REVIEW

International Journal of Clinical Practice

Antihyperglycaemic therapy in elderly patients with type 2 diabetes: potential role of incretin mimetics and DPP-4 inhibitors

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SUMMARY

Management of elderly patients with type II diabetes is complicated by age-related changes in physiology, comorbidities, polypharmacy and heterogeneity of functional status. A minimum goal in antidiabetic treatment in this population is to achieve a level of glycaemic control that avoids acute complications of diabetes, adverse effects and reduction in quality of life. Hypoglycaemia is a particular problem in elderly patients, and many antidiabetic agents pose increased risk for hypoglycaemia. In addition, many standard agents pose risks for older patients because of reduced renal function and common comorbidities. Newer agents based on enhancing incretin activity, including the glucagon-like peptide-1 mimetics exenatide and liraglutide and the oral dipeptidyl peptidase-4 inhibitors sitagliptin and vildagliptin, may offer particular advantages in elderly patients with diabetes.

Review criteria

Information for this review was based on MEDLINE literature searches (1970–2006) and abstracts from major diabetes meetings.

Message for the clinician

Optimal strategies for achieving glycaemic control in elderly patients with diabetes must consider the clinical status of the patient. Antidiabetic agents can pose an increased risk of hypoglycaemia in the elderly. Incretin-based therapies are associated with improved glucose-dependent insulin secretion and therefore offer an advantage over other standard medications.

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Disclosure

Development of this review article was supported by an unrestricted educational grant from Novartis Pharma AG.
C.M. is a consultant for Novartis Pharma AG.
K.B. declares no conflicts of interests.

Introduction

The 1999–2002 National Health and Nutrition Examination Survey (NHANES) in the United States reported that more than 20% of adults aged 65 years or older have diabetes (1). These elderly individuals often are undertreated with respect to glucose-lowering medications, and their care is complicated by the heterogeneity of their clinical and functional status. Age-related changes in physiology, diabetes-associated morbidities and other comorbidities, and polypharmacy make standard oral antihyperglycaemic therapy and insulin use problematic in many cases. Avoidance of hypoglycaemia is paramount in elderly persons with diabetes, and many commonly used antidiabetic medications are associated with substantial risk for hypoglycaemia. The new classes of antidiabetic therapies based on enhancing the activity of incretin hormones – glucagon-like peptide-1 (GLP-1) mimetics or receptor agonists such as exenatide and liraglutide and oral inhibitors of dipeptidyl peptidase-4 (DPP-4) such as sitagliptin and vildagliptin – have a number of characteristics that may make them particularly suitable for use in elderly patients. This review discusses the pathophysiology of diabetes and challenges that uniquely confront the elderly and considers the role of current and future therapies for this population.

Pathophysiology of diabetes in the elderly

Ageing is associated with alterations in insulin secretion, insulin action and hepatic glucose production (2–5), and elderly patients are likely to have comorbidities and to be receiving medications that can also alter glucose metabolism. Moreover, the evolution of type II diabetes with age and the data on pathophysiology of elderly-onset diabetes lead to differences in presentation of the disease in elderly individuals compared with middle-aged individuals (5–7). Whereas disease of earlier onset typically involves resistance to insulin-mediated glucose disposal, impaired glucose-dependent insulin production, and increased fasting hepatic glucose production, elderly patients may not exhibit an increase in fasting hepatic glucose. Obese elderly patients still have a greater deficit in insulin-mediated glucose disposal, but in most elderly patients, especially the leaner patients, a deficit in glucose-dependent insulin secretion because of failing β-cell function is prominent. Typically, elderly patients will require β-cell-stimulating drugs and very often insulin to reach acceptable glucose levels. The age-related reduction in counter-regulatory responses to decreased glucose levels is part of

the increased risk of hypoglycaemia in the elderly (8,9).

Burden of disease in the elderly

The recently reported NHANES data indicate prevalence rates of 15.3% for diagnosed diabetes and 6.9% for undiagnosed diabetes among individuals 65 years or older (1). As shown in Table 1, elderly individuals with diabetes have much higher rates of vascular disease than do their counterparts without diabetes. Those with middle age-onset diabetes have a similar prevalence of macrovascular disease but higher rates of microvascular disease and worse glycaemic control when compared with individuals with elderly-onset disease. Use of glucose-lowering medications was less common in those with elderly-onset diabetes.

Other studies have demonstrated that elderly patients with diabetes are at increased risk for microvascular and macrovascular complications and heart failure compared with age-matched controls (3,10,11). Cardiovascular disease is also more common in elderly patients with diabetes than in younger patients (12–14), as are diabetes-related end-stage renal disease, retinopathy and visual impairment, and lower-extremity amputation (12,13,15). Elderly patients with diabetes also have higher frequencies of depression, decreased neuropsychologic function and vascular dementia (16,17). These individuals may exhibit such syndromes as diabetic amyotrophy and diabetic neuropathic cachexia, as well as accidental hypothermia (3). Elderly patients with diabetes are at increased risk of hypoglycaemia because of impaired counter-regulatory responses, comorbidities and polypharmacy, with the risk of severe or fatal hypoglycaemia associated with oral antihyperglycaemic agents or insulin increasing exponentially with age (3,18,19). Older patients with diabetes have poorer quality of life and increased hospital days and use of outpatient services compared with their counterparts without diabetes (20).

Reducing burden of disease in the elderly

Management of elderly patients with diabetes requires efforts at both improving glycaemic control and reducing other risk factors. Goals depend on the physical and functional status of patients and their life expectancy. A number of studies have indicated that risk factor reduction through treatment of hypertension (21–23) and dyslipidaemia (24,25) decreases poor outcomes in older patients with diabetes. For example, the Heart Outcomes Prevention Evaluation trial in patients older than 55 years (23) showed large reductions in risk for myocardial infarction (22%), stroke (33%), cardiovascular death (37%) and overt nephropathy (24%) with ramipril treatment. Both European and American recommendations include aspirin use in elderly patients with diabetes in whom it is not contraindicated. European guidelines (26) indicate that blood pressure should be reduced to <140/80 mmHg in relatively healthy patients (e.g. no other major comorbidities) and to <150/<90 mmHg in the frail elderly. Abnormal lipid levels that may require intervention consist of total cholesterol ≥5 mmol/l, LDL cholesterol ≥3 mmol/l and triglycerides ≥2.3 mmol/l. American guidelines for elderly patients (27) indicate a blood pressure target of <140/80 mmHg (with potential additional benefit by reduction to <130/80 mmHg) and lipid targets of LDL cholesterol <100 mg/dl, HDL cholesterol >40 mg/dl and triglycerides <150 mg/dl.

There are few data specifically on the benefits of long-term tight glycaemic control in reducing vascular complications in elderly patients. However, a sizeable proportion of patients in the United Kingdom Prospective Diabetes Study (UKPDS) (28) were older than 65 years by the end of the study, and it is generally accepted that the benefits of tight glycaemic control observed in this study may be extrapolated to the elderly population. Several studies have indicated, however, that poor glycaemic control is associated with poor outcome in elderly patients. The Verona Diabetes Study in patients aged 75 years or older (29) showed that the coefficient of variation of the fasting glucose level is an independent predictor of mortality. A study in patients with an average age of 66 years who had newly diagnosed diabetes (30) showed that average fasting blood glucose level above 7.8 mmol/l is associated with a 50% greater mortality than an average level below 7.8 mmol/l. Another study in patients with an average age of 68.9 years with or without diabetes (31) showed significant relationship of stroke risk with fasting and postprandial glucose, A1C, and duration of illness in patients with diabetes. Cardiovascular mortality and non-fatal cardiovascular problems were significantly increased in those with A1C >7% compared with lower A1C. It is recognised that improved glycaemic control results in improved affective and cognitive function in elderly patients (16,32), which may also improve ability to manage their illness.

Antidiabetic treatment in the elderly should, at the very least, focus on efforts to achieve glycaemic control that avoids acute complications of diabetes, including symptomatic hyperglycaemia and hypoglycaemia, and that do not put patients at risk for serious adverse effects or diminish quality of life. Older patients often lack the typical symptoms of hyperglycaemia; they do not develop glucosuria until there are marked elevations in blood glucose and frequently do not experience polydipsia because of

Table 1 Characteristics of middle-aged and elderly adults with and without diabetes, NHANES 1999–2002

	Middle aged, 40–64 years		Elderly, ≥65 years		
	No diabetes	Diabetes	No diabetes	Middle age-onset diabetes	Elderly-onset diabetes
n	3391	374	2344	272	193
Mean fasting glucose (mg/dl)	99.8	148.9	105.4	172.4	132.3*
Mean A1C (%)	5.4	7.7	5.6	7.4	6.9*
A1C >7% (%)	1.4	55.3	2.1	59.9	41.6*
A1C >8% (%)	<1	36.7	<1	27.9	20.2
Mean age at diagnosis (years)†		46.7		53.2	71.8*
Years since diagnosis (%)†					
>10		25.4		76.7	10.9*
5–10		26.9		17.6	24.1
<5		47.7		5.7	65.0*
Glucose-lowering medication (%)†					
No medication	100	18.9	100	9.0	22.5
Insulin		9.4		31.7	6.9*
Oral medication		61.4		45.6	67.5
Both insulin and oral		10.2		13.7	3.2*
Conditions (%)					
Cardiovascular disease	5.6	13.9	19.6	36.1	34.7
Stroke	1.7	5.0	7.8	14.0	11.4
Coronary heart disease	4.3	10.4	14.0	30.1	28.2
Peripheral arterial disease	2.4	6.0	12.0	22.4	18.4
Peripheral neuropathy	7.9	16.9	21.5	35.5	37.1
Retinopathy†	–	24.8	–	39.4	12.6*

*$p < 0.05$ for comparison of middle age-onset vs. elderly-onset diabetes. †Question asked only for individuals with diagnosed diabetes. Adapted from Ref. (1).

impaired thirst mechanisms (3,5). Older patients with poor glycaemic control are more likely to have such acute complications as hyperglycaemic hyperosmolar coma. Hypoglycaemia is probably the major safety concern in pharmacologic treatment of diabetes in elderly patients. Many of the classes of antihyperglycaemic medications have hypoglycaemia as a prominent adverse effect, and elderly patients have reduced awareness of the autonomic symptoms of impending hypoglycaemia (5,33). Risk factors for hypoglycaemia in elderly patients with diabetes are shown in Table 2 (33). In the attempt to balance the potential benefits of tight glycaemic control against the risk of adverse effects in elderly patients, both European and American authorities suggest basing glycaemic targets on functional and physical status and life-expectancy (26,27,34). Thus, for example, European guidelines suggest a target A1C of <6.5% to 7.5% in relatively healthy elderly patients and a target of >7.5% to ≤8.5% in the frail elderly (26). The American Diabetes Association (ADA) notes that elderly patients with life-expectancy long enough to derive benefits from glycaemic control (~10 years) and who are active, cognitively intact, and able to undertake self-management should have the same target of <7.0% as younger patients (34); the guidelines promoted by the American Geriatrics Society (27) and supported by the ADA include a recommendation of <7.0% in relatively healthy/functional patients and a less stringent goal (e.g. ≤8.0%) in the

Table 2 Risk factors for hypoglycaemia in elderly patients with type II diabetes

Advanced age
Polypharmacy
Use of sulfonylurea or insulin
Poor nutrition or fasting
Intercurrent illness
Chronic liver, renal or cardiovascular disease
Prolonged physical exercise
Alcohol ingestion
Endocrine deficiency (thyroid, adrenal, pituitary)
Loss of normal counter-regulation
Hypoglycaemic unawareness

From Ref. (33).

frail elderly, those with life expectancy below 5 years, and those in whom the risks associated with attempting to achieve tight control outweigh the potential benefits.

Antihyperglycaemic medications

Any antihyperglycaemic medication that can be used in younger patients can also be used in older patients. However, many of these medications have adverse effects that are of particular concern in the elderly, and elderly patients have age-related decreases in renal function, higher frequency of polypharmacy and higher rates of comorbidity, including diabetes-related conditions, that increase their risk for adverse effects. As noted, hypoglycaemia is a primary concern in the elderly population, because it can have such a profound impact on patient health, function and quality of life. Avoiding hypoglycaemia can significantly improve quality of life and patient compliance with antidiabetic treatment.

Sulfonylureas (SUs) pose considerable risk for hypoglycaemia in elderly patients (18,27,33,35–37). In addition to age, risk factors for SU-related hypoglycaemia include disability, poor nutrition and polypharmacy. SUs with longer time-action characteristics are associated with greater risk; it is recommended that chlorpropamide not be used in elderly patients (27), and gliclazide (including its extended-release form), glipizide and glimepiride are associated with less risk than glyburide (glibenclamide) (33). It should be noted that many drugs may potentiate the activity of SUs and/or contribute to risk of hypoglycaemia via displacement of SUs from plasma proteins, reducing hepatic metabolism of SUs, decreasing SU urinary excretion, or exhibiting intrinsic hypoglycaemic activity that is additive to the effects of SUs (33). The rapid-acting secretagogues repaglinide and nateglinide do pose risk for hypoglycaemia, but this risk appears to be less than that associated with SUs (35–39). These agents may pose particular benefits for elderly patients because they target postprandial hyperglycaemia, which may possibly be a better predictor of risk for diabetic complications than fasting glucose in elderly patients (5,39). Insulin is associated with increased risk of hypoglycaemia in elderly patients (Table 3) (33), and its use in this population is complicated by the need for good visual/motor skills and cognitive function for appropriate administration (19,33). The most common causes of hypoglycaemia associated with insulin use appear to be excessive dosing and use of improper insulin combinations. Missing of meals and failure to adjust insulin for physical exercise also contribute to risk of hypoglycaemia. Insulin is also associated with substantial weight gain.

Table 3 Risk factors for insulin-induced hypoglycaemia in elderly patients with diabetes

Insulin administration errors
Excessive dose
Improper timing relative to food intake
Wrong insulin type
Decreased glucose influx
Missed meals
Fasting
Gastroparesis with delayed carbohydrate absorption
Increased insulin sensitivity
Weight loss
Intensive insulin therapy
Increased exercise
Delayed insulin clearance, erratic absorption
Renal failure
Insulin injection in hypertrophic sites
Decreased endogenous glucose production
Severe liver disease
Defective glucagon or epinephrine counter-regulation
Alcohol ingestion

From Ref. (33).

Metformin, thiazolidinediones (TZDs) and the α-glucosidase inhibitors pose little risk for hypoglycaemia when used as monotherapy. Metformin is currently recommended as first-line therapy along with lifestyle interventions in all patients with type II diabetes (38). In addition to minimal risk of hypoglycaemia, metformin is also associated with weight neutrality or a small reduction in body weight, which is advantageous in obese elderly patients. However, care should be taken when using metformin in the frail elderly patient and metformin should preferentially be avoided in older patients with elevated serum creatinine levels (≥1.5 mg/dl in men, 1.4 mg/dl in women) or reduced creatinine clearance (indicative of reduced renal function), because the risk of lactic acidosis is increased in these patients (27,35,36). Metformin is especially contraindicated in patients with heart failure and in patients with other conditions that are associated with increased risk of lactic acidosis. However, the stringent contraindication formulated for metformin, based solely on age, should be dropped (37). Whenever possible, patients should be given an opportunity to use metformin. Older patients receiving metformin should have regular monitoring of renal function and whenever there is a dosage change. In addition, metformin is associated with a high frequency of gastrointestinal (GI) adverse effects that may be poorly tolerated by older patients. Although there is also minimal risk of hypoglycaemia with TZDs, these agents are

associated with substantial weight gain and oedema, with the oedema frequently causing or exacerbating heart failure (35–38,41,42). TZDs are contraindicated in patients with evidence of heart failure, and the use of these agents in combination with insulin was even until recently contraindicated in Europe exactly because of the risk of heart failure. TZDs are also contraindicated in patients with active hepatic disease. Increased plasma volume may require monitoring of haemoglobin or haematocrit. Although the agents can be used in patients with mild or moderate renal impairment, vigilance should be maintained for the possibility of oedema. The α-glucosidase inhibitors (e.g. acarbose) lower postprandial glucose levels while posing little risk for hypoglycaemia (5,35,36). However, these agents have to be taken three times daily before meals containing digestible carbohydrates, and they are associated with a high frequency of GI adverse effects that many patients cannot tolerate. In addition, patients experiencing hypoglycaemia while receiving these agents in combination with other antihyperglycaemic agents must ingest glucose rather than complex carbohydrates.

Injectable GLP-1 mimetics and oral DPP-4 inhibitors

Effects of the incretin GLP-1 include regulation of glucose-dependent insulin secretion and glucose-dependent glucagon release, inhibition of gastric emptying and appetite suppression, with preclinical studies also showing an effect in expansion of islet β-cell mass (43–46). The oral DPP-4 inhibitors selectively inhibit the DPP-4 enzyme responsible for rapidly degrading the incretin hormones GLP-1 and gastric inhibitory polypeptide, with most of the pharmacologic effects of these agents being attributed to the ability to increase levels of biologically active intact GLP-1 (46–48), whereas the larger-molecule injectable GLP-1 mimetics act as GLP-1 receptor agonists. These agents regulate glucose homeostasis by improving glucose sensitivity of α and β cells, promoting glucose-dependent insulin secretion and suppressing inappropriate glucagon secretion and thus hepatic glucose production. Initial studies of exogenously administered GLP-1 infusions showed that the glucose-dependent nature of the GLP-1 insulinotropic effect resulted in little risk of hypoglycaemia compared with SU treatment in elderly patients (49) and that the glucose-dependent effect on glucagon preserved the counter-regulatory response to hypoglycaemic levels of glucose (50). Perhaps because of the more modest stabilisation of postprandial GLP-1 levels, the oral DPP-4 inhibitors do not promote slowing of gastric emptying and weight loss associated with the GLP-1 mimetics; as a result, the oral agents, which have weight-neutral effects, are also associated with a lower frequency of GI adverse effects.

The GLP-1 mimetic exenatide is approved for use in the United States as a twice-daily subcutaneous injection for add-on treatment to SU and/or metformin. It reduced A1C by about 1% and resulted in significant weight loss (0.9–2.5 kg) in 6-month studies as add-on treatment (51–53), with maintained reduction in A1C and continued weight loss observed in overweight patients over 82 weeks (54). Effects on hyperglycaemia include sizeable reductions in both fasting and postprandial glucose levels (55). Rates of hypoglycaemia were similar in the two groups, with overnight hypoglycaemia being less common with exenatide and daytime hypoglycaemia being less common with insulin glargine. Severe hypoglycaemia has been rare with exenatide alone; however, there are dose-related increases in frequency of hypoglycaemia in combination with SU, metformin or SU plus metformin (Table 4), with dose adjustments being recommended for SU in combined therapy (55). Exenatide is associated with a relatively high frequency of GI adverse events (Table 5). A once-weekly formulation of exenatide has been studied as add-on to SU and/or metformin in a small group of patients, with promising results; sizeable reductions in A1C were observed at both tested doses, with no severe hypoglycaemia reported

Table 4 Incidence of hypoglycaemia with exenatide plus metformin and/or sulfonylurea (SU) in three 30-week trials

	Exenatide + metformin			Exenatide + SU			Exenatide + metformin/SU		
	Placebo	Exenatide 5 μg b.i.d.	Exenatide 10 μg b.i.d.	Placebo	Exenatide 5 μg b.i.d.	Exenatide 10 μg b.i.d.	Placebo	Exenatide 5 μg b.i.d.	Exenatide 10 μg b.i.d.
n	113	110	113	123	125	129	247	245	241
Hypoglycaemia (%)	5.3	4.5	5.3	3.3	14.4	35.7	12.6	19.2	27.8

From Ref. (55).

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