies with different treatment regimens. In the UKPDS (UK Prospective Diabetes Study), 2.4% of patients using metformin, 3.3% using sulfonylurea, and 11.2% using insulin experienced hypoglycaemia requiring medical attention or hospital admission over 6 years of follow-up.[16] The incidence of hypoglycaemia also increases with longer duration of diabetes and insulin treatment.[17] It has been reported that the frequency of severe hypoglycaemia is comparable in type 1 and 2 diabetes matched for duration of insulin therapy.[18] These findings indicate that as type 2 diabetic patients become insulin-deficient, hypoglycaemia becomes more frequent as in type 1 diabetes.

In a local study, drug-induced hypoglycaemia accounted for approximately 0.5% of admissions to a local hospital.[19] The most vulnerable group was elderly people with co-morbidities including macrovascular complications, renal insufficiency, and concurrent infection, and those living in an institution or with high dependency.

Elderly people are at risk of hypoglycaemia

Risk factors for hypoglycaemia in type 2 diabetes are excessive exogenous insulin or insulin secretagogue, exercise, erratic meal intake with respect to anti-diabetic therapy intake, treatment with insulin for more than 10 years, prior hypoglycaemia, renal insufficiency, alcohol intake, and polypharmacy.[4,18,20-22] Advanced age is an independent risk factor for serious hypoglycaemia. In the Tennessee Medicaid study, diabetic patients aged ≥80 years treated with insulin or sulfonylureas

had a 1.8-times increased risk of developing serious hypoglycaemia when compared with those aged 65 to 70 years.[23] In a survey of emergency department visits for hypoglycaemia, diabetic patients aged ≥75 years had twice the number of visits as the general diabetic population.[24] Why are elderly diabetic patients prone to hypoglycaemia?

Defective glucose counter-regulation and lack of awareness of hypoglycaemia

A fall in blood glucose level initiates a sequence of hierarchical counter-regulatory responses to limit the hypoglycaemia.[6,7,25] Prior to a blood glucose level fall below the physiological range (ie 4.7-4.4 mmol/L), insulin secretion from pancreatic islet β-cells is decreased. A further fall in blood glucose level below the physiological range (ie 3.9-3.6 mmol/L) precipitates increased glucagon secretion from pancreatic islet α-cells and epinephrine secretion from the adrenal medulla. These counter-regulatory hormones are important to protect against acute hypoglycaemia. With prolonged hypoglycaemia, growth hormone and cortisol secretion are increased to restore the normal blood glucose level. With a further fall in blood glucose level to 3.1-2.8 mmol/L, hypoglycaemic warning symptoms develop to prompt a behavioural defence of food ingestion. Neurogenic or autonomic symptoms—such as palpitations, tremor, and sweating—that enable a subjective awareness of hypoglycaemia, are the result of autonomic activation (both sympathoadrenal and parasympathetic) and begin at 3.2-3 mmol/L. Neuroglycopenic symptoms—such as confusion, seizure, and loss of consciousness—are the result of brain glucose deprivation and begin at 2.8 mmol/L. The higher blood glucose level for initiation of neurogenic warning symptoms than that of onset of neuroglycopenic symptoms allows time to take measures to avoid neuroglycopenia and severe hypoglycaemia.

Glucose counter-regulatory mechanisms are intact in the early stage of type 2 diabetes and can effectively protect against hypoglycaemia, thus the frequency of hypoglycaemic episodes is low. With progression to insulin deficiency in type 2 diabetes and in insulin-deficient type 1 diabetes, however, all three physiological defences of glucose counter-regulation (decreased insulin secretion, increased glucagon and epinephrine secretion) are compromised.[12,26] In the absence of endogenous insulin, the insulin level is unregulated and depends on the interplay of absorption and clearance of exogenous insulin. In the absence of an intra-islet insulin signal, the glucagon response to hypoglycaemia is lost. In the absence of both endogenous insulin and glucagon response, epinephrine is the main defence against hypoglycaemia in patients with type 1 and advanced type 2 diabetes requiring insulin. Nonetheless, the epinephrine response is often attenuated with the glycaemic threshold for response shifts to a lower blood glucose level.[12,26] This attenuated epinephrine response is the result of an attenuated sympathoadrenal response to the falling blood glucose level that also causes a decrease or loss of neurogenic warning symptoms, and leads to hypoglycaemia unawareness.[12,26] Compromised glucose counter-regulation and hypoglycaemia unawareness increase the risk of severe iatrogenic hypoglycaemia by 25-fold and 6-fold, respectively.[27,28]

In addition, recent hypoglycaemia induces hypoglycaemia-associated autonomic failure in type 1 and advanced type 2 diabetes.[12,20,26,29] It causes further defective glucose counter-regulation and hypoglycaemia unawareness by reducing the epinephrine and symptomatic response to subsequent hypoglycaemia, and thus, a vicious cycle of recurrent hypoglycaemia ensues.

Since a longer duration of diabetes with endogenous insulin deficiency often correlates with advancing age, elderly people are at risk of compromised glucose counter-regulation and hypoglycaemia.

Ageing and the physiological response to hypoglycaemia

With increasing age, hypoglycaemic warning symptoms are less intense and reduced hypoglycaemic awareness becomes more common, even with intact counter-regulatory responses.[30-33] This is reflected by the lower autonomic symptom scores in older people compared with younger people in the hypoglycaemic clamp studies,[30-33] and that is independent of the presence or absence of diabetes.[34] In addition, half of the middle-aged (39-64 years) diabetic patients but only one of 13 older (≥65 years) diabetic patients were aware that their blood glucose level was low during a hypoglycaemic episode.[30] This diminished hypoglycaemia symptom intensity may be the consequence of the impaired counter-regulatory response,[32] or the impaired end-organ response to counter-regulatory hormones (catecholamine) that occurs with advancing age.[31] Impaired perception of the warning symptoms of hypoglycaemia put elderly diabetic patients at a high risk of severe hypoglycaemic episodes.

The glycaemic threshold gap between the development of neurogenic and neuroglycopenic symptoms becomes narrower or even lost in older people. In a study that compared the response of healthy younger diabetic men (aged 22-36 years) with older men (aged 60-70 years) to stepped reduction in the blood glucose level, neurogenic symptoms began at a lower blood glucose level in older men than in younger men (3 ± 0.2 mmol/L vs 3.6 ± 0.1 mmol/L) and their symptoms were less intense.[33] Furthermore, the difference between the blood glucose level

for subjective awareness of hypoglycaemia and the onset of cognitive dysfunction was lost in the older men but retained in the younger men (0 ± 0.2 mmol/L vs 0.8 ± 0.1 mmol/L). This narrower or absent glycaemic threshold gap between the onset of neurogenic and neuroglycopenic symptoms may limit the time available for self-treatment and increase the risk of evolving into neuroglycopenia and severe hypoglycaemia in the elderly.

Older people have an increased susceptibility to cognitive impairment during a hypoglycaemic episode. In normal situations, they tend to have a longer reaction time for cognitive performance (a measure of cognitive function) than younger people and this reaction time is further prolonged by hypoglycaemia.[30] Psychomotor incoordination is also more marked and occurs earlier during the course of hypoglycaemia in older people.[33] Thus, the earlier onset and greater degree of cognitive dysfunction in the elderly during an episode of hypoglycaemia may impair their ability to perceive the warning symptoms to prompt corrective action.

The effect of ageing on the physiological response to hypoglycaemia indicates that elderly people are intrinsically at greater risk for asymptomatic serious hypoglycaemia even before the start of anti-diabetic therapy.

Co-morbidities and polypharmacy

The prevalence of multiple chronic conditions increases with advancing age: as many as 40% of elderly people with diabetes have four or more chronic conditions.[35] In a population-based study, advanced age and multiple co-morbidities, especially renal impairment, were the most frequent contributing factors to severe hypoglycaemia in type 2 diabetic patients.[36] In another study of hypoglycaemia-associated mortality in patients admitted to general wards, those who developed hypoglycaemia were older and had more co-morbidities, regardless of whether they had diabetes.[37] Renal insufficiency and hepatic disease affecting glucose homeostasis and drug metabolism increase the hypoglycaemic risk. Cognitive dysfunction and depression affecting self-care ability and functionality may cause erratic timing of medication intake, irregular eating, inability to self-monitor blood glucose, and failure to recognise hypoglycaemic symptoms to enable prompt management, and thus increase the risk of hypoglycaemia.[38-40] Elderly people with multiple co-morbidities are also likely to be admitted to hospital for worsening or developing complications of underlying medical illness, which is another risk factor for subsequent hypoglycaemia. Recent hospitalisation (first 30 days after discharge) was associated with a 4.5-times increased risk of developing serious hypoglycaemia compared with the risk of ≥366 days after discharge.[23] The risk was further increased with advancing age when patients aged ≥80 years were compared with those aged 65 to 69 years.

Medications prescribed for co-morbidities make patients prone to the impact of polypharmacy and increase the risk of drug side-effects and drug-to-drug interactions. Adverse effects are further exacerbated in the elderly because of the age-related changes in pharmacokinetics and pharmacodynamics that affect drug deposition. Elderly diabetic patients using four or more concomitant medications have been found to be at increased risk of developing serious hypoglycaemia.[23,36] In addition to the insulin and insulin secretagogues, a number of drugs (beta-blockers, angiotensin-converting enzyme inhibitors, quinine, indomethacin, lithium, levofloxacin) have been reported to cause hypoglycaemia although evidence for the associated hypoglycaemia is poor.[4,41] Non-selective beta-blockers exert a potential hypoglycaemic effect by blunting the signs and symptoms of hypoglycaemia, diminishing the physiological response to hypoglycaemia and direct potentiation of the effect of insulin. However, the evidence to support the increased hypoglycaemic risk among those prescribed non-selective beta-blockers is weak despite a 2-fold increased risk reported in patients on insulin.[42] Selective beta-blockers appear to be safe.[42,43] Angiotensin-converting enzyme inhibitors may increase insulin sensitivity in diabetic patients. They have been found to increase the risk of hypoglycaemia by nearly 3-fold in patients prescribed insulin or oral antidiabetic drugs[44] although other studies have failed to show any effect.[42,43] Overall, the combination of these commonly used drugs with insulin and insulin secretagogues in daily practice may potentiate the hypoglycaemic risk in the elderly diabetic patients.

Impact of hypoglycaemia

Patients with a hypoglycaemic attack are at risk of adverse outcomes. The immediate adverse effects range from unpleasant symptoms, to significant morbidities such as fall and accident with fracture and injury,[45-47] cardiovascular events,[48,49] transient cognitive impairment,[50,51] seizure, coma and death. Some of these adverse effects can endure for a period of time after the hypoglycaemic episode or have long-term sequelae. In addition to physical morbidity, hypoglycaemia has a long-term psychological impact. It is associated with lower health-related quality of life and greater burden of depression and fear of hypoglycaemia.[52,53] These may preclude patients from adherence to treatment in order to prevent hypoglycaemic attacks.

Fall and fracture

Elderly people with diabetes are at risk of fall even

in the absence of hypoglycaemic episodes. Diabetes complications (such as autonomic dysfunction with orthostatic hypotension, peripheral neuropathy with gait disorder, and diabetes retinopathy with poor vision[54]) and the treatment complications (such as metformin-associated vitamin B_{12} deficiency with resultant neuropathy[55]) increase the susceptibility of diabetic patients to fall. Diabetes is itself a factor for increased fracture risk and elderly diabetic patients are at even higher risk.[56] The underlying mechanisms are complex.[57] Nevertheless, the frail elderly with multiple co-morbidities including osteoporosis are vulnerable to bone fracture after fall; both thiazolidinediones and insulin administration are found to be associated with increased risk of fracture.[47,56-58] In this way, a hypoglycaemic episode precipitates the pre-existing increased fall and fracture risk in the elderly diabetic patients.

Cardiovascular complications

Severe hypoglycaemia is a potential risk factor for cardiovascular disease in people with type 2 diabetes. A meta-analysis of six studies with 903 510 participants and mean age of 60 to 67 years revealed that severe hypoglycaemia was associated with approximately twice the risk of cardiovascular disease, including myocardial infarction, congestive heart failure, stroke, and cardiovascular death.[48] A study of 21 type 2 diabetic patients treated with insulin with good glycaemic control but concomitant coronary artery disease showed that significantly more patients experienced chest pain and demonstrated ischaemic electrocardiogram changes when blood glucose level was <3.8 mmol/L compared with blood glucose level of normal range during 72 hours of continuous glucose monitoring.[59] Hypoglycaemia can also cause alteration of ventricular repolarisation with prolongation of the QT interval that can precipitate ventricular arrhythmia and result in sudden death.[49,60] Although the causal link between hypoglycaemia and cardiovascular disease is unknown, hypoglycaemia can trigger a series of responses with detrimental effects on the cardiovascular system. The responses include sympathoadrenal activation, inflammation, endothelial dysfunction, and increased platelet activation and coagulability.[61-63] These pose an adverse effect on the myocardium and vascular system, and may induce a cardiovascular event. Thus, elderly diabetic patients at risk of cardiovascular disease are particularly prone to hypoglycaemia-associated cardiovascular events.

Dementia

Many epidemiological studies have demonstrated that patients with diabetes are at increased risk of dementia. The underlying pathophysiology linking diabetes to cognitive impairment is potentially complex and is not well understood. Diabetes is known to cause cerebrovascular disease that can in turn cause vascular cognitive impairment. Hyperglycaemia with hyperinsulinaemia, and increased formation of advanced glycation end products and reactive oxygen species may play a role in causing cognitive impairment.[50,51]

Recently, hypoglycaemia has been increasingly recognised to be associated with subsequent dementia in elderly patients. During an acute hypoglycaemic episode, numerous aspects of cognition—such as immediate verbal and visual memory, working memory, delayed memory, visual-motor skills, visual-spatial skills, and global cognitive function—are impaired.[50,51] These transient deficits might translate into long-term cognitive deficits, especially if the hypoglycaemic episode is severe or recurrent. The exact mechanism is not completely understood although it has been proposed that hypoglycaemia reduces the brain's supply of sugar causing neuronal damage or death that in turn accelerates the development of dementia.[64] The elderly patients are particularly vulnerable because of less brain reserve.

A large-scale longitudinal cohort study from 1980 to 2007 in the United States, based on the electronic hospital records of 16 667 type 2 diabetic patients with a mean age of 65 years, showed that severe hypoglycaemic episodes (requiring hospitalisation or an emergency department visit) were associated with increased risk of dementia.[65] Patients with a history of hypoglycaemia had a 2.4% increase in absolute risk of dementia per year when compared with patients without a hypoglycaemic history. There was also a graded increase in the dementia risk according to the number of severe hypoglycaemia episodes experienced, such that the risk was almost double with three or more episodes. Another similar study in Taiwan involved 15 404 type 2 diabetic patients with a mean age of 64 years and over 7 years of follow-up found that prior hypoglycaemia had a significant increased risk of dementia with a risk ratio of 1.6 after adjustment for age and sex.[66] In a cross-sectional study of 1066 type 2 diabetic patients aged 60 to 75 years, self-reported history of severe hypoglycaemia was associated with poorer late-life cognitive ability after adjustment for the estimated prior cognitive ability.[67]

A recently published prospective study gives further support to the association between hypoglycaemia and dementia in elderly patients with diabetes. Since 1997, a total of 783 diabetic patients without dementia and with a mean age of 74 years have been followed up for at least 12 years.[39] In contrast to previous studies, this study showed a bidirectional association of hypoglycaemia with dementia; patients who experienced at least one episode of significant hypoglycaemia were twice as

likely to develop dementia compared with those who did not have a hypoglycaemic event. Furthermore, demented patients were 2.2 times more likely than those diabetic patients without dementia to become hypoglycaemic. The results suggest that hypoglycaemia and dementia can create a vicious cycle in which hypoglycaemia damages the brain that in turn decreases the ability to manage diabetes or recognise hypoglycaemic symptoms, and thus leads to increased risk for hypoglycaemia.

The association of hypoglycaemia with cognitive dysfunction has implications for clinical practice. Detecting and avoiding hypoglycaemia is important to prevent or delay cognitive impairment. Cognitive function should be taken into account in the clinical management of elderly diabetic patients to minimise the risk of hypoglycaemic complications.

Management of hypoglycaemia

The primary aim of diabetes management is optimisation of glycaemic control to avoid acute hyperglycaemia complications and prevent long-term diabetes complications, both microvascular and macrovascular, and at the same time to minimise the treatment side-effect of hypoglycaemia. In younger people with new-onset diabetes, stringent glycaemic control before the establishment of long-term complications is of paramount importance. On the other hand, in those with advanced age and limited life expectancy or with longer duration of diabetes and established complications and multiple co-morbidities, the benefit of stringent glycaemic control is dubious. Diabetes management guidelines, mainly based on studies of a younger population, may not be appropriate for the older population with heterogeneous health status. A more patient-centred approach for type 2 diabetes management that takes account of the potential benefits and risks of treatment, health and functional state, and social background for an individual patient has been emphasised recently.

Does stringent glycaemic control benefit the elderly diabetic patients?

The long-term benefit of good glycaemic control seems to be affected by the duration of type 2 diabetes and the presence or absence of the established macrovascular and microvascular complications.

In the UKPDS, newly diagnosed type 2 diabetic patients (mean age, 53 years) who received intensive therapy (HbA1c achieved, 7%) with a median follow-up of 11 years showed borderline significance for reduction in risk of myocardial infarction but a 25% risk reduction in microvascular complications, mainly due to fewer cases of retinal photocoagulation.[68] During 10 years of post-trial follow-up, the previous intensive therapy group continued to show fewer microvascular complications and had emergent macrovascular benefit in terms of a 15% risk reduction for myocardial infarction.[69]

In three more recent large-scale trials, ACCORD, ADVANCE and VADT (Veterans Affairs Diabetes Trial) that recruited older people (mean age, 60-66 years) with longer type 2 diabetes duration (8-11.5 years) and of whom 32% to 40% had a history of cardiovascular events, the intensive therapy group (HbA1c achieved, 6.4%-6.9%) showed no benefit in reduction of overall major cardiovascular events and death over 5 years of follow-up,[15,70,71] but only a lower rate of non-fatal myocardial infarction in the ACCORD trial.[72] Instead, there was a higher mortality rate in the intensive therapy group of the ACCORD trial that led to premature discontinuation of intensive therapy after 3.5 years of follow-up. In the VADT subtype analysis of the effect of calcified coronary atherosclerosis on the cardiovascular outcomes of intensive therapy, patients with a higher coronary calcium score (>100; associated with more advanced vascular disease or atherosclerosis) on intensive therapy showed no reduction in cardiovascular events.[73] On the other hand, those with lower scores (≤100) showed benefit from intensive therapy but the benefit diminished progressively with increasing coronary calcium score. For microvascular renal outcomes, most renal benefits derived from reduced development of macroalbuminuria. Both ADVANCE and ACCORD trials showed that the intensive therapy group had 30% lower macroalbuminuria development whilst VADT showed only borderline significant reduction in any worsening of albumin excretion in the intensive therapy group.[70,71,74] None of them showed any effect on the progression of renal impairment. The ACCORD trial showed that intensive therapy was associated with decreased progression of retinopathy by 33%[75] and modest risk reduction in development of peripheral neuropathy.[74] The ADVANCE trial and VADT showed no such effect.

Treatment benefit is also affected by underlying co-morbidity. In a 5-year observational study of Italian patients with type 2 diabetes and baseline HbA1c of ≤6.5% to 7%, those with low-to-moderate co-morbidity (mean age, 61.7 years) had a lower incidence of cardiovascular events than those with high co-morbidity (mean age, 64.3 years).[76]

Targeting HbA1c to a low level may increase mortality. A retrospective study from the UK General Practice Research Database showed a U-shaped relationship between HbA1c level and mortality in type 2 diabetic patients (mean age, 64 years) who received intensified treatment, with the lowest hazard ratio for mortality at HbA1c level of 7.5%.[77] An HbA1c level higher or lower than 7.5% was associated with higher all-cause mortality and cardiac events, which was independent of treatment regimen.

These findings imply that good glycaemic control does not always have a positive effect: most benefit appears to be derived if such control commences earlier, before the establishment of long-term complications. It is important to note, deduced from the studies, that it takes over 5 years of intensive glycaemic control to reap microvascular benefit[68,70,71,74,75] and over 10 to 20 years for macrovascular benefit.[69] For those with a limited life expectancy and multiple co-morbidities, the adverse effects are likely to outweigh the benefit.

Individualised glycaemic targets

There are various frameworks or guidelines based on patient characteristics and health status to assist in determining glycaemic treatment goals in elderly patients with type 2 diabetes.[78-82] In generally healthy young and active elderly people without significant co-morbidities, the same glycaemic target as for young adults may be worthwhile to prevent long-term complications. For the frail elderly with multiple illnesses and limited life expectancy, the aim of glycaemic control is to prevent acute hyperglycaemic complications (polyuria, dehydration, hyperglycaemic hyperosmolar syndrome, infection, and poor wound healing) and to avoid treatment adverse effects, but not to gain long-term benefit. Thus glycaemic control can be less stringent.

The suggested target HbA1c level varies from <7.5% for healthy young elderly people to 8%-9% for those with very poor health and limited life expectancy. The Table[79] shows a framework for considering treatment goals in elderly patients with diabetes produced by the American Diabetes Association and American Geriatrics Society. It classifies elderly patients into three groups: (1) relatively healthy with longer life expectancy; (2) multiple co-morbidities and decreased self-care ability; (3) very poor health with significant co-morbidities and functional impairment and limited life expectancy. Although the framework may not address the health status of all elderly patients, it gives an idea of individualised treatment decisions. Further studies are needed to guide the glycaemic target and clinical care plan for heterogeneous elderly patients.

Pharmacotherapy

Metformin, which is associated with a low risk for hypoglycaemia, is the preferred initial therapy in the elderly with type 2 diabetes.[79,80] The dosage must be reduced in chronic kidney disease and should be avoided in patients with an estimated glomerular filtration rate of <30 mL/min per 1.73 m^2 or in patients at risk of lactic acidosis. Long-acting sulfonylurea, such as chlorpropamide and glibenclamide, is associated with a high risk of hypoglycaemia[83,84] and is not recommended for the elderly.[85] It should be replaced by a short-acting sulfonylurea such as glipizide as it is less associated with hypoglycaemia.[84] An α-glucosidase inhibitor for postprandial hyperglycaemia has a low risk of hypoglycaemia and can be considered for the elderly.[79] Thiazolidinedione—with side-effects of weight gain, water retention with oedema and heart failure, bone fractures, and possible bladder cancer—may not be suitable for elderly people.[58,86,87] More recently approved therapy, the incretin-based therapies such as glucagon-like peptide receptor agonists and dipeptidyl peptidase-IV inhibitors, are useful for postprandial hyperglycaemia. They have a low risk of hypoglycaemia, are well tolerated without weight gain, and may be beneficial for the elderly people.[88]

In those treated with insulin, substitution of long-acting basal insulin analogue (glargine and detemir) for intermediate-acting insulin and substitution of preprandial rapid-acting insulin analogue (lispro and aspart) for short-acting (regular) insulin are associated with lower overall and nocturnal hypoglycaemia, less weight gain, and greater reduction in postprandial blood glucose level.[89-91] The higher cost, however, may limit their popularity in the elderly.

Properties of anti-diabetic medications, their

TABLE. American Diabetes Association/American Geriatrics Society consensus guideline for glycaemia goal in elderly people with diabetes[79]

Patient type	Patient characteristics/health status	HbA1c target	Fasting/ preprandial glucose (mmol/L)	Bedtime glucose (mmol/L)
Healthy (longer life expectancy)	Few co-existing chronic illnesses, intact cognitive and functional status	<7.5%	5-7.2	5-8.3
Complex/intermediate (intermediate remaining life expectancy, high treatment burden, hypoglycaemia vulnerability, fall risk)	Multiple co-existing chronic illnesses or >2 instrumental ADL impairment or mild-to-moderate cognitive impairment	<8%	5-8.3	5.6-10
Very complex/poor health (limited remaining life expectancy makes benefit uncertain)	Long-term care/end-stage chronic illness, moderate-to-severe cognitive impairment, >2 ADL dependencies	<8.5%	5.6-10	6.1-11.1

Abbreviations: ADL = activities of daily living; HbA1c = glycated haemoglobin

adverse effects, and patient's tolerability should be considered when planning treatment. Management of other cardiovascular risk factors (eg smoking, hypertension, and hypercholesterolaemia) is also important. Patients should be assessed for glycaemic control and any hypoglycaemic events during follow-up with the treatment regimen adjusted accordingly. Adequate diabetes education should be offered to patients or their caregiver. It includes goal setting, self-monitoring of blood glucose level, regular meal intake in relation to drug intake, recognising risk factors and symptoms of hypoglycaemia and self-management.

Recent hypoglycaemia

Patients with recent episodes of hypoglycaemia are at risk of a blunted counter-regulatory response to subsequent hypoglycaemia within a short period of time. This may lead to recurrent hypoglycaemia of a severe degree and hypoglycaemia unawareness.[8] Patients with episodic severe hypoglycaemia or hypoglycaemia unawareness, which indicates underlying defective glucose counter-regulation, are particularly at risk. A 2-to-3-week period of scrupulous avoidance of hypoglycaemia with loose glycaemic control for restoring the glucose counter-regulatory response and hypoglycaemia awareness is advised in order to prevent the recurrent hypoglycaemia.[4]

Conclusion

Elderly people are potentially at risk of hypoglycaemia. Longer duration of diabetes with endogenous insulin deficiency, which is often linked with advancing age, compromises the glucose counter-regulation. Together with the decreased hypoglycaemia symptomatic response with ageing, elderly people are prone to hypoglycaemia unawareness and severe hypoglycaemic episodes. Multiple co-morbidities and polypharmacy further exacerbate this hypoglycaemic risk. Hypoglycaemia can have a significant acute and long-term impact on the elderly. Accident, fall with injuries, or a cardiovascular event following hypoglycaemia can all be life-threatening. Dementia risk in the long term can compromise self-management of diabetes and further increase the hypoglycaemic risk. More importantly, stringent glycaemic control offers only modest benefit to the elderly; it takes over 5 years for microvascular and over 10 to 20 years for macrovascular benefits to appear; and in patients with established complications and multiple co-morbidities, the additional benefit of stringent control is in doubt. An individualised treatment target that takes account of the heterogeneous health status with the intention of avoiding hypoglycaemia and acute hyperglycaemic complications should be emphasised, especially in the frail elderly. Multifactorial and multidisciplinary approaches to integrate a patient's needs, preference, and social supportive network should be considered; management of other cardiovascular risk factors, nutritional assessment and nutritional plan and serving meal strategies, physical activity and exercise advice, and education are all useful. Finally, studies on elderly diabetic patients, especially the older old, are limited. Further studies are needed to reach a clear consensus on the management of the elderly diabetic patients.

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