Challenges in the Management of Type 2 Diabetes in the Elderly

a report by

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It is estimated that diabetes currently affects 195 million people worldwide. This figure is expected to rise to over 330 million by 2030.[1,2] The overwhelming scale of the problem will present significant challenges to healthcare systems and clinical practices. Furthermore, the population in general is ageing. Both the prevalence and the incidence of type 2 diabetes increase with increasing age, consequently leading to a large rise in the number of elderly with diabetes: approximately 15% of people over the age of 60 years in the US are affected by diabetes, and it is estimated that half of all type 2 diabetes cases occur in those over 65 years of age.[3] In Europe, data from the Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe (DECODE) study suggests that the prevalence of diabetes is 10–20% in those aged between 60 and 69 years, rising to 15–20% in the oldest age groups.[4]

Management of diabetes in the elderly has unique challenges. With increasing age, there is an increased prevalence of co-morbid illnesses and functional disability that will contribute to the complexity of managing diabetes in the elderly cohort. Thus, treatment must take into consideration not only the standard micro- and macrovascular complications associated with both ageing and diabetes, but also conditions such as cognitive impairment and impaired function. Importantly, elderly diabetic patients have an increased risk of cardiovascular disease.[5]

Diagnosis of diabetes in the elderly also presents challenges, and it is estimated that half of the diabetic elderly population are not diagnosed correctly with the condition. This is due to many factors, including the observation that this cohort rarely presents with the typical symptoms of hyperglycaemia,[6,7] the renal threshold for glucose increases naturally with age, making it difficult to identify glucosuria, and fasting blood glucose measurements or oral glucose tests are not routinely performed in this population. Additionally, common symptoms such as fatigue, blurred vision and polyuria are often not recognised as abormal in this population, and polydipsia can go unnoticed because of the decreased thirst usually associated with advanced age.

The primary considerations for the treatment of elderly type 2 diabetes are the evaluation of functional status, life expectancy, social and financial support and the patient's own desire for treatment. Individual assessment should be carried out to ascertain the best course of treatment to allow avoidance of potential problems that could impair its effectiveness. Alterations in diet and exercise are the first-line treatments for the diabetic elderly. However, this is not always successful at controlling the condition, and early medical therapy often becomes necessary. Ideal management regimens for geriatric diabetic patients require a multidisciplinary approach. Co-existing medical or psychiatric disorders and the potential of antidiabetic agents contributing to the development of treatment-related complications, as well as the greater risk of hypoglycaemia in older patients,[8] are also important considerations.

Oral Antidiabetic Drugs

Oral antidiabetic drugs (OADs) remain first-line medical therapy for elderly patients with type 2 diabetes. Currently, there are five classes of OAD available, with similar efficacy but with different mechanisms of action.[9] To reduce side effects from each drug class, current practice is to begin with the lowest effective dose, with gradual titration of a single agent. In the event of monotherapy with OADs being ineffective, an additional oral agent from an alternative drug class is advised.

Biguanides

Metformin hydrochloride is a biguanide whose major action is to reduce the overproduction of hepatic glucose production and thus lower fasting glucose concentrations. The major benefits of using metformin as monotherapy in the elderly is the low risk of hypoglycaemia and the potential added benefit of increase in weight loss in obese patients. Long-term treatment with metformin has been shown to reduce the total mortality rates and macrovascular events in overweight patients with newly diagnosed type 2 diabetes.[10] The most common adverse effects from the treatment include diarrhoea and abdominal pain, which generally occur during the first few weeks of administration; therefore, the dose should be kept to a minimum on commencement of treatment. The most severe side effect of metformin is the increased risk of lactic acidosis; however, one meta-analysis has noted that this was rare under normal treatment.[11]

The risk of lactic acidosis is significantly higher in patients with renal impairment because metformin is entirely cleared through the kidney and does not undergo hepatic metabolism. Thus, it is contraindicated in people with significantly impaired renal function. Renal insufficiency is common in the elderly and limits the use of metformin in this

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population. Furthermore, metformin should not be used in haemodynamic instability, sepsis, dehydration, acute or advanced heart failure, hypoxaemia or liver failure. Even with these contraindications, metformin has been demonstrated to lower the risk of death within one year and cause fewer remissions for heart failure in a retrospective study.[12] Metformin remains the drug of choice for overweight elderly type 2 diabetes patients without renal impairment.

Sulfonylureas

The principle mode of action of the sulfonylureas is to stimulate the release of insulin through the depolarisation of pancreatic beta cells. Some of the sulfonylurea compounds are not specific to pancreatic cells and theoretically may affect ischaemic pre-conditioning in the heart. However, the clinical relevance of this remains unclear.

In the elderly, there is concern with use of sulfonylurea because of the increased risk of hypoglycaemia, even with low doses of the drug. The elderly are already at a higher risk of the development of hypoglycaemia through renal impairment and poor diet, and may develop severe, prolonged hypoglycaemia when treated with sulfonylureas. Mortality from severe sulfonylurea-induced hypoglycaemia in the elderly has been estimated at 10%.[13] Moreover, drugs in this category with longer metabolic half-lives and activated metabolites, such as the first-generation sulfonylureas, should be avoided in patients with renal insufficiency. Therefore, in general, shorter-acting sulfonylureas are preferred. Another potential downside to treatment with sulfonylureas is unwanted weight gain. All sulfonylureas are metabolised hepatically and are not advised in patients with liver disease.

Thiazolidinediones

Thiazolidinediones are insulin sensitisers and improve glucose levels by increasing the sensitivity of muscles and adipose tissues to insulin.[14] Thiazolidinediones have delayed onset and it may take up to eight weeks to achieve maximal effects. They also frequently result in weight gain and fluid retention.

The American Diabetes Association (ADA) and American Heart Association (AHA) issued a consensus statement on the use of thiazolidinediones in patients with pre-existing heart failure, stating that these drugs should not be used in patients with New York Heart Association (NYHA) class III or IV heart failure.[15] A retrospective analysis of hospitalised elderly patients with heart failure suggested that treatment with thiazolidinediones slightly increased the risk of re-hospitalisation for heart failure.[12] A recent meta-analysis suggested that there may be an increased risk of myocardial infarction and death from cardiovascular causes associated with treatment with the thiazolidinedione rosiglitazone in type 2 diabetes.[16] In response to these data, the investigators of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial published interim data that suggest that rosiglitazone was associated with an increased risk of heart failure, although the data were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalisation or death from cardiovascular causes.

The RECORD study was designed as a non-inferiority trial. After a four-week run-in period, patients who were already taking a sulfonylurea were randomly assigned to receive either additional rosiglitazone or metformin; those taking metformin were assigned to receive either additional rosiglitazone or a sulfonylurea. The authors of the study noted that there is currently no evidence of any increase in death from either cardiovascular causes or all causes in the trial and that the data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction.[17]

Currently, the debate is confounded by the fact that only one large-scale cardiovascular outcome study has been completed and published for the thiazolidinediones in type 2 diabetes: the Prospective pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, which involved the thiazolidinedione pioglitazone and in itself has been a source of controversy. The PROactive study was a prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-group study in patients with type 2 diabetes who had evidence of macrovascular disease. Patients were assigned to pioglitazone titrated from 15 to 45mg or matching placebo, to be taken in addition to their glucose-lowering drugs and other medications. The primary study end-point was the occurrence of mortality (including non-cardiac mortality), non-fatal myocardial infarction, stroke, major amputation, acute coronary syndrome (ACS), percutaneous transluminal coronary intervention (PTCI), coronary artery bypass graft (CABG) or leg revascularisation. Data from the study showed that pioglitazone reduced the composite of all-cause mortality, fatal and non-fatal myocardial infarction, stroke and the risk of recurrent stroke in patients with type 2 diabetes who had a high risk of macrovascular events.[18–20]

However, the study also reported that the incidence of serious heart failure was increased with pioglitazone versus placebo in the total PROactive population of patients with type 2 diabetes and macrovascular disease, although subsequent mortality or morbidity was not increased in patients with serious heart failure.[21] There has also been criticism of the statistical validity of the additional secondary end-point of all-cause mortality, non-fatal myocardial infarction (excluding silent myocardial infarction) and stroke. The clinical use of thiazolidinediones is also restricted in the elderly due to adverse effects such as weight gain and fluid retention.[22]

Newer Antidiabetic Agents

The pathogenesis of type 2 diabetes is characterised by a combination of factors that eventually lead to the loss of glycaemic control. These factors include insulin resistance, impaired glucose-induced insulin secretion due to a progressive decline in beta-cell function and defective suppression of post-prandial glucagon levels with consequent increased hepatic glucose production.

GLP-1 is an incretin that is released from the intestinal tract in response to nutrient ingestion. The hormone is also regulated by neural and endocrine factors.[23] Once released, GLP-1 potentiates glucose-stimulated insulin secretion from beta cells[24] and reduces glucagon secretion. At high concentrations, GLP-1 also acts to inhibit gastric emptying and to suppress food intake in both diabetic and non-diabetic humans.[25–28] GLP-1 does not cause hypoglycaemia because little or no insulin is secreted at a glucose level of less than 4mmol per litre.[29] Peripherally administered GLP-1 has a satiating effect, and when administered continuously through subcutaneous infusion over a period of six weeks results in significant weight loss.[30,31]

In type 2 diabetes, the incretin effect is significantly impaired or even absent.[32]

GLP-1's physiological properties incorporate characteristics of a promising antidiabetic agent, but endogenous GLP-1 has an extremely short half-life (approximately 90 seconds) due to both rapid inactivation by dipeptidyl peptidase (DPP)-4 and renal clearance. This has led to the development of alternative approaches to harness the potential of GLP-1 activation. One alternative has been the development of new agents that mimic the actions of GLP-1, while at the same time being DPP-4-resistant. Another approach is to extend the actions of endogenous GLP-1 by inhibiting the enzymatic activity of DPP-4, thereby preventing the rapid inactivation of endogenous GLP-1 and prolonging its physiological effects.

Incretin Mimetics

Exenatide was the first incretin 'mimetic' approved for type 2 diabetes. Exenatide acts by activating the GLP-1 receptor and lowers glucose concentration by enhancing insulin secretion by beta cells in a glucose-dependent fashion. In the US it is indicated as adjunctive therapy to improve glycaemic control in patients who have not achieved adequate glycaemic control with other OADs either as monotherapy or as combination therapy. In Europe it is approved for use in combination with metformin and/or sulfonylureas in type 2 patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. It is administered by injection twice daily.

In clinical trials, combination therapy with exenatide reduces glycated haemaglobin (HbA_{1c}) levels by ~1.0% from baseline (8.4%), with 44% reaching ≤7%. it also results in modest weight loss, and both weight loss and glycaemic improvements are sustained.[33]

As previously mentioned, the elderly population is at a greater risk of hypoglycaemia; therefore, incretin mimetics may provide a safe therapeutic option for type 2 diabetes patients in this population, as this class of drug does not cause hypoglycaemia when used with other drugs that do not increase circulating insulin levels. However, clinical experience in the elderly cohort is limited.

Dipeptidyl Peptidase-4 Inhibitors

The two predominant incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. Studies have shown that in people without diabetes, up to 70% of the insulin response to oral glucose is due to these incretin hormones, with GLP-1 and GIP contributing almost equally to the incretin effect.[34] In subjects with type 2 diabetes, the incretin effect is severely impaired or absent.[35] DPP-4 is a widely distributed serine protease that plays a significant role in the metabolism of GLP-1. This knowledge has led to the development of oral DPP-4 inhibitors that increase endogenous GLP-1 levels. Thus, orally administered DPP-4 inhibitors can increase circulating levels of endogenous GLP-1 and GIP, and have been shown to improve glucose homeostasis in patients with type 2 diabetes.[36,37]

Sitagliptin was the first oral DPP-4 inhibitor to be approved in Europe, and it is currently indicated in patients with type 2 diabetes to improve glycaemic control in combination with metformin when diet and exercise plus metformin do not provide adequate glycaemic control. It is also indicated for patients with type 2 diabetes in combination with thiazolidinediones when diet and exercise plus the thiazolidinediones alone do not provide adequate glycaemic control. In the US, sitagliptin has been approved for use as a monotherapy or in combination with metformin or thiazolidinediones.

Sitagliptin has been evaluated as an add-on to ongoing metformin therapy in patients with type 2 diabetes (baseline HbA_{1c} of 8.0%). After 24 weeks of treatment with sitagliptin 100mg, active treatment demonstrated a placebo-subtracted reduction of HbA_{1c} from a baseline of 0.65%.[38] Data from another study using sitagliptin or glipizide as add-on therapy to existing metformin therapy in type 2 diabetes patients (baseline HbA_{1c} of 7.5%) found that similar levels of glycaemic control were obtained in the two groups. Sitagliptin therapy resulted in significantly fewer hypoglycaemic episodes compared with glipizide treatment.[32] Similarly, addition of sitagliptin to metformin or pioglitazone therapy did not increase the incidence of hypoglycaemia.[39,40] Overall, sitgliptin has been shown to be weight-neutral.

The safety and pharmocokinetics of sitagliptin were tested in 10 healthy elderly (aged 65–80 years) males, and no significant difference was noted in the creatinine clearance taken from the elderly subjects compared with younger healthy participants.[41] Therefore, dose adjustments for the elderly with mild renal insufficiency appear not to be required. However, the older population is more at risk of kidney problems, and data for patients with moderate or severe renal insufficiency are limited. In phase II and III clinical trials of sitagliptin, 725 patients were aged ≥65 years and 61 patients were aged ≥75 years.[42,43] In these patients, no overall difference was noted in the safety or efficacy of the drug compared with younger patients.

Vildagliptin is a DPP-4 inhibitor with a low protein binding administered as 50mg once or twice daily. The drug and its fixed-dose formulation in combination with metformin (Eucreas®) is the most recent addition to the OAD armamentarium in Europe, and was recently approved for the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or with sulfonylureas or thiazolidinediones. Pooled data from two 24-week, placebo-controlled monotherapy trials in drug-naïve patients, one study of vildagliptin (100mg daily) added to metformin and one study of initial combination therapy with pioglitazone found that the target HbA_{1c} of <7.0% was achieved by 40% of patients receiving vildagliptin 100mg daily versus 20% of patients receiving placebo. The proportion of patients reaching goal is dependent on the baseline HbA_{1c}; indeed, in patients with baseline HbA_{1c} ≤8%, more than half of those receiving vildagliptin reached target goals.[44] Overall, vildagliptin has been shown to be weight-neutral.

Interestingly, recent data presented at the 43rd European Association for the Study of Diabetes (EASD) conference suggest that vildagliptin is both safe and effective in the elderly cohort. Data pooled from phase III vildagliptin trials, including monotherapy arms (100mg daily; 50mg bid or 100mg qd) of two placebo-controlled trials and three active-controlled trials, were analysed. From the trials, 283 type 2 diabetes patients with a mean age of 70 years were treated with vildagliptin. This group showed a greater reduction in HbA_{1c} (baseline 8.3%, -1.2%) compared with the younger subgroup (mean age 50 years) treated with

vildagliptin (baseline 8.7%, -1.0%).[45] Vildagliptin was well tolerated in the older patients, with a low risk of hypoglycaemia. Vildagliptin has also been shown to be safe in 1,864 patients with mild kidney impairment, a common condition in elderly patients with type 2 diabetes.[46] Ongoing trials are continuing to examine the relevance of vildagliptin in the treatment of elderly type 2 diabetics.

Conclusion

Treating type 2 diabetes in elderly patients presents unique challenges. In all people with type 2 diabetes, many patients still remain inadequately treated because existing therapies have a number of shortcomings, including safety and tolerability issues. These issues are even more profound in the elderly cohort. The ideal management regimens for geriatric diabetic patients require a multidisciplinary approach that must take into account co-existing medical or psychiatric disorders and the potential for treatment-related complications, as well as the greater risk of hypoglycaemia in older patients. Moreover, the ideal HbA_{1c} target of <7% may be difficult to achieve in the elderly, and research is lacking regarding the benefits of tight control in those above 80 years of age. The introduction of newer agents to the OAD armamentarium, in particular DPP-4 inhibitors, represents a significant advance in the treatment of the overall type 2 diabetes population. The lower risk of hypoglycaemia and weight neutrality associated with DPP-4 inhibitors supports the considerable early evidence that DPP-4 inhibitors may prove to be useful for the treatment of type 2 diabetes in the elderly. ■

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