



Inside Bangladesh

Rising prevalence of type 2 diabetes in rural Bangladesh

Diabetes mellitus has a high prevalence worldwide in both developed and developing countries. Recent epidemiological studies have shown an increased prevalence of diabetes in India (12.1%), Pakistan (11.1%), and China (6.1%). Bangladesh has recently been facing rapid urbanization. The country is also in a stage of demographic transition with an increasing proportion of older population. Urbanization has been found to be associated with a sedentary lifestyle, higher calorie food intake and stressful life conditions, which may be contributing to the increasing prevalence of diabetes mellitus.

A total of 4757 subjects age 20 years both male and female were enrolled randomly in a cross-sectional study in 1999. The same area and population was reinvestigated in 2004 following the same selection procedure, on a sample of 3981 individuals. Structural and economical changes were noted for the last 5 years in the locality. An increased prevalence of diabetes was found with 6.8% in the present survey compared with 2.3% in the earlier survey ($p < 0.05$). Age, BMI and systolic blood pressure were found to be significant risk factors following both for FBG and for OGTT. WHR was found to be a significant risk factor for men only. A substantial agreement was observed between FBG and OGTT (kappa 0.63) compared to the previous investigation in 1999 (kappa 0.40). Differences in the indices of obesity, that is BMI, WHR and waist girth, may in part explain the increased prevalence, which in turn may explain due to fast-expanded urbanization. The state of affairs warrants immediate measures necessary to prevent the epidemic particularly in the localities that are in the transition phase from rural to semi-urban facilities.

Table 1: Mean values with 95% CI for age, BMI, WHR, SBP, DBP, height and waist girth for 1999 and 2004 in rural Bangladesh

Variables □	1999 (n = 4757) □		2004 (n = 3981) □		p for the differences of mean values
	Mean values	95% CI	Mean values	95% CI	
Age (years)	37.5 □	36.9-37.9	37.2	36.8-37.7	0.90
BMI (kg/m ²)	20.2	19.8-20.6	20.7*	20.6-20.8	<0.05
WHR □	0.85	0.85-0.85	0.86*	0.86-0.86	<0.05
SBP (mmHg)	119.7	119.2-120.2	119.6	119.1-120.2	0.78
DBP (mmHg)	77.2 □	76.9-77.5	77.0	76.4-77.4	0.60
Height (cm)	154.4 □	154.2-154.6	154.4	154.2-154.8	0.90
Waist girth (cm)	67.6 □	67.5-67.9	73.1**	72.8-73.5	<0.000

*p = 0.05; **p < 0.001, Body mass index (BMI), Waist to hip ratio (WHR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP)

diabetes

NEWSLETTER

Diabetescope

Liver Fat Increased in Type 2 Diabetes

Patients with type 2 diabetes have substantially more fat in their livers than nondiabetics of the same weight, investigators in Finland report. However, liver enzyme levels underestimate liver fat content in diabetics.

It is important to develop tools to diagnose a fatty liver in type 2 diabetic patients because nonalcoholic steatohepatitis is more common in type 2 diabetic patients than in nondiabetic subjects and can progress to cirrhosis and liver failure.

Knowledge of a patient's liver fat content is also an important parameter to consider when making treatment choices.

Dr. Kotronen at the University of Helsinki and colleagues studied 70 patients with type 2 diabetes and 70 nondiabetic subjects matched for body mass index, age, and sex.

Liver fat content was measured using proton magnetic resonance spectroscopy and body composition was measured using magnetic resonance imaging.

Liver fat content was about 80% higher in the diabetics (mean 13% vs 7.3%, $p = .005$), with the discrepancy between groups widening with increasing obesity, irrespective of antihyperglycemic therapy.

An intriguing observation in the present study was that the type 2 diabetic patients had 40-200% more liver fat at the same serum alanine aminotransferase and serum aspartate aminotransferase concentrations than the nondiabetic subjects.

Thus, there is a need to develop new serum markers of steatosis.

Source: Diabetes Care 2008;31:165-169.

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High Blood Pressure Predicts New-Onset Type 2 Diabetes in Women

New findings from the Women's Health Study show that baseline blood pressure and progressive increases in blood pressure are strong and independent predictors of incident type 2 diabetes in initially healthy women.

The findings are reported by a team from Harvard Medical School in Cambridge, Massachusetts.

The analysis involved 38,172 women without heart disease or diabetes at baseline. The investigators stratified them into four groups according to baseline blood pressure: group 1, < 120/75 mm Hg; group 2, 120-129/75-84 mm Hg; group 3, 130-139/85-89 mm Hg; and group 4, > 140/90 mm Hg, classified as hypertensive.

The primary outcome measure was the development of type 2 diabetes, which occurred in 1,672 women during 10.2 years of follow-up.

For women with blood pressure progression during the first 48 months of follow-up but who remained normotensive, the hazard ratio for type 2 diabetes was 1.26, and it was 1.64 for those who developed hypertension during the first 48 months, compared to women with no blood pressure progression.

This study provides strong evidence that baseline blood pressure and blood pressure progression are associated with an increased risk of incident type 2 diabetes. Clinicians should be aware of these relationships to optimize the management of patients at increased risk for cardiovascular disease.

The findings ideally would ask the question of whether lifestyle advice is superior, equal or inferior to drug therapy for cardiovascular prevention.

Source: Eur Heart J 2007;28:2832-2833,2937-2943.

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Metabolic Syndrome in Children Predicts Adult Metabolic Syndrome and Diabetes

A clustering of cardiovascular risk factors that define the metabolic syndrome in children is strongly associated with adult metabolic syndrome, cardiovascular disease and type 2 diabetes. These findings stem from a 25-30 year follow-up of 814 students who were between 5-19 years old when enrolled in the Princeton Prevalence Study between 1973 and 1976.

Established definitions for pediatric metabolic syndrome have not yet been established, so the researchers used the following parameters: triglyceride levels of 150 mg/dL and glucose levels of 110 mg/dL or greater were defined as high, while HDL-C levels of 50 mg/mL or lower among females and 40 mg/dL or lower among males were defined as low. BMI and systolic or diastolic blood pressure were defined as high if they exceeded the age-specific 90th percentile.

In the follow-up study, participants who had metabolic syndrome as children were about 13 times more likely to have cardiovascular disease and 6.5 times more likely to have type 2 diabetes. Evaluating 5-19 year-old children for metabolic syndrome and family history of diabetes could identify children at increased risk of adult metabolic syndrome and type 2 diabetes mellitus, allowing prospective primary prevention of these outcomes. The follow-up data also confirm that metabolic syndrome is strongly associated with overweight and obesity. Of 210 people with the metabolic syndrome as adults, 200 were either overweight or obese.

The follow-up data also show that for each increase in the age-specific BMI percentile of 10 points, the risk of adult metabolic syndrome increased 24% -- but the opposite was true as well. For each decrease in the age-specific BMI percentile of 10 points, the risk of adult metabolic syndrome decreased 24%.

Source: J Pediatr 2008;152:201-206.

Diabetescope

Low Vitamin B12 in Pregnancy Linked to Insulin Resistance in Offspring

Low plasma vitamin B12 in the first trimester and high folate levels in the second trimester of pregnancy predispose offspring to insulin resistance, according to the results of a study conducted in India. As a part of the Pune Maternal Nutrition Study researchers evaluated the dietary intake, vitamin B12, folate, total homocysteine and methylmalonic acid levels of 700 women at 18 weeks' and 28 weeks' gestation.

Six hundred fifty-three offspring of these mothers were followed-up at 6 years of age with physical and biochemical measurements, body composition using X-ray absorptiometry, and insulin resistance using homeostatic models. The plasma B12 levels were low (<150 pmol/L) in a majority of the women at 18 weeks and 28 weeks gestation, but were significantly higher among mothers whose diet included dairy products and non-vegetarian foods. The median red cell folate was significantly elevated at 28 weeks gestation.

Insulin resistance at 6 years of age was significantly more common in the offspring of mothers who had low B12 levels at 18 weeks and high folate levels at 28 weeks of pregnancy, and was highest among those with a combination of both. Adiposity was greater among the offspring of mothers with higher folate levels.

Increased plasma levels of homocysteine and methylmalonic acid as a consequence of low plasma B12 results in lipogenesis, reduced protein synthesis and reduced lean body mass, and may be the precursor of insulin resistance, the researchers postulate. Epigenetic regulation, involving DNA methylation, may be another mechanism of nutritional programming. An imbalance in the vitamin B12 and folic acid levels produces the undesirable effects. High folate intakes in vitamin B12-deficient mothers could increase the risk of type 2 diabetes in the offspring.

Source: Diabetologia 2008; 51:29-38.



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Considerations for the Pharmacological Treatment of Diabetes in Older Adults

Physiological Changes of Aging

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. 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. 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. 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 completely cleared by the kidneys, including metformin and other diabetes agents. 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. 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). 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.

Total liver volume also decreases with advanced age. Many factors affect the ability of the liver to metabolize drugs, including other drugs, genetics, nutrition, and smoking status. In general, the liver has a reduced capacity to metabolize some drugs that undergo oxidation (Phase I reactions) within the cytochrome P450 system but with little influence on the metabolism of medications that undergo glucuronidation (Phase II metabolism), indicating that drugs undergoing this mechanism of metabolism may be safer alternatives than those with Phase I mechanisms.

Guidelines for the Treatment of Diabetes in Older Adults

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. 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 consensus statement from the ADA and the European Association for the Study of Diabetes 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 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.

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

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

Treatment in Older Adults

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.
Glimepiride	<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 (Glibenclamide)	<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 \geq 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 is 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 \geq 25 ml/min: No dosage adjustments necessary. Creatinine clearance \leq 24 ml/min: Not recommended. 	<ul style="list-style-type: none"> Gastrointestinal side effects may be limiting. Hold dose if meal is 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 \geq 25 ml/min: No dosage adjustments necessary. Creatinine clearance \leq 24 ml/min: Not recommended. 	<ul style="list-style-type: none"> Recommended maximum dose of 300 mg/day. Hold dose if meal is missed.
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 failures. Pioglitazone should be discontinued if any deterioration in cardiac status occurs and is contraindicated for patients with preexisting 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, 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"> 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 A_{1C}. Not recommended in patients with Class III or IV heart failure.

Continued on Page 6

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

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

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. The treatment of older adults with diabetes involves careful attention 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. Clinical trial data indicate that 8 years of glycemic control may be required for risk reduction from microvascular complications of diabetes. 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. 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. It may be appropriate to set less stringent A_{1C}, fasting plasma glucose, and postprandial glucose goals to prevent unnecessary and often dangerous hypoglycemia. Other risks include decreased medication adherence, increased drug costs, and the increased risk for drug-drug interactions resulting from polypharmacy.

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. Oral antihyperglycemic therapies (e.g., sulfonylureas or metformin) and the new injected hormonal therapies lower A_{1C} levels only 1-2% at best. For patients with A_{1C} 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. 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. 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. 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 are 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).

Of the second-generation sulfonylureas, glimepiride and glipizide are preferred for older adults. Both tend to be safer in older adults, particularly those with compromised renal function. Hepatic metabolism converts glipizide to inactive metabolites with both the parent compound and its metabolites excreted in the urine. In older adults, glimepiride is commonly initiated at 1 mg per day and

Treatment in Older Adults

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

glipizide is initiated at 2.5 mg daily. Glyburide is associated with an increased likelihood of hypoglycemia, most likely because of the accumulation of active metabolites. Therefore, it should be avoided in patients with a creatinine clearance of < 50 ml/min.

Improving prandial glucose levels

Glinides. The glinides, like the sulfonylureas, promote insulin release. However, this effect is directed primarily at mealtimes 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. Although nateglinide is primarily renally eliminated, no altered pharmacokinetics have been documented in patients with a creatinine clearance as low as 15 ml/min. Nateglinide has also been studied in patients with mild to moderate hepatic cirrhosis, and no dose adjustments appeared to be warranted.

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. 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.

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.

Miglitol does not undergo any hepatic metabolism, and its use is of no concern in patients with cirrhosis. Systemically absorbed miglitol is excreted renally. Patients with severe renal impairment have concentrations up to two times those of patients with normal renal function. Therefore, miglitol is not recommended 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 < 30 ml/min, and dose adjustments are not recommended for patients with a creatinine clearance greater than this value. Although not specifically studied, hepatic disease does not alter the pharmacokinetics or clinical response to exenatide.

Sitagliptin. The new dipeptidyl peptidase-IV inhibitor sitagliptin undergoes minor metabolism and is primarily renally eliminated. Dose adjustments should be made based on creatinine clearance. The recommended dose is 100 mg/day with a creatinine clearance < 50 ml/min.

Pramlintide. The synthetic amylin analog pramlintide is not appropriate for patients with hypoglycemic unawareness, possibly precluding its use in older adults. Severe hypoglycemia is common.

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 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 = 60 ml/min. Furthermore, many older adults have comorbidities that limit the use of metformin, such as cardiac, pulmonary, or hepatic disease. Many older patients are not candidates for metformin therapy, and, specifically in those > 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 preclude 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. 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), preexisting edema or current treatment with loop diuretics, insulin coadministration, and chronic renal failure (serum creatinine > 2.0 mg/dl). Females having 20-60% higher mean area-under-the-curve values than males, which may be clinically significant when treating older women. A recent trial indicated that rosiglitazone may increase the risk of myocardial infarction and other serious adverse cardiovascular events. 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.

Reference: Considerations for the Pharmacological Treatment of Diabetes in Older Adults, Diabetes Spectrum Volume 20, Number 4, 2007.

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The Winners of diabetes Quiz Competition



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Dear Doctor, This issue of your *diabetes newsletter* is focused on "Considerations for the Pharmacological Treatment of Diabetes in Older Adults". We appreciate your comments and queries. Please participate in quiz competition & win prizes.

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