Treatment of Hyperglycemia in the Elderly

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This article presents a summary of recent recommendations for the diagnosis and treatment of Type 2 diabetes in the elderly. Onset of nephropathy, neuropathy and retinopathy can be slowed by treatment designed to reach realistic target values for fasting plasma glucose and HbA1c. Therapy also should minimize the dangers of hypoglycemia. Hepatic and renal function must be monitored when selecting drugs and dosages. Significant reductions in renal function may be associated with serum creatinine within the normal reference range. A stepwise approach to therapy beginning with diet and exercise and proceeding to single and multidrug treatment is outlined. The mode of action, advantages, disadvantages and contraindications for five groups of hypoglycemic agents are summarized.

Key words: Type 2 diabetes, diagnosis, stepped treatment, oral drugs, elderly.

Introduction

Type 2 diabetes arises from increased resistance to insulin's metabolic effects and inadequate insulin secretion by pancreatic beta cells. Insulin resistance is part of Metabolic Syndrome X.[1] In a recent population study, this condition was defined as three or more of the following abnormalities:

- waist circumference greater than 102cm in men and 88cm in women;
- serum triglycerides of at least 1.69mmol/L;
- high-density lipoprotein (HDL) cholesterol less than 1.04mmol/L in men and 1.29mmol/L in women;
- blood pressure of at least 130/85 mmHg or;
- serum glucose of at least 6.1mmol/L.

More than 40% of U.S. citizens over age 60 fit this description and are at risk for Type 2 diabetes.

For some diabetics, insulin resistance is the primary defect; for others, defective insulin secretion predominates. Over time the nature of the imbalance alters, so that what began as insulin resistance becomes predominantly a defect in insulin secretion.

Initially, glycemic control may be achieved by diet and exercise (see article, page 27), but as insulin resistance and relative insulin deficiency progress, oral hypoglycemic drugs are required and eventually insulin also may be needed. Glycemic control deteriorates with age and duration of Type 2 diabetes up to age 80. However, this inexorable process slows for octagenarians with long-standing Type 2 diabetes, who are more likely to have satisfactory glycosylated hemoglobin levels and less likely than younger individuals to experience hyperglycemia.[2] Type 1 diabetes, arising from destruction of beta cells, is less common in the elderly.

Treatment of hyperglycemia is directed at lowering glucose production or increasing insulin secretion to prevent acute and long-term effects of diabetes. Infectious or other disease processes may precipitate acute hyperglycemic hyperosmolar states or ketoacidosis. Clearly, treatment must be directed at preventing these relatively rare, potentially serious, episodes. Effective treatment may reduce the incidence of urinary tract infections, improve wound healing and combat decreased cognitive function.

Over the long term, hyperglycemia causes microvascular disease that damages the kidney, retina and peripheral and autonomic nervous systems. The relationship between hyperglycemia and microvascular disease is linear. Tight glycemic control slows the onset of nephropathy, neuropathy and retinopathy.[3] A 0.01 (1%) increase or decrease in HbA1c—a measure of blood glucose—is paralleled by a 30% increase or decrease in microangiopathic events.

The relationship between hyperglycemia and macrovascular disease is less clear. Intensive glycemic control may reduce the risk of macrovascular disease[4] by controlling other risk factors such as hypercholesterolemia, low HDL cholesterol, hypertriglyceridemia and/or insulin resistance, all of which are part of Metabolic Syndrome X. The etiology of hypertension, hypercoagulation, vasculopathy and atherosclerotic cardiovascular disease in this syndrome is probably multifactorial.

Although tight glycemic control is very imporant, lowering glucose production or increasing insulin secretion carries the risk of nocturnal hypoglycemia—and that risk increases exponentially with age. Multiple comorbidities and dementia may complicate treatment of elderly diabetic patients, so that therapy recommended for younger diabetics may not be feasible in the elderly.[5] Compliance is enhanced by keeping treatment regimens as simple as possible; monotherapy with single daily doses improves compliance.

Monitoring Response to Treatment

Fasting plasma glucose (FPG) is the most convenient and reliable measurement for defining, monitoring and controlling the diabetic state. Glycated hemoglobin, which reflects the average plasma glucose over many days, is useful for following the disease, but both expense and lack of standardization among laboratories limit its use for the diagnosis of diabetes. Population studies have shown that when FPG exceeds 7mmol/L, the risks of microvascular disease outweigh the hazards of treatment.[6] This level correlates with a two-hour postprandial glucose of

11.1mmol/L (two hours after a 75g glucose load). Impaired FPG (6.1–7 mmol/L) or impaired glucose tolerance (two-hour post-glucose load 7.8–11.0) imparts an increased risk of developing cardiovascular disease and diabetes.[6] Currently, the Canadian and U.S. consensus is that glucose tolerance tests are not necessary for the diagnosis of diabetes.[3,6] Self-monitored blood glucose testing may help to improve glycemic control in diabetics taking oral hypoglycemics, but there are no data to support this concept.

Monitoring renal and hepatic function is essential because they will influence the choice of therapy. Currently, The Compendium of Pharmaceuticals and Specialties recommends avoiding the antihyperglycemic drug metformin if serum creatinine is greater than 136µmol/L in men or 124µmol/L in women. Unfortunately, serum creatinine is not a reliable index of glomerular function in the elderly because creatinine production falls as muscle mass declines with age. A large proportion of the population older than 60 years has a low glomerular filtration rate (30–80mL/min) despite serum creatinine being within the normal reference range.[7] Unfortunately, creatinine clearance estimated with formulas such as the Cockcroft-Gault formula can be misleading; therefore, it is prudent to assume that glomerular filtration rate is low when choosing the initial drug dosage. If in doubt, a creatinine clearance may be measured but requires collection of an accurately timed urine

Figure 1: Mechanisms of Action of Hypoglycemic Agents

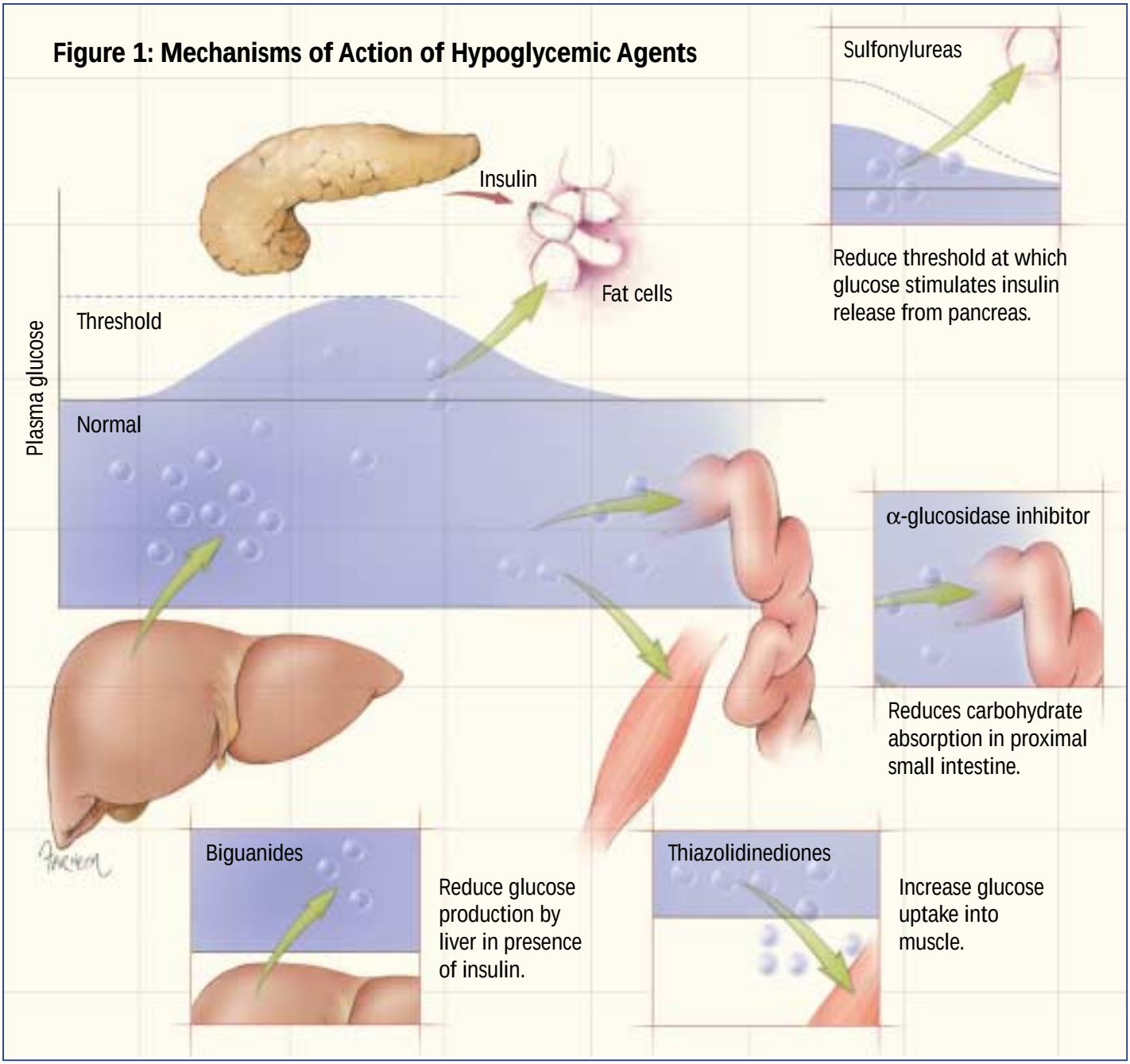

Table 1

Properties of Hypoglycemic Agents

Insulin Sensitizers		Insulin Secretogogues		α-Glucosidase Inhibitor
Biguanides *metformin*	Thiazolidinediones *pioglitazone* *rosiglitazone*	Non-sulfonylureas *repaglinide* *nateglinide*	New Sulfonylureas *glyburide* *gliclazide* *glimepiride*	*acarbose*
Mode of Action				
Decrease glucose production by the liver in the presence of insulin	Increase glucose uptake by muscle cells	Increase pancreatic insulin secretion	Increase insulin release at lower levels of glucose	Decrease carbohydrate absorption in the proximal small intestine
Advantages				
– First choice for obese with good kidney function – Decrease microvascular risk – Weight loss – No hypoglycemia – Decrease lipids – Increase fibrinolysis – Decrease hyperinsulinemia	– No hypoglycemia – Improve lipid levels – Increase fibrinolysis – Decrease hyperinsulinemia – Improve endothelial function – May preserve beta-cell function – Convenient dosing	– Reduce postprandial glycemia when taken with meals – Possibly less hypoglycemia and weight gain than with sulfonylureas	– Well established – Decrease microvascular risk – Convenient dosing – Least expensive	– Reduces postprandial glycemia (taken with meals) – No hypoglycemia – Small reduction in triglycerides and postprandial insulin levels – Nonsystemic
Disadvantages				
– Diarrhea, nausea, vomiting in up to 50% of subjects – Lactic acidosis (rare)	– Requires monitoring of liver function – Weight gain like sulfonylureas – Edema, especially when taken with insulin – Slow onset of action (weeks to months) – No long-term information	– Complex dosing (t.i.d. with meals) – Hypoglycemia and weight gain – Metabolized by liver and removed by kidney – No long-term information	– Hypoglycemia – Weight gain (2–5 kg) – Hyperinsulinemia – Metabolized by liver and removed by kidney	– Complex dosing (t.i.d. with meals) – Flatulence, diarrhea, abdominal discomfort – No long-term information
Contraindications				
– Decreased glomerular filtration rate – Congestive heart failure – Hepatic failure – Binge alcohol use	– Class III or IV congestive heart failure – Hepatic failure	– Use with caution in advanced renal and hepatic failure	– Use with caution in advanced renal and hepatic failure	

Adapted and modified from Informed, July 2002, Vol. 8 No. 3, page 3.

sample, which may be difficult to obtain in elderly patients.

Those with increased insulin resistance tend to have higher triglyceride concentration and blood pressure, and lower HDL cholesterol.[8] However, over age 69, lipid indices such as total cholesterol, low-density lipoprotein (LDL) cholesterol and serum apo-B do not predict the risk for coronary heart disease and ischemic stroke. Measures of renal function, such as proteinuria and serum uric acid, and of respiratory function are more significant predictors in the elderly.[9]

Urinary albumin excretion correlates with blood pressure in the elderly.[10] Biological variability of urine protein concentration is high (coefficient of variation for 24-hour urine albumin is 62%) and is not significantly improved by using an albumin / creatinine ratio. Proteinuria is a weak risk factor for all-cause mortality in older men and women: the hazards ratio is 1.3 (95% confidence ratio 1.0–1.8) for greater than trace proteinuria.[11]

Treatment

The following stepped approach to treatment is applicable when mild diabetes presents in overweight individuals. Step 1 does not apply to lean diabetics or those with signs of ketonemia or severe hyperglycemia.

Step I

Weight loss through improved dietary control and increased exercise can be effective at least initially in achieving glycemic control. However, other infirmities and disabilities can limit the effectiveness of this approach in the elderly. Success is more likely when care is provided by a team that includes educators, dietitians and social workers. Ideal FPG levels may be attainable early in the course of Type 2 diabetes, when FPG can be controlled by diet alone, but rarely once control requires drug therapy. Only 5% of the individuals in the intensive therapy group of the Diabetes Control and Complication Trial (DCCT) attained the ideal FPG.[4] Lifestyle modification should be tried for several months.

Step II

If FPG remains greater than 10mmol / L after two to three months of lifestyle modification, then a single oral hypoglycemic agent should be started. Even of those who respond to lifestyle changes, most will eventually progress to needing oral hypoglycemic control. Oral hypoglycemic drugs operate either to counteract the consequences of insulin resistance or to increase insulin secretion (secretagogues). Some drugs reduce glucose production in the liver, whereas others increase removal of glucose by muscle cells or decrease glucose absorption from the intestine (Table 1; Figure 1). The aim of treatment with any of these hypoglycemic drugs should be to maintain plasma glucose as close as possible to the target range (Table 2), while avoiding potentially lethal hypoglycemia.

For obese patients (body mass index >27 kg / m^2), metformin is the treatment of choice because it tends to reduce weight and is unlikely to precipitate nocturnal hypoglycemia. Metformin works by reducing glucose production by the liver in the presence of insulin. D-lactic acidosis, a consequence of carbohydrate malabsorption, may develop if metformin is used when there is significant renal or hepatic failure. Up to half of patients will experience gastrointestinal side effects such as diarrhea, nausea, anorexia or vomiting. These side effects are less likely to occur if the dose is increased gradually.

Insulin resistance is the predominant factor in the early stage of Type 2 diabetes; therefore, it appears logical to use drugs that increase insulin sensitivity. The thiazolidinediones (TZDs) pioglitazone and rosiglitazone increase insulin sensitivity by increasing glucose uptake into muscle. TZDs may improve lipid levels, increase fibrinolysis, reduce hyperinsulinemia, improve endothelial function and preserve beta cell function; in addition, hypoglycemia is not a problem. On the negative side, however, hepatic function needs to be monitored and TZDs tend to cause more weight gain than sulfonylureas. Edema also can be a problem, and TZDs are contraindicated in the presence of congestive heart failure. It may take weeks to months before their full benefit is seen. They are three times as expensive as metformin and sulfonylureas.

If congestive heart failure precludes the use of TZDs, then an insulin secretagogue should be used. These drugs sensitize insulin secretion to extracellular glucose by altering K+ and Ca++ flux across the beta-islet cell membranes. Taken with meals, short-acting non-sulphonylurea secretogogues, such

Table 2

Target Levels of Plasma Glucose

	Nondiabetic	Ideal: Least long-term complications	Attainable: Reduces but may not prevent complications	Greatly increased risk of complications
Plasma Glucose Fasting (mmol/L)	3.8–6.1	4–7	7.1–10	>10
Plasma Glucose Fasting 1–2 hours after meal (mmol/L)	4.4–7	5.0–11	11.1–14	>14
HbA1c	0.04–0.06	< 0.07	0.07–0.084	>0.084

Adapted from Meltzer, 1998.

as repaglinide or nateglinide, are least likely to cause hypoglycemia compared to the longer acting sulphonylureas. By targeting postprandial hyperglycemia, these drugs control HbA levels more effectively than therapy directed at lowering fasting glucose levels. However, because these drugs must be taken with meals, there may be problems with compliance, in which case a longer acting second generation sulphonylurea taken once daily is more appropriate. Sulfonylureas work by lowering the threshold at which glucose stimulates insulin release from pancreatic beta cells. With these new sulphonylureas, careful dosing is necessary to avoid hypoglycemia; gliclazide is less likely to induce hypoglycemia than other sulfonylureas. These drugs should not be used in the presence of hepatic or renal failure because they are metabolized by the liver and excreted by the kidney. Weight gain and hyperinsulinemia may occur.

Step III

As time passes, it usually becomes necessary to add a second drug to maintain an acceptable level of glycemic control. There are no rules to follow when choosing a second or third drug. One may choose to attack insulin resistance by combining metformin with a TZD. Alternatively, one could balance the insulin-sensitizing actions of metformin with the addition of a secretogogue. If postprandial hyperglycemia is a problem, carbohydrate absorption may be slowed by taking the α-glucosidase inhibitor, acarbose.

Step IV

When oral hypoglycemics are no longer sufficient to maintain control and signs of metabolic decompensation (symptomatic hyperglycemia or ketosis) appear, it becomes necessary to include insulin in the mixture. Most guidelines recommend beginning with small doses of intermediate or long-term insulin at bedtime; however, better control of HbA1c levels may be obtained with short-acting insulin before meals.[12]

Risk Factors

Treatment of hypertension greatly reduces the incidence of renal dysfunction among diabetics. Diabetic patients with hypertension or consistent albuminuria in the absence of hypertension should be given an angiotension-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) to reduce the risk of nephropathy. Treatment of hypertension and careful monitoring of blood pressure, with a target value of 130/80 mmHg, is an essential component of overall management. Second-step therapy for hypertension should be low-dose thiazide-like diuretics, cardioselective beta-blockers or long-acting calcium channel blockers. Systolic hypertension without proteinuria can be treated with ACE inhibitors, thiazide diuretics or long-acting dihydropyridine calcium channel blockers. Hyperlipidemia should be treated with statins.[13]

Target levels for someone with diabetes and no other risk factors are: LDL cholesterol <5 mmol/L; total to HDL cholesterol ratio <7; and triglycerides <3 mmol/L. These targets are lower if other risk factors are present. Low-dose acetylsalicylic acid is recommended for prevention in those with or at high risk for cardiovascular disease. ◆

No competing financial interests declared.

Useful Websites

Ontario Program for Optimal Therapeutics. http://www.opot.org/guidelines/diabetes.pdf

Diabetes Mellitus Care Flow Sheet. Chinook Health Region & Alberta Clinical Practice Guideline Program. http://www.albertadoctors.org/resources/cpg/careflowsheet.pdf

A New Script. Oral Hypoglycemic Therapy in Type 2 Diabetes. Informed, July 2002, Vol. 8 No. 3. http://www.ices.on.ca

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