

Considerations for the Pharmacological Treatment of Diabetes in Older Adults

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More than 20 million people in America are estimated to have diabetes, with the prevalence in adults > 60 years of age now > 20%.¹ The increased prevalence in older adults may be the result of several factors, including physiological changes in glucose metabolism that occur with aging, reduced physical activity, and increased prevalence of the metabolic syndrome with aging. As the proportion of the population of older adults increases with the aging of the Baby Boomer generation, so will the proportion of those who are older and have diabetes. This older population will also be faced with increasing prevalence of many other conditions, such as arthritis and high blood pressure, underscoring the need for effective management of diabetes in this population to optimize health.

This article reviews the normal physiological and pharmacodynamic changes of aging and relates this information to the process of making optimal therapeutic decisions for the pharmacological treatment of diabetes in older adults. The evidence basis for treatment of older adults, or lack thereof, is discussed, and a general approach to therapy is suggested.

Physiology of Diabetes in Aging

Aging is associated with defects in glucose metabolism. In healthy older adults, glucose metabolism is characterized by reduced non-insulin-mediated glucose uptake under basal conditions, with normal response during hyperglycemia compared with younger adults.² In older adults with diabetes, the defect in basal glucose uptake is further accentuated, and

there is a weaker uptake response during hyperglycemia.³

In addition to this effect on basal conditions, glucose-stimulated insulin response is diminished in older adults with diabetes compared with nondiabetic younger adults and nondiabetic older adults or those with impaired glucose tolerance.⁴ β -Cell sensitivity to the incretin hormones may also be reduced with aging, and delayed gastric emptying or gastroparesis is frequently reported for older adults with diabetes.^{5,6} These age- and diabetes-related defects in glucose metabolism and altered physiology may result in hyperglycemia throughout the day, with more pronounced postprandial glycemic excursions.

In addition to age-related changes in glucose utilization, the risk of hypoglycemia is increased in older adults compared with younger adults.⁷ This may result from several factors, including reduced renal or hepatic clearance of some anti-diabetic agents, drug-drug interactions, and impaired counter-regulatory hormonal responses to hyperglycemia.⁷

These age-related physiological changes in glucose metabolism and the increased risk for hypoglycemia have important implications for the pharmacological treatment of diabetes in older adults. Ideally, treatment should address patients' basal needs for glucose control and provide adequate coverage for postprandial glucose excursions. At the same time, the risk for side effects such as hypoglycemia should be minimized by individualizing therapy for age-related physiological changes in drug metabolism or elimination.

Physiological Changes of Aging and the Effects on Pharmacotherapy

Age- and disease-related changes within the body can affect how well medications are distributed, act, and are eliminated from the body. A variety of physiological changes occur as a result of the normal aging process, leading to alterations in an individual's general body composition. Older adults tend to have less muscle than younger people and generally have a higher percentage of body fat.⁸ For this reason, many older adults require lower doses of medications that have an affinity for muscle and are at increased risk for toxicity if taking medications that accumulate within adipose tissue. The elderly are generally less hydrated than younger individuals and thus tend to have less total body water, with an estimated 10–15% reduction in body water in the elderly.⁹ This may result in increased serum concentrations of water-soluble drugs if dosages are not adjusted accordingly. Blood flow to organs such as the kidneys and liver is diminished with age, which can lead to decreased metabolism and elimination of many drugs, including many of those used to treat diabetes.^{5,8,9} Table 1 outlines common geriatric considerations and dosing adjustments required for oral diabetes medications in patients with renal or hepatic impairment.

Age-related changes in kidney and liver function are the most important physiological changes to consider when selecting an appropriate diabetes regimen for older adults. The progressive decline in renal function that occurs with age may result in slower elimination of drugs that are partially or

Table 1. Hepatic, Renal, and Geriatric Considerations in the Elderly

Metformin	<ul style="list-style-type: none"> • Generally avoid in hepatic impairment • Hepatic disease increases the risk of metformin-associated lactic acidosis 	<ul style="list-style-type: none"> • Contraindicated with creatinine clearance <60 ml/min 	<ul style="list-style-type: none"> • Use should be avoided in elderly patients ≥ 80 years of age unless normal renal function is documented • Doses of metformin should generally be conservative in elderly or debilitated patients
Glimeperide	<ul style="list-style-type: none"> • Initiate therapy conservatively, and titrate based on clinical response 	<ul style="list-style-type: none"> • Initiate therapy conservatively, and titrate based on clinical response 	<ul style="list-style-type: none"> • Recommended initial dose of 1 mg daily
Glipizide	<ul style="list-style-type: none"> • 2.5 mg daily for regular release • 5 mg daily for extended release formulation 	<ul style="list-style-type: none"> • No specific dosage adjustment is needed • Conservative initial and maintenance dosing is recommended 	<ul style="list-style-type: none"> • Recommended initial dose of 2.5 mg daily
Glyburide	<ul style="list-style-type: none"> • Conservative initial and maintenance dosing is recommended • 1.25 mg/day for conventional formulations • 0.75 mg/day for micronized formulation 	<ul style="list-style-type: none"> • 50% renally excreted • Avoid use if creatinine clearance is < 50 ml/min 	<ul style="list-style-type: none"> • Not preferred for older adults because of increased risk for hypoglycemia • Consider lower initial dose of 1.25 mg (conventional formulations) or 0.75 mg (micronized formulation) daily, with slow titration to reach desired clinical response
Repaglinide	<ul style="list-style-type: none"> • Use with caution • Initiate at 0.5 mg preprandially, followed by slow and careful titration to desired clinical response 	<ul style="list-style-type: none"> • Creatinine clearance ≥ 40 ml/min: No initial dosage adjustment required • Creatinine clearance 20–39 ml/min: Initiate with 0.5 mg preprandially followed by slow and careful titration to desired clinical response • Creatinine clearance < 20 ml/min: No data available 	<ul style="list-style-type: none"> • Recommended maximum dose of 16 mg/day • Hold dose if meal is missed
Nateglinide	<ul style="list-style-type: none"> • Dose adjustment does not appear to be necessary 	<ul style="list-style-type: none"> • No dosage adjustment required 	<ul style="list-style-type: none"> • Recommended maximum dose of 360 mg/day • Hold dose if meal missed
Acarbose	<ul style="list-style-type: none"> • Contraindicated in cirrhosis • Elevated liver function test results may require dose reduction or drug discontinuation 	<ul style="list-style-type: none"> • Creatinine clearance ≥ 25 ml/min: No dosage adjustments necessary • Creatinine clearance ≤ 24 ml/min: Not recommended 	<ul style="list-style-type: none"> • Gastrointestinal side effects may be limiting • Hold dose if meal missed • Maximum dose recommendations based on weight: < 132 lb: 150 mg/day > 132 lb: 300 mg/day
Miglitol	<ul style="list-style-type: none"> • No dose adjustments needed 	<ul style="list-style-type: none"> • Creatinine clearance ≥ 25 ml/min: No dosage adjustments necessary • Creatinine clearance ≤ 24 ml/min: Not recommended 	<ul style="list-style-type: none"> • Recommended maximum dose of 300 mg/day • Hold dose if meal missed

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Table 1. Hepatic, Renal, and Geriatric Considerations in the Elderly, continued

Pioglitazone	<ul style="list-style-type: none"> • Dose adjustment may be necessary, but no specific recommendations are available • If patient exhibits clinical or laboratory evidence of liver disease or elevated alanine aminotransferase at the beginning of therapy, pioglitazone should not be initiated 	<ul style="list-style-type: none"> • No dose adjustment required when used as monotherapy 	<ul style="list-style-type: none"> • Initiate at the lowest dose, and increase gradually after several months of therapy • The risk of edema, weight gain, or congestive heart failure is increased when higher doses of pioglitazone are used in combination with insulin in patients at risk for heart failure • Pioglitazone should be discontinued if any deterioration in cardiac status occurs and is contraindicated for patients with pre-existing heart failure
Rosiglitazone	<ul style="list-style-type: none"> • Dose adjustment may be necessary, but no specific recommendations are available • If patient exhibits clinical or laboratory evidence of liver disease or elevated alanine aminotransferase at the beginning of therapy, rosiglitazone should not be initiated 	<ul style="list-style-type: none"> • No dose adjustment required when used as monotherapy 	<ul style="list-style-type: none"> • For adults without symptomatic heart disease but with one or more risk factors for congestive heart failure or an ejection fraction < 40%, 4 mg daily initially • For adults with symptomatic heart disease and/or Class I or II heart failure, 2 mg daily initially followed by slow dose titration allowing more time than normal to achieve target A1C • Not recommended in patients with Class III or IV heart failure
Sitagliptin	<ul style="list-style-type: none"> • Guidelines not available 	<ul style="list-style-type: none"> • Creatinine clearance 30–35 ml/min: 50 mg daily • Creatinine clearance < 30 ml/min: 25 mg daily 	<ul style="list-style-type: none"> • Recommended maximum dose of 100 mg/day
Exenatide	<ul style="list-style-type: none"> • Guidelines not available • Appears no dose adjustments are needed 	<ul style="list-style-type: none"> • Creatinine clearance \geq 30 ml/min: No dose adjustments needed • Creatinine clearance < 30 ml/min: Use not recommended 	<ul style="list-style-type: none"> • Available in pen
Pramlintide	<ul style="list-style-type: none"> • Guidelines not available • Appears no dose adjustments are needed 	<ul style="list-style-type: none"> • Guidelines not available • Appears no dose adjustments are needed • Pramlintide has not been studied in patients on dialysis 	<ul style="list-style-type: none"> • Hypoglycemia risk

$$\text{Estimated Creatinine Clearance} = \frac{(140 - \text{age}) \times \text{ideal body weight (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Figure 1. Cockcroft-Gault formula for estimating creatinine clearance.

completely cleared by the kidneys, including metformin and other diabetes agents.^{8,9} Additionally, some drugs are metabolized to active metabolites that are eliminated by the kidneys (e.g., some sulfonylureas and nateglinide) and can build up within the body, leading to toxicity and additive side effects if dosages are not adjusted. Higher serum concentrations may result in greater risk of hypoglycemia when such drugs are used.¹⁰ Fortunately, glomerular filtration rate may be estimated by determining creatinine clearance.

One of the most common methods for estimating creatinine clearance, the Cockcroft-Gault equation, uses patient-specific information, such as age, weight, sex, and serum creatinine (Figure 1).¹¹ It is important to estimate creatinine clearance and not rely solely on serum creatinine as a marker for kidney function because older individuals often have low muscle mass, and, therefore, serum creatinine concentrations may not be elevated even in the presence of renal dysfunction. In general, a creatinine clearance estimated at ≤ 60 ml/min warrants dose adjustments of most renally cleared medications. In an older woman (65 years) weighing 132 lb with a serum creatinine of 1.0, this would translate to an estimated creatinine clearance of 53 ml/min, just under this threshold.

Total liver volume also decreases with advanced age. Given the decreased liver volume and decreased blood flow to the liver with age, it is difficult to reliably predict changes in drug metabolism with aging. Many factors affect the ability of the liver to metabolize drugs, including other drugs, genetics, nutrition, and smoking status. Thus, finding an independent effect of aging has proven difficult. In general, the liver has a reduced capacity to metabolize some drugs that undergo oxidation (Phase I reac-

tions) within the cytochrome P450 system, but this varies on an individual basis. Aging, however, has been associated with little influence on the metabolism of medications that undergo gluronidation (Phase II metabolism), indicating that drugs undergoing this mechanism of metabolism may be safer alternatives than those with Phase I mechanisms.¹⁰

Guidelines for the Treatment of Diabetes in Older Adults

In 2003, the American Geriatrics Society published guidelines for the management of diabetes in older adults. These guidelines were developed by a panel and were based, whenever possible, on high-level evidence for care.¹² They highlight the importance of considering factors such as frailty, time required to reach beneficial outcomes of therapy, and the presence of common geriatric syndromes (e.g., depression) when deciding on diabetes treatments and goals.

The 2007 American Diabetes Association (ADA) clinical practice guidelines promote a goal hemoglobin A_{1c} (A1C) $< 7\%$ in all individuals with diabetes, with premeal plasma glucose goals of 90–130 mg/dl and 2-hour postprandial plasma glucose < 180 mg/dl.¹³ Based on limited information in older adults, some experts have advocated relaxed glycemic targets given the potential

risks of hypoglycemia with tighter glycemic control in older adults resulting from alterations in hypoglycemic responses. At this time, there is a lack of data to substantiate a full shift in glycemic targets in older adults based on age because of variability in patient health status and comorbidities affecting life span. It is reasonable, however, to adjust therapeutic goals when safety is a concern, especially in frail older adults.

A recent consensus algorithm outlines the approach to treatment of complex older adults with diabetes.¹⁴ Another algorithm, recently proposed in a consensus statement from the ADA and the European Association for the Study of Diabetes, provides a framework for the treatment of diabetes in older adults.¹⁵ Given the special needs and the homogeneity of older adults with type 2 diabetes, the algorithm serves as a guide that can be followed and altered for individual patients. The algorithm emphasizes:

- Achievement of glycemic goals,
- Initial therapy with lifestyle and metformin,
- Rapid addition of medications when goals are not met, and
- Early addition of insulin therapy when glycemic goals are not met.

The fourth item is particularly important for older patients. For older adults, some oral agents may

Table 2. Special Considerations for Individualization of Drug Therapy

Patient Factor	Potentially Preferred Drugs
Renal failure	Thiazolidinediones, glinides, insulin
Hepatic disease	Glinides, α -glucosidase inhibitors, insulin
Frequent hypoglycemia	Metformin, thiazolidinediones, insulin glargine
Obesity	Metformin, α -glucosidase inhibitors

not be appropriate given renal, cardiovascular, or hepatic concerns, so earlier initiation of insulin may be warranted. Additionally, many of the newer therapies do not have the needed data to warrant use in older adults. Table 2 summarizes potential therapies given a patient's specific clinical condition.

Benefits and Risks of Diabetes Treatment in Older Adults

Improvement in glycemic control has been demonstrated to significantly reduce the incidence of diabetes-related microvascular complications, including rates of retinopathy, neuropathy, and nephropathy. Numerous studies have also highlighted the importance of preventing macrovascular events associated with diabetes, such as heart attack and stroke, by the implementation of stringent glycemic control, lipid management, aspirin therapy, and blood pressure control.¹⁶ However, all of the landmark trials indicating the importance of tight glucose control and lipid and blood pressure control in the prevention of complications have been conducted in relatively young patients.

Although practitioners should consider the outcomes from such landmark trials as the Diabetes Control and Complications Trial¹⁷ (study participants averaged 27 ± 8 years of age) and the U.K. Prospective Diabetes Study¹⁸ (study participants averaged 53.3 ± 8.6 years of age) when treating older patients, they must also keep in mind that older adults may respond differently and be more sensitive to drug side effects than younger people. To date, there have been no landmark diabetes trials conducted in a geriatric population (mean age ≥ 65 years).¹⁶ The Action to Control Cardiovascular Risk in Diabetes trial, which is currently underway, may provide insight into the needs and outcomes for its subset of older adult (55–79 years of age) participants.¹⁹ With the current paucity of data in geriatric patients with diabetes, practitioners are forced to extrapolate from available evidence in younger adults to meet the needs of their geriatric patients.

The treatment of older adults with diabetes involves careful atten-

tion not only to glucose control, but also to blood pressure, aspirin therapy, and lipid management. This requires a balancing of the risks and benefits of treatment. Although prevention of painful neuropathies, loss of vision, and heart attacks and strokes is of huge concern, the effect of drug therapy on an individual's quality of life is always an important consideration when initiating treatment in older adults. Clinical trial data indicate that only 2–3 years of treatment with blood pressure²⁰ and lipid-lowering²¹ medications are required to result in a significant risk reduction for cardiovascular events such as heart attack and stroke, whereas 8 years of glycemic control¹⁸ may be required for risk reduction from microvascular complications of diabetes.¹⁴ An important consideration for older adults is that many (those ≥ 85 years) may not be able to take those medications long enough to benefit from their clinical effects. Studies and published case reports in older adults and the frail elderly are needed to help us further understand the role and utility of such treatments in the geriatric population.

Although the benefits of strict glycemic control and other strategies in the management of diabetes in older adults are not fully understood, many risks associated with aggressive treatment exist. As with any patient receiving medication to regulate blood glucose, the occurrence of hypoglycemia is of significant concern. Hypoglycemia can lead to an array of problems, and, in the elderly, impaired cognitive abilities and an increased risk for falls and subsequent fractures can lead to significant morbidity and even death. Although the ADA and other organizations have specific blood glucose monitoring goals, it is widely accepted that in frail older adults suffering from frequent bouts of hypoglycemia, it may be appropriate to set less stringent A1C, fasting plasma glucose, and postprandial glucose goals to prevent unnecessary and often dangerous hypoglycemia. Hypoglycemia is associated not only with recurrent physical morbidity, but also with psychosocial morbidity

when patients are in constant fear of experiencing a hypoglycemic event.²²

In addition to the physiological changes with aging that may place older individuals with diabetes at greater risk for treatment-associated hypoglycemia, the elderly are also at increased risk for developing hypoglycemia and other side effects associated with diabetes medications because they are often taking many more medications than younger patients with diabetes. Other risks of treatment include decreased medication adherence, increased drug costs, and the increased risk for drug-drug interactions resulting from polypharmacy. When consulting with older adults with diabetes (or their caregivers) regarding their drug therapy, a careful review of the medication regimen and current side effect profile, including adherence difficulties, is warranted to prevent adverse events.

In summary, the evidence to specifically guide diabetes treatment in older adults is limited and largely based on extrapolation from studies of younger adults with diabetes that have demonstrated some significant benefits of therapy. The primary risk of treatment is hypoglycemia; however, this can often be successfully managed with careful monitoring and effective communication between health care providers and patients. Another risk of treatment is that the use of multiple medications places patients at increased risk for medication-related problems, such as drug-drug interactions, adverse drug reactions, and problems with adherence. Therefore, important decisions must be made about the priorities for treatment to optimize clinical outcomes, patient safety, adherence, and quality of life. Careful consideration of individualized patient goals is paramount.

Pharmacological Treatment of Diabetes in Older Adults

In older adults with diabetes, therapy may be needed to control both basal glucose levels and postprandial glycemic excursions. The use of basal (e.g., once-daily, long-acting) and bolus (e.g., prandial, short-acting) insulin is a model for meeting these physiological needs. However,

because many older adults with type 2 diabetes have sufficient insulin secretion to respond well to oral therapies, these are often tried first.

In this section, diabetes treatments are organized by pharmacological action with regard to the ability to address basal glucose needs, prandial needs, or insulin resistance. Oral antihyperglycemic therapies (e.g., sulfonylureas or metformin) and the new injected hormonal therapies lower A1C levels only 1–2% at best. For patients with A1C levels > 9%, combination therapies or early introduction of insulin may be essential for achieving adequate diabetes control.

Improving basal glucose levels

Basal insulin. Up to 35% of type 2 diabetic patients will require insulin during the course of their disease as a result of progressive β -cell decline.²³ The basal insulins NPH, detemir, and glargine are often a mainstay of treating older adults with type 2 diabetes. For older adults who are resistant to giving injections or may have functional difficulty using multiple insulin products or injections (e.g., cognitive, vision, or dexterity problems), the introduction of a once-daily basal insulin injection is effective and often well accepted as initial insulin therapy.²⁴ Earlier initiation of insulin therapy may benefit many patients, especially those who are older and may be physiologically deficient in insulin. The choice of the specific insulin is often less important than the decision to use some form of basal insulin to improve diabetes control. In some studies, glargine was associated with improved glycemic control with less nocturnal hypoglycemia compared to NPH, although this was not specific to an older patient population.^{25,26} Insulin is eliminated by the kidneys, so dose adjustment may be required in patients for whom renal function has declined to avoid hypoglycemia.

Sulfonylureas. The sulfonylureas work primarily to enhance basal glucose control. First-generation sulfonylureas will not be discussed because they are rarely prescribed and for the most part not recommended for older patients because

of side effects and drug interactions (e.g., chlorpropamide carries an increased risk of hypoglycemia because of its extremely long half-life in elders and the increased likelihood of hyponatremia).^{27,28}

Of the second-generation sulfonylureas, glimeperide and glipizide are preferred for older adults.²⁹ Both tend to be safer in older adults,³⁰ particularly those with compromised renal function. Glimeperide is 99.5% protein-bound and metabolized to M1, a metabolite having one-third the activity of the parent compound in animals. Hepatic metabolism converts glipizide to inactive metabolites with both the parent compound and its metabolites excreted in the urine. In older adults, glimeperide is commonly initiated at 1 mg per day and glipizide is initiated at 2.5 mg daily. Glyburide is associated with an increased likelihood of hypoglycemia (1.9 adjusted relative risk over glipizide),³⁰ most likely because of the accumulation of active metabolites. Therefore, it should be avoided in patients with a creatinine clearance of < 50 ml/min.³¹

Improving prandial glucose levels

Glinides. The glinides, like the sulfonylureas, promote insulin release. However, this effect is directed primarily at mealtime increases in glucose based on the shorter action and prandial activity of the medication. Although more expensive than some of the sulfonylureas, these agents may be a good addition to therapy for older adults with problematic postprandial hyperglycemia not responsive to meal planning.

Because repaglinide's primary metabolism occurs in the liver, it should be used cautiously in patients with any degree of liver impairment. For older patients with liver impairment, initiate it at 0.5 mg preprandially, and adjust doses conservatively. Because of its minor renal elimination, no dose adjustment is required in patients with mild to moderate renal impairment. Repaglinide has not been studied in patients with a creatinine clearance < 20 ml/min or in those on dialysis.²⁹

Although nateglinide is primarily renally eliminated, no altered pharmacokinetics have been docu-

mented in patients with a creatinine clearance as low as 15 ml/min. In one study, 1,170 patients > 64 years of age, many with renal insufficiency, received nateglinide ($n = 333$).³² Elderly patients with renal insufficiency had a decrease in A1C of 1.1% ($P = 0.002$), and tolerability was similar to that of placebo. Nateglinide has also been studied in patients with mild to moderate hepatic cirrhosis, and no dose adjustments appeared to be warranted.³³

Prandial insulins. Available prandial insulins include regular insulin and the rapid-acting analogs lispro, aspart, and glulisine. These formulations are available in pen delivery devices, facilitating ease of use for older adults who may have difficulty drawing up insulin into syringes. One possible benefit of the rapid-acting analogs is the potential for injecting them after meals, which may be an advantage for older adults with delayed gastric emptying or who have inconsistent meal or caloric consumption.³⁴

Inhaled, powdered insulin (Exubera) is a new option for prandial glucose control; however, contraindications for those who smoke or have smoked in the past 6 months and those who have asthma, chronic obstructive pulmonary disease, or other pulmonary conditions or reduced pulmonary function may preclude use in older adults.³⁵ Adequate dexterity is required for dosing and cleaning, which may also challenge effective use for some older adults. There are no specific dose recommendations for the elderly. Insulin dose adjustment should be made based on clinical response.

α -Glucosidase inhibitors. Although α -glucosidase inhibitors slow carbohydrate absorption, the corresponding gastrointestinal side effects may limit their use in older adults who are at increased risk of delayed gastric emptying or other gastrointestinal medical conditions.

The systemic absorption of acarbose is minimal; however, patients with severe renal impairment may have an elevated serum concentration (five to six times greater than normal). Therefore, acarbose is not recommended in patients with a

creatinine clearance < 24 ml/min, whereas those with a creatinine clearance > 24 ml/min do not require any specific dose adjustments. Acarbose is contraindicated in cirrhotic patients.²⁹

Miglitol does not undergo any hepatic metabolism, and its use is of no concern in patients with cirrhosis. Systemically absorbed miglitol is excreted renally. No pharmacokinetic differences are noted based on age; however, patients with severe renal impairment have concentrations up to two times those of patients with normal renal function. Therefore, miglitol is not recommended in patients with a creatinine clearance < 25 ml/min.

Exenatide. The incretin mimetic exenatide has not been specifically studied in older adults; however, weight loss associated with this medication may make it an attractive option for older adults who are overweight. Exenatide is primarily renally cleared and is not recommended in patients with a creatinine clearance \leq 30 ml/min, and dose adjustments are not recommended for patients with a creatinine clearance greater than this value.³⁶ Although not specifically studied, hepatic disease does not alter the pharmacokinetics or clinical response to exenatide. The pen device for exenatide assists with self-administration and may provide a benefit above other injectables that require vials and syringes. A new long-acting exenatide, administered once weekly, may be a welcomed addition for patients who would benefit from this agent but prefer minimal injections.

Sitagliptin. The new dipeptidyl peptidase-IV inhibitor sitagliptin undergoes minor metabolism and is primarily renally eliminated. Although not specifically studied in older adults, dose adjustments should be made based on creatinine clearance, so attention to renal function is important. The recommended dose is 100 mg per day in those with a creatinine clearance \geq 50 ml/min. A dose of 50 mg is recommended in those with a creatinine clearance between 30 and 50 ml/min, and 25 mg is recommended

for those with a creatine clearance < 30 ml/min.³⁷ For patients on intermittent hemodialysis, the recommended dose is 25 mg daily.

Pramlintide. The synthetic amylin analog pramlintide is not appropriate for patients with hypoglycemic unawareness, possibly precluding its use in older adults.³² Severe hypoglycemia is twice as common with pramlintide when compared with placebo³⁸ and requires intensive blood glucose monitoring. In trials where insulin doses were kept constant, severe hypoglycemia tended to occur within the first month of initiation.³⁹ The hypoglycemia associated with pramlintide use, however, tends to be less severe in patients with type 2 diabetes. Unlike exenatide, pramlintide is not currently available in pen form, therefore limiting its use in older adults challenged by the use of vials and syringes. The manufacturer of pramlintide has recently announced that a pen dosage form will be available in the near future. Given the observance of hypoglycemia in clinical trials, pramlintide should be used cautiously in older diabetic patients with risks for hypoglycemia until more data are available.³⁸

Reducing insulin resistance and modifying hepatic glucose production

Metformin. The main concern with the use of metformin in older adults with type 2 diabetes is the decline in renal function often associated with aging. The inherent risk of metformin therapy in patients with renal compromise results from accumulation of metformin and ensuing metformin-associated lactic acidosis. Metformin accumulates in patients with a creatinine clearance \leq 60 ml/min.³⁹ Furthermore, many older adults have comorbidities that limit the use of metformin, such as cardiac, pulmonary, or hepatic disease.³⁰ Many older patients are not candidates for metformin therapy, and, specifically in those \geq 80 years of age, it is not recommended unless normal renal function is documented.

Thiazolidinediones. Fluid retention and the potential for worsening of congestive heart failure may pre-

clude the use of thiazolidinediones in older adults. Neither of the available drugs in this class, pioglitazone and rosiglitazone, should be used in patients with heart failure or hepatic disease.^{40,41} Risk factors associated with the development of heart failure in patients treated with thiazolidinediones include history of heart failure, prior myocardial infarction or symptomatic coronary artery disease, hypertension, left ventricular hypertrophy, significant aortic or mitral valve heart disease, advanced age (> 70 years of age), longstanding diabetes (> 10 years' duration), pre-existing edema or current treatment with loop diuretics, insulin coadministration, and chronic renal failure (serum creatinine > 2.0 mg/dl).⁴¹ Of interest, data on pioglitazone demonstrate a sex-specific effect on pharmacokinetics, with females having 20–60% higher mean area-under-the-curve values than males, which may be clinically significant when treating older women. Patients receiving pioglitazone plus insulin are at increased risk of congestive heart failure compared with patients receiving insulin alone.⁴¹

A recent trial indicated that rosiglitazone may increase the risk of myocardial infarction and other serious adverse cardiovascular events.⁴² As a result of this new information about rosiglitazone and the risk of fluid retention and potential worsening of congestive heart failure demonstrated with both agents, the thiazolidinediones should be used cautiously in older adults with cardiac disease until more data are available.

Summary

Diabetes in older adults is a significant health problem in the United States, with > 20% prevalence and the prospect that this may continue to increase with the aging of the American population. There are several things to consider when planning treatment for diabetes in older adults. The physiology of diabetes in these patients involves impairment of basal glucose control, reduced prandial insulin secretion, and insulin resistance. Older adults are also at increased risk for hypoglycemia, so careful attention must be paid to minimize this risk.

Several oral and injectable medications are available to meet these patients' needs; however, it is important to remember that for individuals with higher A1C levels (> 9%), poor response to oral therapies or a decline in renal or hepatic function may warrant early introduction of at least some level of insulin therapy. Another important consideration when selecting diabetes therapies is the priority for glycemic control, as well as reduction of the risk of heart attack and stroke through blood pressure lowering, aspirin therapy, and lipid management.

In older adults who are challenged by the use of multiple medications (e.g., adherence problems or frequent adverse reactions), decisions on priorities for diabetes care may be required to provide the most beneficial treatments at the lowest risk to the patient.

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