



Diabetes as the years progress: how does management differ?

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It is important to recognise the various functional, medical and social issues that the elderly population with diabetes face and to use the expertise of multiple disciplines to deliver a safe and effective management plan, which needs to be as simple to follow as possible.

Older adults are a heterogeneous group of individuals with varying physical capabilities, cognitive function, comorbidities and life expectancies. This can make the management of diabetes in this population quite challenging. The changing physiology in an ageing population also adds to the level of complexity.

One of the most common considerations in many elderly people with diabetes is the presence of chronic renal impairment rendering certain agents such as some dipeptidyl peptidase (DPP) IV inhibitors and very long acting sulfonylureas unsuitable or at the least requiring some dose adjustment, as is the case with metformin. Guidelines do not generally target this population specifically. It is important for the treating clinician to be familiar with all the therapeutic options available for the elderly with diabetes and how to use these in a simple, safe and effective manner to achieve the goals desired according to the individual patient's circumstances.

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Key points

- Older people with diabetes rarely present with the typical symptoms of hyperglycaemia.
- Asymptomatic elderly people should be screened for undiagnosed diabetes by measurement of fasting plasma glucose levels as recommended for the general population.
- Both type 1 (insulin dependent) and type 2 (noninsulin dependent) diabetes occur in the elderly.
- Elderly people with diabetes should have regular comprehensive clinical and laboratory evaluation of metabolic control and screening for complications of diabetes.
- Treating physicians should individualise the HbA_{1c} target level in people with diabetes, taking into consideration the presence of cardiovascular disease, diabetes duration, diabetes medication regimen, comorbidities and problems with severe hypoglycaemia.
- With the increasing duration of diabetes there will be an ongoing decline in pancreatic function, therefore, insulin will be essential for many people as the years progress.

Who are the elderly?

People aged 65 years and over are usually considered the elderly, although this group can be further defined as the young old (65 to 75 years) and the old old (>75 years). Also, there is the clinically relevant classification of healthy elderly and frail elderly, in which the healthy elderly are independent in activities of daily living, free of cognitive impairment or dementia, and in reasonable physical and mental health. Needs of the frail elderly should be considered on an individual basis with special consideration of physical and mental status.¹

Burden of disease

The population is ageing and the elderly increasingly comprise a larger proportion of newly diagnosed patients with diabetes. The prevalence of diabetes increases with increasing age as shown in the Figure.² Australian studies have shown prevalence rates of 7.5% for the population aged 25 years and over, 17.9% for those aged 64 to 75 years and 23% for those aged over 75 years.³

Presentation

Older people with diabetes rarely present with the typical symptoms of hyperglycaemia. This is in part due to the normal physiological changes associated with ageing that can make the recognition and

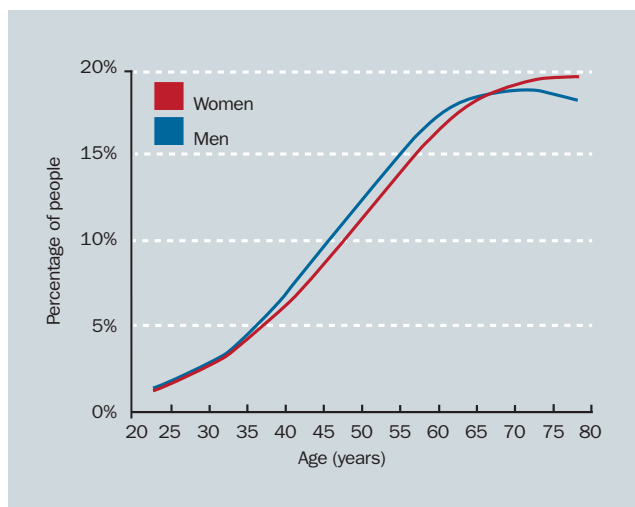


Figure. Prevalence of people with diabetes by age and sex, 2011.²

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treatment of diabetes problematic. Some of these physiological changes and therefore challenges of advancing age are listed below.

- Increased renal threshold for glucose means glucose is not seen in the urine until much higher blood glucose levels are present.^{4,5}
- Reduced thirst in the elderly means polydipsia is usually absent. Dehydration is therefore a more common symptom of hyperglycaemia in the elderly.
- Changes such as confusion, incontinence or complications relating to diabetes are more often the presenting symptoms of hyperglycaemia.⁶

Diagnosis

Asymptomatic elderly people should be screened for undiagnosed diabetes by measurement of fasting plasma glucose levels as recommended for the general population.¹ Australian population studies reveal that type 2 diabetes affects almost one-fifth of people aged 65 to 74 years and almost one-quarter of people over 75 years of age. At least half of all elderly patients identified as having diabetes were previously undiagnosed.⁶ Several studies have also shown increased risk associated with cardiovascular disease and mortality in elderly people with diabetes.¹ For this reason it is important to continue to screen people for diabetes as the years progress.

Some difficulty in the diagnosis of diabetes in the elderly can arise with the use of fasting plasma glucose as a screening tool. Normal ageing is characterised by progressive alterations in all aspects of glucose metabolism, including insulin secretion, insulin action and hepatic glucose production. Blood glucose levels rise with age; however, postmeal glucose levels rise even further. This is due to alterations in carbohydrate metabolism resulting in the loss of first-phase insulin release.⁷ Hence, the initial surge in postprandial insulin does not occur in all elderly patients with diabetes, meaning that some elderly people with normal fasting plasma glucose levels may have an elevation in blood glucose when tested with the two-hour formal oral glucose tolerance test (OGTT). In this population, if this test is not carried out, the diagnosis may be missed. The risk of this has to be balanced against the problems and impracticality of referring all elderly people to have an OGTT. Although it is recognised that the diagnosis of diabetes in some elderly people with OGTT-defined diabetes will be missed, it is felt on balance that the current guidelines used for the general population should also be used in the elderly (see the flowchart on page 9).^{1,8}

Pathophysiology

Both type 1 (insulin dependent) and type 2 (noninsulin dependent) diabetes occur in the elderly. In obese elderly patients the main problem is insulin resistance similar to that seen in the general population with type 2 diabetes. However, in older patients with diabetes who are lean, there may be significant impairment in glucose-dependent insulin release similar to that occurring in the younger type 1 diabetes population. Insulin deficiency is therefore the primary impairment in the lean, older patient with diabetes and islet cell antibodies are commonly detected when screened for. Obese elderly patients may, therefore, benefit more from insulin sensitisers as first-line therapy, whereas lean elderly patients need to have the problem of impaired insulin secretion addressed with secretagogues or insulin.⁷

Management

The goals of diabetes control in the elderly include:

- control of hyperglycaemia
- risk-factor management
- prevention and treatment of macrovascular and microvascular complications.

These goals are similar to those in the general population with diabetes; however, the changes in functional status and increasing

comorbidities that often develop with age need to be considered when determining an appropriate management plan for the elderly.⁹ Such issues that need to be addressed include cognitive impairments, visual impairment, limitations in activities of daily living, undiagnosed depression and difficult social circumstances.⁶

In addition, the specific circumstances of the elderly patient with dementia and diabetes also need to be considered. Goals in

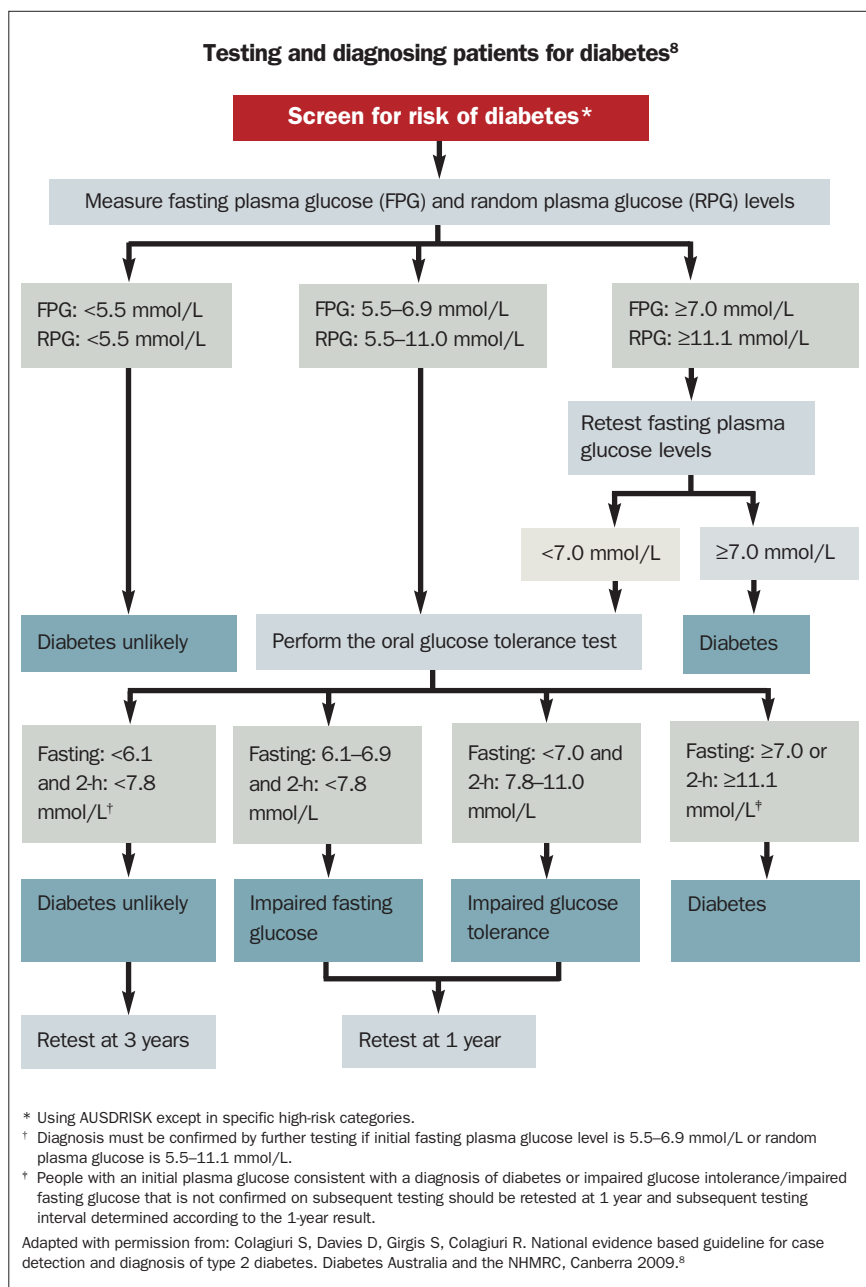


Table 1. Recommended glycated haemoglobin (HbA_{1c}) target ranges for adults with type 2 diabetes¹⁴

	HbA _{1c} target (%)	Rationale for recommendation	Level of evidence for the target category
General target	≤7.0*	UKPDS demonstrated improved outcomes with median HbA _{1c} ≤7%, supported by NHMRC systematic review	I
Specific clinical situations			
Diabetes of short duration [†] and no clinical cardiovascular disease			
– requiring lifestyle modification ± metformin	≤6.0*	UKPDS showed benefits with early treatment of diabetes. Epidemiological data indicate increased mortality and cardiovascular events with threshold below 6%. Negligible risk of hypoglycaemia with lifestyle or metformin	Consensus
– requiring any antidiabetic agent other than metformin or insulin	≤6.5*	UKPDS showed benefits with early treatment of diabetes. The risk of hypoglycaemia increases with use of most antidiabetic agents other than metformin hence we are not recommending a target HbA _{1c} ≤6.0% for this group. ADVANCE demonstrated reduced microvascular disease with an HbA _{1c} target ≤6.5%	II
– requiring insulin	≤7.0*	UKPDS demonstrated improved outcomes with median HbA _{1c} 7%, in people with newly diagnosed diabetes, including people treated with insulin. The Kumamoto study demonstrated improved outcomes with intensive insulin with mean HbA _{1c} 7.2%	II
Pregnancy or planning pregnancy	≤6.0*	Almost all observational data (albeit mainly in type 1 diabetes) demonstrate a relationship between HbA _{1c} and adverse pregnancy outcomes with a threshold below 6%	Consensus
Diabetes of longer duration [†] or clinical cardiovascular disease (any therapy)	≤7.0*	UKPDS demonstrated improved outcomes with median HbA _{1c} ≤7%. ACCORD indicates that attempts for even tighter control in people with relatively long duration of diabetes and cardiovascular disease associated with increased mortality. VADT found tighter control associated with increased cardiovascular events in people with diabetes >20 years (unpublished). We therefore do not routinely recommend tighter control in this group	II
Recurrent severe hypoglycaemia or hypoglycaemia unawareness (any therapy)	≤8.0*	Severe hypoglycaemia is associated with significant morbidity and mortality. The risks of tight glycaemic control outweigh the benefits for such patients	Consensus
Patients with major comorbidities likely to limit life expectancy [‡] (any therapy)	Symptomatic therapy of hyperglycaemia [§]	Tight glycaemic control will be of no benefit as diabetic complications take many years to develop	Consensus

ABBREVIATIONS: ACCORD = Action to Control Cardiovascular Risk in Diabetes trial; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation trial; NHMRC = National Health & Medical Research Council; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

* Achievement of HbA_{1c} targets must be balanced against risk of severe hypoglycaemia, especially in the elderly.

† In an older adult long duration might be considered to be >10 to 20 years, but for a person who develops type 2 diabetes at a young age, it may be considerably longer.

‡ Examples of major comorbidities include chronic medical conditions such as chronic kidney disease stages 4 or 5; New York Heart Association heart failure stages III or IV; incurable malignancy; and moderate to severe dementia.

§ Where practical, suggest blood glucose level target <15 mmol/L to help minimise risk of infections.

Reproduced with permission from: Australian Diabetes Society Position Statement: Individualisation of HbA_{1c} Targets for Adults with Diabetes Mellitus, 2009. Available online at: www.diabetessociety.com.au/downloads/positionstatements/HbA1ctargets.pdf.¹⁴

this context would be essentially to avoid symptomatic hyperglycaemia as well as hypoglycaemia. Choice of therapy will depend on whether the patient is living in the community or in a residential facility. Rationalisation of therapy with the aim of making it as uncomplicated and safe as possible for family members or care workers to follow is important.

Treatment targets

For the general population, most authorities including the Australian Diabetes Society (ADS) recommend an HbA_{1c} target of 7% or less based on the results from the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS).¹⁰ This recommendation also takes into account the results of the recent large studies (Action to Control Cardiovascular Risk in Diabetes trial [ACCORD],¹¹ the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation trial [ADVANCE]¹² and the Veterans Affairs Diabetes Trial [VADT]¹³) designed to examine even tighter control. Interestingly, the results on cardiovascular mortality were conflicting with apparent lack of cardiovascular benefit (and in some settings potential harm) associated with more intensive control. The ADS position statement on individualisation of glycated haemoglobin targets for adults with diabetes mellitus makes specific recommendations suggesting that ‘attempts to achieve tight glycaemic control need to be balanced against the increased risk of severe hypoglycaemia’ (see Table 1).^{10,14}

In the more frail elderly population, one would aim for a postprandial blood glucose level of less than 14 mmol/L and a fasting blood glucose level of less than 10 mmol/L. Treatment should not be directed at achieving a HbA_{1c} target of less than 7% in the frail elderly because this would be unsafe and dangerous.

Management of diabetes also includes: adequate control of other cardiovascular risk factors (e.g. weight, blood pressure and serum lipid levels), antiplatelet therapy, and smoking cessation. Table 2 lists the broad guidelines for some of these targets.

Managing hypoglycaemia

Due to changes in counter-regulatory hormones with ageing, the experience of hypoglycaemic symptoms can be somewhat blunted in the elderly. In addition, their ability to respond and treat the event may be reduced. It is therefore essential that patients receive education about warning symptoms, clear instructions on how to treat hypoglycaemia as well as education on the use of blood glucose monitors. The clinician should consider each individual patient’s circumstances and prescribe and revise medication regimens to minimise the risk of hypoglycaemia.

There have been several studies assessing the impact of hypoglycaemia on cognitive decline. It has been suggested that recurrent and severe episodes of hypoglycaemia may increase cognitive impairment and dementia.¹⁵ There are also studies that show an association between hypoglycaemia and increased mortality in patients with pre-existing cardiovascular disease as mentioned above.¹¹

Lifestyle modification

Lifestyle modification is important in patients who are significantly overweight; however, more commonly the elderly are at risk of undernutrition. Therefore, careful advice should be given about maintaining a healthy, balanced diet. Remaining active and undertaking exercise within functional capabilities is also important.

Pharmacotherapy

Metformin

Metformin is a biguanide derivative that has been available for over 50 years. It is a very useful first-line agent for patients at any age with a good safety profile. Risk of hypoglycaemia is very low in patients taking metformin. This agent improves peripheral and liver sensitivity to insulin, as well as decreasing basal hepatic glucose output. Several studies have shown benefit in all-cause mortality, cardiovascular mortality as well as cancer risk.¹⁶

It is important to start patients on a low dose and up-titrate slowly to avoid gastrointestinal side effects, such as stomach upset and diarrhoea, which may limit compliance. Use of metformin interferes with vitamin B₁₂ absorption but is rarely associated with anaemia.

Metformin should be used with caution in patients with renal impairment (estimated glomerular filtration rate [eGFR] less than 45 mL/min) and is contraindicated when eGFR is less than 30 mL/min. Lactic acidosis is a serious but rare side effect and predisposing factors include renal, hepatic and cardiac failure.

Metformin is especially useful in overweight patients because it is weight neutral; however, it is important to avoid in very lean elderly patients due to a possible further appetite suppressant effect.

Sulfonylureas

Sulfonylurea agents that are available include gliclazide, glimepiride, glipizide and glibenclamide. Side effects include weight gain and hypoglycaemia. These agents are usually well tolerated and have been shown to reduce the rate of diabetic complications, particularly microvascular complications. This was shown in the ADVANCE¹² trial, which randomly allocated 11,140 people with type 2 diabetes (mean age,

Table 2. Treatment targets for healthy and frail elderly who have diabetes^{4,7}

	Healthy elderly	Frail elderly
Fasting blood glucose level (mmol/L)	<7	<10
Two-hour postprandial blood glucose level (mmol/L)	<10	<14
HbA _{1c} (%)	<7	<8.5
Blood pressure (mmHg)	<140/<80	<150/<90
Low-density lipoprotein level (mmol/L)	<3.0	
Triglyceride level (mmol/L)	<2.0	

66 years; mean diabetes duration, eight years) and major macrovascular or microvascular complications to intensive or standard glycaemic control. The intensive therapy group who were treated with gliclazide had a mean HbA_{1c} of 6.5% with a 10% relative risk reduction in the combined outcome of microvascular and macrovascular complications and no difference in mortality at five years. Severe hypoglycaemia was more common in the intensive therapy group.¹⁰

This class of drugs is a potent and useful alternative to insulin in older people; however, it is important to use these agents, particularly extended-release preparations, with caution in patients with renal impairment as accumulation can increase the risk of hypoglycaemia.

DPP IV inhibitors

DPP IV inhibitors that are available include sitagliptin, vildagliptin, saxagliptin and, most recently, linagliptin. They work by inhibiting DPP IV, which degrades incretin hormones such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide. These gastrointestinal peptides are released in response to a meal. Therefore, by inhibiting their breakdown, the incretin peptides are increased, as is glucose-induced insulin release from the pancreas, while the release of glucagon is suppressed.

These agents can only be used as dual therapy with either metformin or a sulfonylurea except for linagliptin, which is also approved by the TGA for use with metformin plus a sulfonylurea. However, none of these agents is currently PBS approved for triple therapy. These agents also have the advantage of being weight neutral with some potential for weight loss and can be useful when trying to avoid any further weight gain, which may be a side effect of a sulfonylurea.

Due to the mechanism of glucose-dependent insulin release, the risk of hypoglycaemia is minimised. Thus these agents are relatively safe to be used in the elderly; however, there are various contraindications in those with renal impairment and liver dysfunction that vary between agents. Linagliptin is not renally excreted and therefore can be used without dose adjustment in elderly patients. Sitagliptin can also be used in patients with renal impairment but requires dose adjustment depending on the level of impairment. Vildagliptin and saxagliptin are not authorised for use in patients if their eGFR is less than 50 mL/min.

DPP IV inhibitors may not be as effective in patients with a long duration of disease due to pancreatic failure and therefore may not be as useful in elderly people with longstanding diabetes.

GLP-1 analogues

The only GLP-1 analogue currently available in Australia is exenatide. Exenatide is resistant to DPP IV degradation and enhances glucose dependent insulin secretion, suppresses postprandial glucagon secretion and slows gastric emptying. It has also been shown in some studies to increase beta cell mass and function.¹⁷

Exenatide is given as a twice-daily injection, with a starting trial dose of 5 µg/day for the first month, followed by the full dose of 10 µg twice daily with breakfast and dinner.

GLP-1 analogues can be a very effective treatment for diabetes

Case 1. A frail 75-year-old man with type 1 diabetes presents with hyperglycaemia and developing dementia

A 75-year-old man with type 1 diabetes for the past 50 years presented to hospital with hyperglycaemia and confusion. He was living at home with his wife and had been independent. The diabetes educator involved with his care had concerns over the past year for his safety and ability to manage at home. He had been on a basal bolus analogue insulin regimen, with doses decided by himself based on his blood glucose level and carbohydrate intake. His wife had reported him having frequent nocturnal hypoglycaemic seizures.

The patient had also been developing dementia, which had now rendered him incapable of making treatment decisions safely. He was also unable to self-administer insulin safely as he had been doing all his life. Insulin treatment was rationalised with two main objectives:

- to avoid hypoglycaemia as well as symptomatic hyperglycaemia
- to avoid precipitating diabetic ketoacidosis.

The patient was changed to a lower dose long-acting insulin in the morning and a fixed small dose of rapid-acting insulin with breakfast and lunch only. He was transferred to a dementia-specific nursing home with the aim to keep his blood glucose level between 10 and 15 mmol/L. The nursing staff were educated about the importance of not withholding long-acting insulin in this man due to the risk of diabetic ketoacidosis, while at the same time not being overly concerned with high blood glucose levels as long as he was not symptomatic.

in overweight patients. Exenatide is indicated as an adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control. It is PBS listed for dual oral combination therapy with metformin or a sulfonylurea (see the full Schedule).

The main side effects of exenatide limiting its use are nausea, vomiting and appetite suppression, therefore it is not suitable for the frail, anorexic elderly. Its use is associated with a risk of acute renal failure and there have been case reports of acute pancreatitis; therefore, exenatide is contraindicated in patients with renal failure or a history of pancreatitis. It may therefore be best avoided except in the obese elderly with diabetes.

Thiazolidinediones

Both rosiglitazone and pioglitazone are available in Australia. They work by improving insulin resistance and peripheral tissue sensitivity to insulin. They can be used in patients with renal impairment and are thus well tolerated in older adults; however, due to concerns regarding peripheral oedema, fluid retention and fracture risk in women, use can be limited in older adults with diabetes.

Rosiglitazone has been associated with increased risk of myocardial ischaemia and is contraindicated in people with ischaemic heart disease or congestive heart failure.¹⁸

Pioglitazone is contraindicated in patients with class II to IV heart failure. There has also been recent evidence to suggest a slightly increased risk of bladder cancer in a large cohort of patients treated with pioglitazone.¹⁹

Sodium glucose cotransporter 2 (SGLT2) inhibitors

Dapagliflozin, which is not yet available, but in late phase clinical trials, works by inhibiting the sodium glucose cotransporter 2. This is the major transporter responsible for renal glucose reabsorption. The glucose-lowering ability of this drug is due to the renal excretion of glucose and is dependent on the amount of glucose filtered through the glomeruli, therefore the risk of hypoglycaemia is minimal. However, by virtue of this same pharmacological action, efficacy is lost as glomerular filtration rates decline with progressive renal impairment. There is also a potential increase in risk of genitourinary infection. This makes it less likely to be an effective option for elderly patients with declining renal function.

Insulin

Insulin has a role to play in all stages of diabetes. In the healthy older adult with good glycaemic control on oral agents this may not be necessary; however, in patients who have declining glycaemic control, symptomatic hyperglycaemia or other comorbidities that limit the use of oral agents, insulin may form the mainstay of treatment. With increasing duration of diabetes there will be ongoing decline in pancreatic function, therefore insulin will be essential for many patients as the years progress. The risks and benefit of insulin are summarised in the box below.²⁰

There are many different formulations of insulin available, all of which can be useful depending on the circumstances. Glargine may be a relatively simple option for patients who have globally elevated blood glucose levels throughout a 24-hour period. The advantage of insulin is that it is given as a once-daily injection, which does not necessarily have to be followed by a main meal in close proximity, making it potentially safer for the elderly. If the problem is elevated fasting blood glucose levels then an intermediate-acting insulin,

Benefits and risks of insulin therapy in the elderly

Benefits

- Improved glucose control
- Better post-meal glucose management
- Treatment of the dawn phenomenon
- Lower risk of long-term complications by improvement in HbA_{1c} levels
- Avoidance of oral agent side effects and contraindications

Risks and drawbacks

- Possible need for multiple injections and regimen complexity
- Requires frequent daily blood glucose monitoring
- Associated with weight gain
- Increased risk of hypoglycaemia

Case 2. A fit and healthy 76-year-old man with type 2 diabetes managed with lifestyle modifications

A fit and well 76-year-old man with type 2 diabetes for the past 10 years experienced an increase in HbA_{1c} to 7.8% over the past 6 months. This increase was mainly due to reduced physical activity and a weight gain of 2 kg over the winter months. He had been taking metformin with an average HbA_{1c} of 7%. His usual routine previously comprised a one-hour walk every day, and if he missed his walk he rode his bike. He also did Tai Chi weekly. Addition of another hypoglycaemic agent to improve glycaemic control was discussed; however, he was motivated to resume his more active lifestyle to help his glycaemic control. Regular review with the dietician and diabetes nurse educator to facilitate ongoing beneficial adjustments to his lifestyle was arranged.

The patient had no microvascular complications of diabetes; however, he did have a history of stable ischaemic heart disease. The general glycaemic target of 7% is important to continue to prevent development of microvascular complications and keep his macrovascular disease under control. With supported resumption of his exercise and minor dietary modifications, he was able to reduce his HbA_{1c} back to 6.9% over the next three months. In addition, he had further reduction in his cholesterol profile and blood pressure with these lifestyle interventions.

neutral protamine Hagedorn (NPH), taken before bed may be more suitable. Basal bolus insulin also has a role to play in the elderly with diabetes and may be well tolerated and allow for greater flexibility and improved glycaemic control in those who can manage the complexities of such a regimen. Premixed preparations are a useful alternative in patients who can reliably remember to take their insulin with meals.

Conclusion

The care of older people with diabetes can be quite complex and challenging (as illustrated by the case scenarios in the boxes on pages 13 and 14). It is important to recognise the various functional, medical and social issues that this particular population face and to use the expertise of multiple disciplines to deliver a safe and effective management plan, while at the same time being as simple to follow as possible. This requires ongoing evaluation and assessment of patients and of the benefits and risks of recommended treatment. **ET**

References

A list of references is available on request to the editorial office.

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