DIABETES IN THE ELDERLY

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ABSTRACT

The number of older adults with diabetes is increasing in the United States and worldwide due to increased lifespan and the increased prevalence of diabetes in the geriatric population. One-third of the U.S. population over 65 years old has diabetes with a projection of two-fold increased prevalence for those 65-74, and four-fold increased prevalence for those >75 years of age from 2005 to 2025. Diabetes is a major cause of morbidity and mortality in this population, with the latter largely attributable to macrovascular complications. Older diabetics also carry a disproportionate burden of microvascular complications, presumably related to longer duration of diabetes. This chapter reviews goals of diabetes care and how to achieve these goals in the geriatric population.

PREVALENCE

The number of older adults with diabetes is increasing in the United States and worldwide due to increased lifespan and the increased prevalence of diabetes in the geriatric population. One third of the U.S. population over 65 years old has diabetes, and one half of older adults have prediabetes (1). Diabetes is a major cause of morbidity and mortality in this population, with the latter largely attributable to macrovascular complications. Older diabetics also carry a disproportionate burden of microvascular complications, presumably related to longer duration of diabetes (2). This chapter reviews the goals of diabetes care and how to achieve these goals in the geriatric population.

Age and weight are both risk factors for the development of diabetes. It has been noted that in normal aging there is a 2 mg/dL/decade rise in fasting plasma glucose, placing elderly patients at increased risk for the development of diabetes. Weight gain and decreased muscle mass are often seen with increasing age, resulting in worsened insulin resistance at the level of muscle and fat. Hence, beta cell function is taxed not only by impaired function with age per se, but also through worsening insulin resistance. Additionally, in the elderly there are often concomitant diseases, decreased activity, and medications which can worsen insulin resistance.

CLASSIFICATION OF DIABETES

The types of diabetes in the elderly population span the spectrum, including Type 1, Type 2, latent autoimmune diabetes of adulthood, and other types. The last classification group includes diabetes due to underlying defined genetic syndromes; drugs, toxins, or endocrinopathy induced diabetes; and a variety of other relatively uncommon etiologies (see the American Diabetes Association [ADA] diabetes classification for further details) (3).

Type 1 diabetes mellitus results from autoimmune destruction of the beta-cells of the pancreas, ultimately leading to insulin deficiency. It occurs in genetically susceptible people and is influenced by environmental factors. Latent autoimmune diabetes of adulthood is a subset of type 1 diabetes with onset in adulthood. These patients have a slower loss of beta cell function than do traditional type 1 patients. Hence, they may initially be able to achieve glycemic control on oral agents for a period of time before needing to be transitioned to insulin. These patients are more often thin and may lack a family history of diabetes. They should be closely monitored for beta cell failure with need for transition to insulin to prevent development of ketosis (3).

Type 2 diabetes mellitus results from increased insulin resistance which is superimposed on an inability of the pancreas to keep up with the insulin needs of the person (3). Type 2 diabetes can generally be treated with lifestyle changes and oral agents early in its course. However, beta cell function progressively declines, often with ultimate beta cell failure, thereby requiring insulin treatment. Over 90% of diabetics are type 2; they tend to be overweight or obese and have a strong family history of diabetes (4).

DIAGNOSIS

The diagnostic criteria for diabetes remain constant across all ages. Diabetes is diagnosed with fasting glucose greater than or equal to 126 mg/dl; symptoms of hyperglycemia and a random glucose equal to or greater than 200 mg/dl; a 75-gram oral glucose tolerance test with a two- hour value equal to or greater than 200 mg/dl; or A1C≥ 6.5%. For diagnosis of diabetes, two abnormal test results on the same test sample are needed, or confirmation of the abnormal test must be done on another day, unless unequivocal symptoms of hyperglycemia are present (5).

In an elderly population, screening for diabetes should be considered in light of its increased prevalence. The ADA recommends that all adults over age 45 are screened for diabetes and prediabetes, and if the results are normal, it can be repeated in three years. If the patient is found to have prediabetes (impaired fasting glucose with FPG 100-125 mg/dl, impaired glucose tolerance with 2-hour glucose 140-199 mg/dl on 75-gram oral glucose tolerance test, or A1C 5.7-6.4%,), screening is recommended yearly (5).

There is a distinction between diabetes diagnosed at an earlier age as opposed to diagnosis while elderly. Patients who have had diabetes for a longer period of time have an increased rate of microvascular complications compared with those with a diagnosis of diabetes at a later age. The incidence of macrovascular complications appears to be similar in older patients with diabetes regardless of duration of the disease (6).

MANAGEMENT

This section will address some common diabetes management issues in an elderly population. Please see the chapters of Endotext on modalities of treatment of diabetes for further details.

The American Geriatrics Society (AGS) guidelines for the management of diabetes in the elderly identify syndromes which elderly patients with diabetes are at increased risk of having in comparison to age matched non-diabetic patients (Table 1) (5, 6). Care of the elderly diabetic patient should include heightened screening and treatment of these syndromes. In addition to the areas targeted by the AGS, other targeted areas of therapy of elderly patients with diabetes include: hypoglycemia, hyperglycemia, medication errors, and vision problems.

Table 1. Associated Syndromes in Elderly Diabetic Patients
Polypharmacy
Depression
Cognitive Impairment
Urinary Incontinence
Injurious Falls
Vision Impairment
Pain

Polypharmacy

The AGS guidelines (6) indicate that elderly diabetics are often on multiple prescription medications for their diabetes as well as other comorbidities. This can lead to increased side effects, drug-drug interactions, and confusion about how and when to take medications. Each assessment of an elderly patient with diabetes should address and document what medications a patient is taking and how they are being taken. Documentation of potential adverse effects as well as benefits and risks of a medication should occur with each new medication prescribed (6).

Depression

When compared with age-matched non-diabetic patients, elderly patients with diabetes are at increased risk of depression. Additionally, older adults with diabetes and depression have higher risk for functional disability (7). The AGS guidelines identify that there is under-detection and undertreatment of depression in the elderly diabetic population. It is therefore recommended that one screens for depression in an older adult (≥65-year-old) with diabetes mellitus during the initial evaluation period (first 3 months) (5, 6). In addition, when an elderly patient with diabetes presents with new symptoms, consideration should be given to depression as an etiology of these symptoms (6).

Cognitive Impairment

There is an increased risk of cognitive impairment in elderly patients with diabetes (8, 9). Diabetic retinopathy (10) and hypoglycemia (11, 12) have been linked to memory loss and increased risk of dementia. This impairment may hinder their ability to comply with treatment recommendations and medications (6), and may contribute to increased mortality (13). The AGS recommends an assessment of cognitive status with the initial visit of a patient with diabetes and with any change in clinical condition (6).

Urinary Incontinence

It is well known that elderly female patients with diabetes have an increased risk of urinary incontinence. However, it has been recently reported that there is also an increased risk of incontinence in older men with diabetes (14); this should be kept in mind in the evaluation and management of these patients. Urinary incontinence may be associated with social isolation, as well as increased risk of falls and fractures. An initial assessment and examination to evaluate the etiology of urinary incontinence should be performed. The AGS guidelines note that factors which may exacerbate urinary incontinence in female patients with diabetes include: polyuria due to hyperglycemia, neurogenic bladder, fecal impaction, bladder prolapse, atrophic vaginitis, vaginal candidiasis, and urinary tract infections (6).

Injurious Falls

The increased risk of falls in elderly patients with diabetes is associated with significant morbidity and

mortality. It has been reported that 30.6% of older individuals with diabetes have recurrent falls compared with 19.4% of individuals without diabetes (15). Potential factors related to this increased risk include polypharmacy, visual impairment, peripheral neuropathy, and hypoglycemia. The increased fall risk is particularly true in elderly patients using insulin (16). Hence, it is recommended that one screen for fall risk as well as provide education on fall prevention (6, 17).

Vision Impairment

Older adults with diabetes have a higher prevalence of vision impairment (18), and visual impairment has been linked to increased risk of falls, isolation, and depression.

Pain

Elderly patients with diabetes are at risk for neuropathic pain. This pain is often undertreated. The AGS recommends screening for evidence of persistent pain during the initial evaluation and treatment of this pain (6).

Hypoglycemia

The UKPDS showed that hypoglycemia was one of the limiting factors in achieving optimal glycemic control (19). Older age is an important risk factor for hypoglycemia (20). Several factors contribute to the greater frequency of hypoglycemia, including declining renal function and drug interactions. Moreover, elderly adults may be more susceptible to severe hypoglycemia due to reduced recognition of hypoglycemic symptoms. Hypoglycemia is also associated with increased morbidity and mortality in the geriatric population.

To minimize the risk of hypoglycemia, the hemoglobin A1c goal should be less restrictive for elderly who are frail, have significant comorbidities, or have life expectancy of less than 5 years (5). Moreover, it is important to simplify the treatment regimen with the aim to reduce polypharmacy. Also, if insulin treatment is initiated, it is imperative to avoid use of solely insulin sliding scale, as this increases risk of both hypoglycemia and hyperglycemia (21).
Continuous glucose monitoring (CGM) can also be considered in selected elderly patients. A recent randomized clinical trial showed a significant improvement in hypoglycemia in older adults with type 1 diabetes (22).

TREATMENT

Treatment goals in older patients with diabetes should reflect the significant heterogeneity of this population in terms of comorbidities, life expectancy, self-care capabilities, psychological elements, and social support. Hence, they need to be individualized to be consistent with these factors as well as based upon patient and/ or family goals and willingness/ capability to comply with medication and lifestyle recommendations (6, 11, 23, 24). Additionally, patients with dementia represent a unique challenge that may necessitate modification of treatment goals. For all elderly patients, treatment goals should reflect a high level of concern over the risks associated with hypoglycemia (25); further, we must recognize the risks of excessive hyperglycemia, including dehydration, electrolyte abnormalities, urinary incontinence, dizziness, falls, and hyperglycemic crisis. Many studies of tight glycemic control excluded the elderly, and it is only more recently that we have guidelines of specific recommendation for elderly patients with diabetes. The AGS, Endocrine Society, and ADA recommend an A1C target of 7.5-8% in most older adults, whereas higher A1C is reasonable in frail adults with multiple comorbidities and with a life expectancy less than 5 years (6-7, 24). Lower A1C (7.5%) may be appropriate in an older adult with few comorbidities and good functional status (6-7, 24) (see Table 2).

Table 2. Treatment Targets for Older Patients with Diabetes				
Patient characteristics and overall health	**A1C goal**	**Fasting/ pre-prandial and HS BGs**	**BP goal**	**Lipid goal**
Generally healthy (0-2 coexisting chronic illnesses, intact cognitive and functional status.) Longer life expectancy.	<7.5%	90-130 mg/dl premeal, 90-150 mg/dl QHS	<140/90	On statin therapy.
Intermediate health (3 or more comorbidities and mild cognitive or functional impairment). Intermediate life expectancy	<8.0%	90-150 mg/dl 100-180 mg/dl QHS	<140/90	On statin therapy
Very poor health (End stage medical condition, residence in LTC facility, severe cognitive impairment), Limited life expectancy, tight control of uncertain benefit	<8.5%	100-180 mg/dl 150-180 mg/dl QHS	<150/90	Consider statin therapy

Diet and exercise remain the cornerstones of therapy for diabetes and should be emphasized at each patient visit (5). Medication choices are presented as described in the treatment algorithm published by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) (26-28) and Endocrine Society Guidelines (24); we have incorporated limitations related to treatment of older persons (Table 3).

Of note, based upon the 2020 ADA guidelines, providers should consider GLP-receptor agonist and SGLT2 inhibitor therapy after metformin independent of A1c in patients at high risk or with established atherosclerotic cardiovascular disease (ASCVD), heart failure, or kidney disease. In patients with ASCVD, GLP-1 receptor agonist therapy is preferable, whereas SGLT2 inhibitors are preferred in patients with heart failure or kidney disease with adequate renal function (3).

Table 3. Glucose Lowering Medications			
Medication	**A1C % reduction**	**Hypoglycemia risk**	**Limitations in older adults**
Initial therapy (monotherapy)			
Biguanide (metformin)	1-2	negligible	- Caution with decreased renal function (use submax dose for eGFR<45 ml/min, stop if <30 ml/min) - GI side effects - Possible weight loss -Monitor yearly for B12 deficiency
Addition of a second drug (Two-drug Therapy)			

GLP1 receptor agonist	0.5-1.5	Negligible (as monotherapy)	-GI side effects (pancreatitis contraindication) - Injectable (requires training) except for oral semaglutide - Weight loss - Cost
SGLT-2 Inhibitors	0.4-1.16	Negligible	-Hypovolemia - Acute Kidney Injury - Urinary tract infection - Genital candidiasis
Sulfonylurea	1-1.5	Moderate/ high	-Fasting hypoglycemia -Caution with decreased renal function (not recommended if eGFR<30 ml/min) -Avoid glyburide
Meglitinide	0.5-1.5	Moderate	- Complexity: frequent dosing, carbohydrate counting - Hypoglycemia if not correctly used
Thiazolidinedione	0.5-1.4	Negligible	- Edema: contraindicated in NYHA Class III or IV heart failure - Increase risk of long bone fracture -Increased risk bladder cancer? -Weight gain
DPP-4 Inhibitor	0.5-0.8	Negligible	- Contraindicated w/ history of pancreatitis - Potential increased risk of CHF (saxagliptin, alogliptin) - Dose adjustment for renal impairment except linagliptin - Cost
Basal Insulin	variable	High	- Injectable (requires training) - Weight gain

Biguanides (Metformin)

The main action of metformin is reducing hepatic glucose production. Significant benefits of metformin include absence of hypoglycemia when used as monotherapy as well as absence of weight gain (28). The most common side-effects associated with metformin include bloating, flatulence, and diarrhea. These generally improve with low dose initiation and slow titration.

The most worrisome, although very rare, side-effect of metformin is lactic acidosis. It is seen in patients with impaired renal function, active liver disease, sepsis, heart failure, or advanced pulmonary disease. Since metformin is exclusively excreted by the kidneys, submaximal doses should be used when creatinine clearance is below 45 ml/min; its use is absolutely contraindicated when the creatinine clearance is ≤30 ml/min (29). Additionally, metformin should not be

newly initiated when the eGFR is <45 ml/min, and it should be temporarily suspended in situations in which renal function may rapidly decline such as during hospitalizations and at the time of iodine related contrast exams.

Long term treatment with metformin is associated with vitamin B12 deficiency, and the B12 level should be checked in patients on long term therapy, with repletion as indicated (30).

Metformin is optimal first line therapy for diabetes management in elderly patients in whom it is important to avoid hypoglycemia.

GLP-1 Receptor Agonists

Exenatide (Byetta®, Bydureon®), Liraglutide (Victoza®), Dulaglutide (Trulicity®), Lixisenatide (Adlyxin®) and Semaglutide (Ozempic®, Rybelsus®) act as analogs of the incretin glucagon-like peptide-1. They thereby enhance glucose stimulated insulin secretion, inhibit secretion of glucagon in a glucose dependent manner, slow gastric emptying, and act centrally to promote satiety. These agents result in significant weight loss in most, but not all patients. They are indicated as monotherapy as well as for use in combination with sulfonylureas and/or metformin, long acting insulin (31), or in combination with prandial insulin (32, 33). Exenatide and lixisenatide generally reduce A1c by 0.5-1%, whereas extended release exenatide, liraglutide, dulaglutide and semaglutide have been noted to be more potent in A1C lowering, achieving reductions of up to 1.5%. Further, studies comparing addition of prandial insulin or GLP-1 receptor agonists to basal insulin therapy have revealed similar A1C efficacy with less hypoglycemia and weight gain (33, 34). Up to 40% of patients have gastrointestinal side effects including nausea, vomiting and abdominal discomfort. These tend to decrease over time, but sometimes require the drug to be stopped (35). The association between these agents and acute pancreatitis is controversial; a recent meta-analysis of four large cardiovascular outcome studies did not demonstrate an increased risk of pancreatitis or pancreatic cancer with GLP-1 receptor agonist treatment (36).

Longer acting agents have also been associated with an increased risk of thyroid C-cell tumors in rodents; they should not be used in patients with a personal or family history of MEN-2 or medullary thyroid cancer. Additionally, these agents are associated with hypoglycemia when used in combination with sulfonylureas and/ or insulin, and one may consider decreasing the dose of sulfonylurea when an incretin mimetic is initiated or titrated. The cardiovascular outcome trials for liraglutide, semaglutide, and dulaglutide revealed a decreased risk in fatal and nonfatal myocardial infarction and stroke as well as death over a 2-5.4-year period (37, 38, 39). Exenatide is dosed twice daily by subcutaneous injection (35), liraglutide and lixisenatide are dosed once daily and exenatide extended release, dulaglutide and semaglutide are dosed weekly. An oral formulation of semaglutide is now available.

A GLP-1 receptor agonist should be considered in patients with diabetes and known cardiovascular disease or high cardiovascular risk (age >55 with vascular stenosis, left ventricular hypertrophy, eGFR<60 ml/min, or albuminuria).

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

Canagliflozin (Invokana®), empagliflozin (Jardiance ®), ertugliflozin (Steglatro ®) and dapagliflozin (Farxiga ®) are FDA approved drugs that inhibit renal absorption of glucose resulting in increased urinary glucose excretion. They reduce A1c by 0.37%-1.16%, have low risk for hypoglycemia and result in a modest decrease in blood pressure as well as weight loss. Empagliflozin and canagliflozin have shown decreased risk of fatal and nonfatal myocardial infarction and stroke in diabetic patients with

cardiovascular disease (40,41), and all agents in this class decrease hospitalization for heart failure (hHF) and progression of chronic kidney disease (40-43). There is an increased risk of genital candidiasis as well as urinary infection (44) associated with SGLT2 inhibitor use; lightheadedness is uncommon but a concern for older patients. Notably, for individuals 75 years of age or older, canagliflozin has been shown to have a higher incidence of adverse events secondary to osmotic diuresis and volume depletion (45). All agents are most effective for glucose lowering with eGFR of >60 ml/min, but they have been shown greater benefit for preventing cardiovascular events with lower eGFR (46). An SLGT2 inhibitor should be considered in patients with diabetes and heart failure, especially those with reduced ejection fraction, to decrease hospitalization for HF, MACE, and cardiovascular death. This class should be considered for patients with known cardiovascular disease (after the GLP-1 receptor agonists), or eGFR<60 ml/mins. Additionally, these agents slow the progression of renal disease.

Sulfonylureas

Glyburide (Diabeta®, Glynase®, Micronase®), glipizide (Glucotrol®), and glimepiride (Amaryl®) bind to the sulfonylurea receptors on pancreatic beta cells and stimulate insulin release in a non-glucose mediated manner. They have a long track record of safety with a very extensive history of use (47).

Sulfonylureas are all hepatically metabolized and should be avoided in active liver disease. Glyburide and its active metabolites are renally cleared and thus should be avoided in those with renal disease as this can lead to profound and prolonged hypoglycemia. Glipizide has inactive metabolites, and glimepiride is cleared through biliary circulation and thus may be safer in patients with renal impairment (28).

Side effects of sulfonylureas include hypoglycemia and weight gain. Glyburide is of most concern in this arena, making glipizide or glimepiride preferred in those >65 years of age. In patients with erratic dietary intake, or if hypoglycemia occurs, sulfonylureas can be changed to a short acting insulin secretagogue (meglitinide) or DPP-4 inhibitor.

Meglitinides

Nateglinide (Starlix®) and repaglinide (Prandin®) also stimulate insulin release by binding to the sulfonylurea receptor, stimulating non-glucose mediated insulin release. In contrast to the older sulfonylurea agents, the meglitinides have a rapid onset and offset of action. Hence, they need to be taken shortly before each carbohydrate containing meal and are more effective in controlling postprandial hyperglycemia. These medications may pose a compliance problem in the elderly population who may have difficulty remembering such frequent dosing. They are, however, ideally suited to patients with inconsistent meal times or variable appetites.

Repaglinide is more efficacious in lowering A1C than nateglinide (47). Side effects include hypoglycemia and weight gain. These medications are metabolized in the liver and should not be used with active liver disease, but they are quite useful in older patients with renal insufficiency.

Thiazolidinediones

Pioglitazone (Actos®) and rosiglitazone (Avandia®) activate PPAR-gamma, which leads to improved insulin sensitivity, mainly at the level of fat and muscle. As a result, they may preserve beta cell function to some degree and increase the duration until additional therapy is required (46). Thiazolidinediones generally have a very slow onset of action, and hence months may elapse before their full impact on glycemic control is evident.

Thiazolidinediones have several remarkable side effects. Weight gain has been noted due to increased

fat deposition in the subcutaneous depot. Both medications in this class cause fluid retention that can result in increased incidence of peripheral edema as well as heart failure; this has resulted in a black box warning by the FDA. Additionally, both agents appear to cause increased appendicular bone loss and fractures (48) which is potentially problematic in our older patients with osteoporosis. Lastly, these medications undergo hepatic metabolism and should not be used in patients with hepatic dysfunction. A meta-analysis concluded that rosiglitazone may cause increased risk of myocardial infarction as well (49). This resulted in rosiglitazone's withdrawal from the European market in September of 2010, and a severe restriction on its use being placed by the FDA; the FDA removed the restriction on rosiglitazone use in 2013 based on additional studies, indicating that there is no increased cardiovascular risk. In contrast, several studies have indicated that pioglitazone reduces cardiovascular risk (50) and appears beneficial for patient with nonalcoholic fatty liver disease and non-alcoholic steatohepatitis (51). In light of the side effects seen with this class of medications, their use should be considered third line.

Dipeptidylpeptidase IV Inhibitors (DPP4 Inhibitors)

Sitagliptin (Januvia®), saxagliptin (Onglyza®), alogliptin (Nesina®) and linagliptin (Tradjenta®) act to inhibit the breakdown of intrinsically made GLP-1 and GIP, thereby enhancing glucose stimulated insulin secretion and suppressing glucagon secretion in a glucose-dependent manner. They can be used as monotherapy or in combination with metformin or thiazolidinedione and insulin. They do not appear to cause hypoglycemia when used as monotherapy or in combination with metformin or thiazolidinediones (52). Treatment with DPP-4 inhibitors provides similar glycemic control as seen with sulfonylureas with less hypoglycemia and weight gain in elderly patients (53). It has been reported that these agents can cause severe joint pain, and this resolves with stopping the medication (54). There is a possible increased risk of pancreatitis and pre-cancerous changes of the pancreas (55,56). The cardiovascular outcome trial with saxagliptin (57) revealed a slightly increased risk of hospitalization for heart failure with its use. This was not seen in the cardiovascular outcome trial with alogliptin (58), but the FDA concluded that it "may increase the risk of heart failure" (2/11/14 FDA Drug Safety Communication), and both drugs have warnings in their labelling. In contrast, there was no observed increased risk with sitagliptin or linagliptin (59-60).

There was no noted increase in pancreatic cancer or pancreatitis in these large, longer trials but meta-analysis of these trials did suggest an increased risk of pancreatitis.

Insulin

Exogenous insulin replaces or augments the total insulin present to achieve glycemic control. Insulin can be added to oral therapy in the elderly diabetic population as a basal injection of intermediate or long acting insulin (61). However, if this does not achieve glycemic control, transition can be made to an insulin regimen with basal and prandial components; in this case, most oral diabetes medications can be discontinued, thus helping to eliminate polypharmacy. In elderly patients with a variable appetite, one can dose the prandial insulin post meal based upon grams of carbohydrate consumed to reduce the risk of hypoglycemia (62, 63). Because of the high risk of hypoglycemia in the elderly population, simplified regimens using long acting morning basal insulin may be preferred to prevent nocturnal hypoglycemia; further, there should be greater caution when titrating the insulin dose (64). Insulin therapy can be especially burdensome for an elderly patient because of the complexity of the treatment. Visual impairment can be addressed with the use of a pen device to dispense insulin or the attachment of a magnifying glass to the syringe. Because insulin is degraded by the kidneys, care must be taken to reduce the dose in the setting of renal impairment to avoid hypoglycemia.

Elderly patients with diabetes who should be considered for insulin therapy at the onset include those with type 1 diabetes, diabetes secondary to pancreatic insufficiency, or those with a history of ketonuria, weight loss, or severe symptoms (26). It is notable that the American Diabetes Association has incorporated in their guidelines an algorithm published by Munshi and colleagues (65) which encourages simplification of regimens consisting of multiple daily injections of insulin for patients with type 2 diabetes and intact C-peptide. This algorithm encourages substitution of prandial insulin with oral therapy(ies) which do not cause hypoglycemia, and use of morning insulin glargine, a long acting insulin analog, as a means of decreasing hypoglycemia overall. Recent studies (66) document that we have not significantly decreased the use of insulin or decreased rates of hypoglycemia in our older patients, and it is key that we make this a focus of our care. Combination of insulin-GLP-1 receptor agonist such as glargine insulin/lixisenatide (iGlarLixi) (Soliqua) and degludec insulin/liraglutide (iDegLira) (Xultophy) are available for use and they can simplify therapy for some patients.

α-Glucosidase Inhibitors

Acarbose (Precose®) and miglitol (Glyset®) reduce absorption of glucose at the level of the small intestine by inhibiting alpha-glucosidase at the brush border. This results in a reduction of postprandial hyperglycemia, with a decrease in A1c by 0.5-1% (67). These medications have the benefit of not causing hypoglycemia when used as monotherapy. However, when used in conjunction with other agents, hypoglycemia can occur and needs to be treated with glucose specifically, as the absorption of other carbohydrates is delayed by inhibition of the intestinal breakdown.

The main side-effects which limit patients' compliance are abdominal bloating, flatulence, and diarrhea. These can be improved by limiting carbohydrate intake in a meal and by slowly titrating the medication.

Acarbose is contraindicated in patients with active hepatic disease. Miglitol is absorbed and excreted by the kidneys and is contraindicated with significant renal disease (67).

Amylin Analogues

The only amylin analog on the market is pramlintide (Symlin®). This agent acts by inhibiting postprandial glucagon release, thereby reducing hepatic glucose output, delaying gastric emptying, and enhancing satiety. These actions lead to improvement in postprandial hyperglycemia, and there may be some associated weight loss. A1C is decreased by 0.3-0.5% (68). Pramlintide is indicated as adjunctive therapy for patients with type 1 or 2 diabetes who inject insulin at mealtimes and have failed to achieve adequate glycemic control. Hypoglycemia associated with its use can be severe, especially in type 1 diabetics, and reduction of mealtime insulin doses is recommended when therapy with pramlintide is initiated. Additional drawbacks of pramlintide therapy include its high cost as well as the need to take additional subcutaneous injections prior to each meal, thereby increasing complexity of treatment for elderly diabetic patients.

GOALS OF TREATMENT

The United Kingdom Prospective Diabetes Study (UKPDS) in patients with type 2 diabetes and the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes revealed decreased onset and slowed progression of microvascular complications with tight glycemic control (20, 69). This came at the expense of increased frequency of hypoglycemia. Hence, in an elderly diabetic population which may be prone to frailty, one needs to carefully

balance the expected benefits with risk. Therapeutic goals should address the wishes of the patient and family and should take into consideration patient co-morbidities as well as life expectancy. Hence, therapeutic goals need to be tailored for each individual patient (5, 26).

In addition to a focus on glycemic control, care should also be taken in the elderly population to focus on additional goals of therapy. The elderly population with diabetes has a very high rate of macrovascular and microvascular complications, and hyperglycemia is only one of the contributors to these complications (16, 69). Hence, other risk factors for complications, including hypertension, hyperlipidemia, and smoking, need to be addressed in order to optimize outcomes.

The AGS, Endocrine Society, and ADA guidelines provide guidance for additional aspects of care for elderly patients with diabetes (5, 6, 24). These include the therapies listed below which target the macrovascular complications of diabetes:

- For older adults with diabetes target A1c should be <7.5% if generally healthy, <8% if multiple coexisting chronic illness, high risk for hypoglycemia and fall, and < 8.5% if limited life expectancy (5, 24).
- Use of daily aspirin for primary prevention of cardiovascular disease is no longer recommended because the increased risk of bleeding outweighs the reduction in cardiovascular events.
- For older adults with diabetes, target blood pressure should be <140/90 mm Hg if tolerated and <150/90 if short life expectancy, end stage chronic disease, or living in a long-term care facility (6). There is a potential harm in lowering the systolic BP <120 mm Hg. The previous systolic BP target <130 mm Hg did not show a better cardiovascular outcome for individuals with diabetes than BP 130-140 mm Hg (70).
- Serum lipids should be treated as well. This includes measurement of an annual fasting lipid panel. Lifestyle modification should be initiated with a focus on heart-healthy diet emphasizing intake of vegetables, fruits, whole grains, legumes, healthy protein sources and oils, as well as increased physical activity. It is recommended to treat all diabetics age 40 and older with statin therapy. Dosing can be moderate-intensity in case of no additional risk factors and high-intensity for patients with additional cardiovascular risk factors. In patients with known atherosclerotic cardiovascular disease (ASCVD) and LDL>70 mg/dl, it is reasonable to add ezetimibe to maximally tolerated statin therapy; if on this combination therapy very high-risk patients still have LDL>70 mg/dl, addition of a PCSK9 inhibitor is reasonable (5, 71). In older adults, lipid lowering therapy should be individualized considering the life expectancy and tolerability (5).
- Tobacco cessation is recommended, and physicians should offer counseling and pharmacological intervention to assist with smoking cessation.

The AGS as well as ADA treatment guidelines also address screening for microvascular complications:

- Retinal exam is recommended at diagnosis and every year in high risk patients (3, 5, 6). This latter group includes elderly diabetic patients with symptomatic eye changes, retinopathy, glaucoma, cataracts, A1c > 8%, type 1 diabetes, and blood pressure above goal (5).
- Foot examination is recommended at least annually (3, 5, 6).
- Screening for microalbuminuria is recommended at diagnosis and annually (3, 5, 6), although there is little evidence supporting

annual microalbuminuria screening in the older adult with limited life expectancy (6).

Finally, the AGS and ADA guidelines recommend education of the patients regarding their diabetes. Education should include home capillary blood glucose monitoring, symptoms, and treatment of hypoglycemia and hyperglycemia, nutrition counseling, exercise, as well as foot care (3, 5, 6).

CONCLUSIONS

The treatment of diabetes in the elderly population depends on clinical recognition and diagnosis of the disease. Individualized treatment goals can be achieved with individualized therapeutic regimens. Lifestyle modification, including diet and exercise, should be the cornerstones of therapy. Care should be taken to avoid complications of therapy, especially hypoglycemia. Finally, prevention of microvascular and macrovascular complications should be undertaken, targeting the multiple contributors noted above, as the elderly diabetic population is especially at risk for these complications.

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REFERENCES

1. Menke A, Casagrade S,,Geiss, L, Cowie CC. Prevalence and Trends in diabetes among adults in the United States, 1988-2012. JAMA. 2015; 314:1021-29.
2. Gregg EW, Engelgau MM, Narayan V. Complications of diabetes in elderly people. BMJ 325:916-917, 2002.
3. American Diabetes Association. Standards of Medical Care in Diabetes- 2020. Diabetes Care 43(Supp1): S14-31, 2020.
4. Laiterpong N, Karter AJ, Liu JY, Mofer HH, Sudore R, Schillinger D, John PM, Huang ES. Correlates of quality of life in older adults with diabetes: the diabetes & aging study. Diabetes Care. 2011; 34: 21749-53..
5. American Diabetes Association. Standards of Medical Care in Diabetes- 2020. Diabetes Care. 43 (Supp 1):S15-22 (classification and diagnosis), S152-62 (older adults)..
6. Guidelines Abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update. JAGS 61:2020-2026, 2013.
7. Egede, LE. Diabetes, major depression, and functional disability among U.S. adults. Diabetes Care 27: 421-8, 2004.
8. Gregg EW, Yaffe K, Cauley JA, et al. Is Diabetes Associated with Cognitive Impairment and Cognitive Decline Among Older Women? Study of Osteoporotic Fractures Research Group. Arch Intern Med 160:174-180, 2000.
9. Chau PH, Woo J, Lee CH, et al. Older people with diabetes have higher risk of depression, cognitive and functional impairment: implication for diabetes services. J Nutr Health Aging 15:751-5, 2011.
10. Ding J, Strachan MW, Reynolds RM, et al. Diabetic retinopathy and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 Diabetes Study. Diabetes 59:2883-9, 2010.
11. Feil DG, Rajan M, Soroka O, et al. Risk of hypoglycemia in older veterans with dementia and cognitive impairment: implication for practice and policy. J Am Geriatr Soc 59:2263-72, 2011.
12. Yaffe K, Falvey CM, Hamilton N, et al. Association between hypoglycemia and dementia in a biracial cohort of older adult with diabetes mellitus. JAMA, 173:1300-6, 2013.
13. Feil D, Unutzer J. Cognitive impairment, chronic medical illness, and risk of mortality in an elderly cohort. Am J Geriatr Psych 11:551-560, 2003.
14. Lu FP, Chan DC, Kuo HK, Wu SC. Sex difference in the impact of diabetes on the risk of geriatric conditions. Geriatr Gerontol Int. 13:116-22, 2013.
15. Pijers E, Ferreira I, De Jongh RT, et al. Older individuals with diabetes have an increased risk of recurrent falls: analysis of potential mediating factor: The Longitudinal Ageing Study Amsterdam. Age Ageing. 41:358-65, 2012.
16. Corriere M, Rooparinesingh N, Kalyani RR. Epidemiology of diabetes and diabetes complications in elderly: an emerging public health burden. Curr Diab Rep, 13: 805-13, 2013.
17. Tinetti ME, Williams TF, Mayewski R. Fall Risk Index for Elderly Patients Based on Number of Chronic Disabilities. Am J Med 80:429-434, 1986.
18. Kalyani RR, Saudek CD, Brancati FL, Selvin E. Association of diabetes, comorbidity and A1c with functional disability in older adults: results from the National Health and Nutrition Examination Survey (NHANES), 1999-20006. Diabetes Care, 33:1055-60, 2010.
19. United Kingdom Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 352:837-853, 1998.
20. Ligthelm RJ, Kaiser M, Vora J, Yale JF. Insulin use in elderly adults: risk of hypoglycemia and strategy for care. J Am Geriatr Soc. 60: 1532-15412, 2012.
21. Munshi N, Florez H, Huang ES. Management of Diabetes in Long-term Care and Skilled Nursing Facilities: A Position Statement of the American Diabetes Association. Diabetes Care 39:308-318, 2016.
22. Pratley RE, Kanapka LG, Rickels MR, et al. Effect of Continuous Glucose Monitoring on Hypoglycemia in Older Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA, 323: 2397-2406, 2020.

23. Selvin E et al. The Burden and Treatment of Diabetes in Elderly Individuals in the U.S., Diabetes Care 21(11):2415-9, 2006.
24. LeRoith D, Biessels GJ, Braithwaite SS, Casaneuva FF, Draznin B, et al. Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2019; 104:1-55.
25. Olson D, Norris S. Diabetes in older adults: Overview of the AGS guidelines for the treatment of diabetes mellitus in geriatric populations. Geriatrics 59:18-24, 2004.
26. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient centered approach. Position statement of the ADA and EASD). Diabetes Care. 35(6):1364-1379, 2012.
27. SE Inzucchi, RM Bergenstal, JB Buse et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, 38:140-149, 2015.
28. Bailey CJ, Turner RC. Metformin. N Engl J Med 334:574-9, 1996.
29. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. 8 April 2016. Accessed at www.fda.gov/Drugs/DrugSafety/ucm493244.htm on 16 June 2016.
30. Kancherla V, Elliott JL Jr., Patel BB, et al. Long-term metformin therapy and monitoring for vitamin B12 deficiency among older veterans. J Am Geritar Soc. doi: 10.111.jgs.14761, 2017.
31. Victoza [package insert]. Princeton, NJ: Novo Nordisk Inc.; Jan 2010.
32. Amblee A. Mode of administration of dulaglutide: implications for treatment adherence. Patient preference adherence. 2016 2:10:975-82.
33. M Diamant, MA Nauck, R Shaginian et al. Glucagon-like peptide receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care. 37:2763-73, 2014.
34. C Eng, CK Kramer, B Zinman and R Retnakaran. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 384:2228-34, 2014.
35. Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? Diabetes Care. 38(7):2118-25, 2013.
36. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol 2018; 6:105-113
37. SP Marso, GH Daniels, K Brown-Frandsen et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. New Engl J Med. 375:311-22, 2016.
38. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. New Engl J Med. 2016; 375:1834-44.
39. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M. Pais P et al. Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND): a double-blind, randomized placebo-controlled trial. The Lancet 2019; 394:121-130.
40. Zinman B, Wanner C, Lachin J. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 373:2117-2128, 2015.
41. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G Desai M, Matthews DR, for the CANVAS Program Collaborative Group. New Engl J Med. 2017; 377:644-57.
42. McMurray JJV, Solomon SD, Inzuchi SE, Kover L, Kosibood MN, Martinez FS, et al for the DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New Engl J Med. 2019; 381:1995-2008.
43. Perkovic V, Jardine JM, Neal B, Bompoint S, et al for the CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New Engl J Med. 2019; 380:2295-306.
44. Dietrich E, Powell J, Taylor JR. Canagliflozin: a novel treatment option for type 2 diabetes. Drug Des Devel Ther. 7:1399-1408, 2013.
45. Sinclair A., Bode B, Harris S, et al. Efficacy and Safety of Canagliflozin in Individuals Aged 75 and Older with Type 2 Diabetes Mellitus: A Pooled Analysis. JAGS. 64:543-552, 2016.
46. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393:31-39)
47. Nateglinide. The Medical Letter. 43(1101): 29-30, 2001.
48. Kahn S, et al. for the ADOPT Study Group. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. N Engl J Med 355:2427-2443, 2006.
49. Nissen S, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. NEJM 356(24):2457-2471, 2007.
50. DeFronzo RA, Inzucchi S, Abdul-Ghani M, Nissen SE. Pioglitazone: The forgotten, cost-effective cardioprotective drug for type 2 diabetes. Diab Vasc Dis Res. 2019 Mar;16(2):133-143. PMID: 30706731.
51. Cusi K, Orsak B, Bril F, et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Int Med. 165(5):305-15, 2016.
52. Budd J, Cusi K. What Does the Primary Care Physician Need to Know? Am J Med. 2020 May;133(5):536-543. PMID: 32017891. 51. Drucker D, Easley C, Kirkpatrick P. Sitagliptin. Nat Rev Drug Dis 6:109-110, 2007.
53. Shankar R, Engel SS, Xu L, et al. Sitagliptin provides similar glycemic improvement with less hypoglycemia in the elderly with type 2 diabetes mellitus compared to sulfonylurea. Diabetes. 61:A278, 2012.
54. Chaicha-Brom T, Yasmeen T. DPP-IV Inhibitor-associated arthralgias. Endocr Pract 2013: 19:377.
55. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med. 173(7):534-9, 2013.
56. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology. 141(1):150-6, 2011.
57. BM Scirica, DL Bhatt, E Braunwald et al. Saxagliptin and Cardiovacscular Outcomes in Patients with Type 2 Diabetes Mellitus. New Engl J Med. 369:1317-26, 2013.
58. WB White, CP Cannon, SR Heller et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. New Engl J Med. 369:1327-35, 2013.

59. JB Green, A Bethel, PW Armstrong et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. New Engl J Med. 373:232-242, 2015.
60. Rosenstock J, Perkovic V, Johansen OE. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA. 2019 Jan 1;321(1):69-79.
61. Riddle M et al. Treat to Target. Diabetes Care. 26:3080-3086, 2003.
62. Brunner GA, Hirschberger S, Sendlhofer G, Wutte A, Ellmerer M, Balent B, Schaupp L, Krejs GJ, Pieber TR. Post-prandial administration of the insulin analogue insulin aspart in patients with Type 1 diabetes mellitus. Diabetic Medicine. 17(5):371-375, 2000.
63. Garg SK, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. Endocrine Practice. 11(1):11-17, 2000.
64. Sakharova O, Inzucchi S. Treatment of diabetes in the elderly: Addressing its complexities in this high-risk group. Postgraduate medicine 119:19-29, 2005.
65. Mushi M, Slyne C, Segal A. Simplification of insulin regime in older adults and risk of hypoglycemia. JAMA Intern Med. 174:1116-1124, 2014.65. Lipska KJ, Yao X, Herin J, McCoy RG, Ross JS, Steinman MA, Inzucchi SE, Gill TM, Krumholz HM, and Shah ND. Trends in Drug Utilization, Glycemic Control, and Rates of Severe Hypoglycemia, 2006013. Diabetes Care 2017; 40:468-75.
66. McCoy RG, Lipska KJ, Van Houten HK, Shah ND. Paradox of Glycemic Management: Multimorbidity, glycemic control, and high risk medication use among adults with diabetes. BMJ Open Diab Res Care.2020; 8:e001007, doi:10.1136/bmjdrc-2019-001007.
67. Derosa G, Maffioli P. α-Glucosidase inhibitors and their use in clinical practice. Arch Med Sci. 8(5):899-906, 2012.
68. Riddle MC and Drucker DJ. Emerging Therapies Mimicking the Effects of Amylin and Glucagon-Like Peptide 1. Diabetes Care. 29:535-49, 2006.
69. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 329: 977-986, 1993.
70. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA., 304:61-68, 2010.
71. Grundy SM, Stone NJ, Bailey AL, Beam C, et al. 2018 Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol. 2018; DOI: 10.1016/j.jacc.2018.11.003.