The Pathophysiology of Hyperglycemia in Older Adults: Clinical Considerations

Pearl G. Lee[1,2] and Jeffrey B. Halter[2]

Diabetes Care 2017;40:444–452 | DOI: 10.2337/dc16-1732

Nearly a quarter of older adults in the U.S. have type 2 diabetes, and this population is continuing to increase with the aging of the population. Older adults are at high risk for the development of type 2 diabetes due to the combined effects of genetic, lifestyle, and aging influences. The usual defects contributing to type 2 diabetes are further complicated by the natural physiological changes associated with aging as well as the comorbidities and functional impairments that are often present in older people. This paper reviews the pathophysiology of type 2 diabetes among older adults and the implications for hyperglycemia management in this population.

Diabetes is one of the leading chronic medical conditions among older adults, with high risk for vascular comorbidities such as coronary artery disease, physical and cognitive function impairment, and mortality. Despite decades of effort to prevent diabetes, diabetes remains an epidemic condition with particularly high morbidity affecting older adults. In fact, nearly 11 million people in the U.S. aged 65 years or older (more than 26% of adults aged 65 years or older) meet current American Diabetes Association criteria for diabetes (diagnosed and undiagnosed), accounting for more than 37% of the adult population with diabetes (1). At the same time, adults 65 years or older are developing diabetes at a rate nearly three-times higher than younger adults: 11.5 per 1,000 people compared with 3.6 per 1,000 people among adults aged 20–44 years old (1). However, increasing research in diabetes and aging has improved our understanding of the pathophysiology of diabetes and its association with aging and led to the development of a number of antihyperglycemic medications. The mechanism of diabetes complications has been previously reviewed (2). The current paper reviews the pathophysiology of type 2 diabetes among older adults and the implications for hyperglycemia management in this population.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes is by far the most prevalent form of diabetes in older adults and is an age-related disorder. The criteria for diagnosing diabetes are the same for all age groups because the risks of diabetes-related complications are associated with hyperglycemia over time across all age groups (3). Older adults are at high risk for the development of type 2 diabetes due to the combined effects of genetic, lifestyle, and aging influences. These factors contribute to hyperglycemia through effects on both β-cell insulin secretory capacity and on tissue sensitivity to insulin. The occurrence of type 2 diabetes in an older person is complicated by the comorbidities and functional impairments associated with aging.

Hyperglycemia develops in type 2 diabetes when there is an imbalance of glucose production (i.e., hepatic glucose production during fasting) and glucose intake (i.e.,

[1]Geriatric Research Education and Clinical Center, VA Ann Arbor Healthcare System, Ann Arbor, MI
[2]Division of Geriatric and Palliative Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

Corresponding authors: Pearl G. Lee, pearllee@med.umich.edu, and Jeffrey B. Halter, jhalter@med.umich.edu.

Received 10 August 2016 and accepted 20 January 2017.

See accompanying articles, pp. 440, 453, 461, 468, 476, 485, 494, 502, 509, 518, and 526.

food ingestion) as opposed to insulin-stimulated glucose uptake in target tissues, mainly skeletal muscle. Multiple factors in an older person contribute to such an imbalance of glucose regulation, as illustrated by Fig. 1. Although resistance to peripheral insulin action contributes to altered glucose homeostasis, current evidence has found that the direct effect of aging on diabetes pathophysiology is through impairment of β-cell function, resulting in a decline in insulin secretion.

GENETICS

There is a strong genetic predisposition to type 2 diabetes (4). The genetic susceptibility to type 2 diabetes is polygenic, involving a number of variants, where each allele has a modest effect on the risk of disease in an individual person. Genome-wide association studies, linkage analysis, candidate gene approach, and large-scale association studies have identified ~70 loci conferring susceptibility to type 2 diabetes (5). These genetic alleles appear to affect the risk of type 2 diabetes primarily through impaired pancreatic β-cell function, reduced insulin action, or obesity risk.

Genome-wide association studies have consistently found that $p16^{INK4a}$, a cyclin-dependent kinase inhibitor (CDKI), encoded by the *Cdkn2a* locus, is associated with type 2 diabetes risks (6). Expression of $p16^{INK4a}$ was increased in aging mice (7), and an additional copy of $p16^{INK4a}$ was associated with markedly reduced pancreatic islet cell proliferation (8). β-Cell proliferation was increased in $p16^{INK4a}$ knockout mice. Therefore, $p16^{INK4a}$ increases with age and appears to mediate an age-associated decline in the replicative capacity of mouse islets; $p16^{INK4a}$ could be a potential link between aging, metabolic derangements, and β-cell failure in type 2 diabetes.

EFFECTS OF AGING

Impaired Insulin Secretion, Insulin Resistance, and Their Interaction

In the setting of genetic and lifestyle-related risk factors, aging contributes to the development of type 2 diabetes through impaired β-cell function and impaired β-cell adaptation to insulin resistance (9,10) leading to impaired insulin secretion (11,12), as illustrated in Fig. 1. Studies in rodents and humans have found that aging may exert a distinct influence on β-cell turnover as well as function.

In older patients who have developed diabetes, autoimmune destruction of β-cells is rarely observed. Limited pathologic investigation suggests that total β-cell mass may be moderately reduced, but severe loss of β-cell mass is uncommon. Pancreatic β-cell mass in adult humans exists in a dynamic state such that the cells can undergo compensatory changes to maintain euglycemia. Aging is thought to be associated with reduced capacity to regenerate β-cells, as suggested by studies involving rodents (13–15) and humans (16–18). On the one hand, for example, the β-cell toxin streptozotocin, partial pancreatectomy, or exendin-4 were more effective in stimulating β-cell proliferation in younger mice (younger than 12 months old) than in older mice (13–15,19). On the other hand, the age-associated decline in β-cell function in older rats has been shown to be reversible with glucagon-like peptide 1 (GLP-1; exendin) treatment (20), suggesting stimulation of β-cell regeneration (21). In humans, the baseline β-cell population and appropriate association with other islet cell types is established before 5 years of age (22). Other studies using C^{14} or Ki67 have found that human adult β-cell turnover is very low (16,17,22,23). Similarly among middle-aged and older adults, minimal β-cell regeneration was observed after a mean follow-up period of 1.8 ± 1.2 years after a 50% partial pancreatectomy: β-cell mass and new β-cell formation were not increased, and β-cell turnover was unchanged (18). The follow-up time of this study may have been too short for human β-cells to replicate, but other studies have also found evidence of slow β-cell proliferation in humans with advancing age (24,25). The decline in β-cell replication was directly associated with a decrease in the expression of a transcription factor known as the pancreatic and duodenal homeobox 1 (pdx1) (26). Thus, the overall evidence suggests that human β-cells survive for a long time and are unlikely to be replenished by replications once adulthood is reached (27). Several age-related potential molecular pathways have been found to restrict β-cell regeneration. For example, the replication refractory period, the time between cell divisions (G0 stage of cell cycle), appears to lengthen with age (28); the replicative capacity of β-cells might be reduced due to accumulation of DNA mutations with aging.

Therefore, β-cell function in human adults might be enhanced in the setting of hyperglycemia or insulin resistance to maintain euglycemia. Pancreatic β-cells appear to primarily compensate for

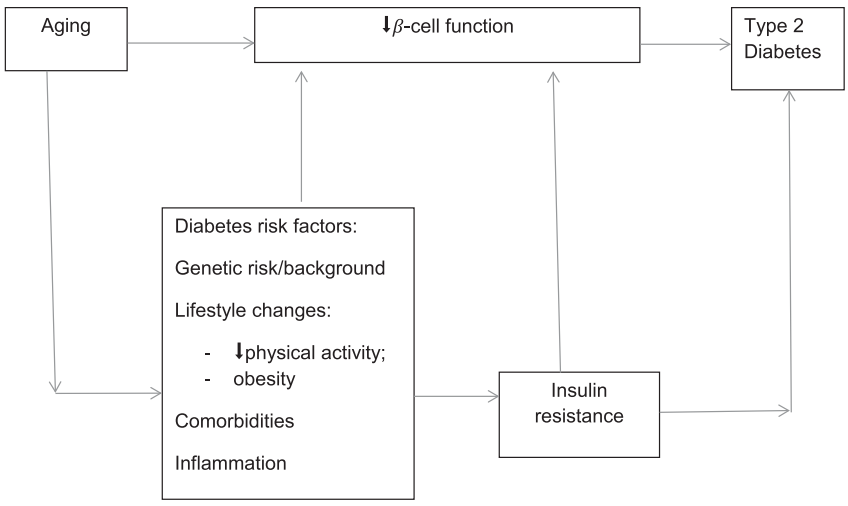

Figure 1—Model for age-related hyperglycemia (12). Aging has direct effects on β-cell proliferation and function and contributes indirectly to impaired insulin sensitivity through lifestyle-related and comorbidity-related risk factors. The insulin resistance in turn may contribute to further impairment of β-cell function.

limited replication capacity through hyperplasia and hypertrophy. However, a number of studies have demonstrated a decline in β-cell function and insulin secretion with age in rodents (26). In humans, as shown in Fig. 2, the insulin secretion rate in response to glucose was significantly and progressively decreased in older individuals, with the greatest impairment in older individuals with impaired glucose tolerance compared with older individuals with normal glucose tolerance or with younger individuals matched for degree of insulin resistance (9). In fact, a 50% reduction in β-cell secretory capacity has been observed in older men compared with younger men in response to arginine stimulation (29).

Impaired pancreatic β-cell adaptation to insulin resistance appears to be an important contributing factor to age-related glucose intolerance and risk for diabetes. Although aging per se has a minimal effect on insulin action directly (30), many older individuals develop insulin resistance as a result of diminished physical activity, obesity, and loss of lean body mass, particularly those with a disproportional loss of skeletal muscle over adipose tissue. Age had no independent effect on insulin sensitivity when controlled for obesity; age-related reductions in insulin sensitivity are likely the result of an age-related increase in adiposity rather than a consequence of advanced chronological age (31).

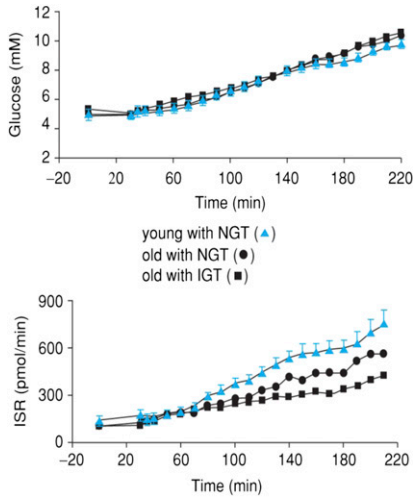

Figure 2—Impaired β-cell function in human aging: response to nicotinic acid–induced insulin resistance. Reprinted with permission from Chang et al. (9). Plasma glucose concentrations and insulin secretion rate (ISR) are shown over time during intravenous glucose infusions, comparing young people (mean age, 26 years) with normal glucose tolerance (NGT; *n* = 15) and old people (mean age, 70 years) with NGT (*n* = 16) or with impaired glucose tolerance (IGT; *n* = 14). Glucose levels during the variable glucose infusion rate and degree of insulin resistance were similar in the three study groups. ISR was significantly and progressively decreased in the two older groups, with the greatest impairment in old IGT. *P* = 0.0002, old IGT vs. young and old IGT vs. old NGT; and old NGT vs. young NGT. Data are means ± SE.

Insulin resistance with aging appears to reflect predominantly lifestyle factors such as poor diet and diminished physical activity. These changes lead to decreased lean body mass and increased adiposity, particularly visceral adiposity, with aging. More than 35% of U.S. adults aged 60 years or older are obese, having a BMI of 30 kg/m^2 or greater (3). An absolute or relative increase of body adiposity, particularly central body adiposity, often associated with advancing age, appears to account in large part for the age-related increase in insulin resistance (32,33). Even among adults without diabetes, intraabdominal fat mass correlates with insulin resistance and age after controlling for obesity (34). However, insulin resistance is more closely associated with abdominal adiposity than with age (35,36). In addition to excessive caloric intake, increased body adiposity is partly related to a sedentary lifestyle, which is common among older adults; for example, only 12% of adults aged 75 or older engage in 30 min of physical activity 5 or more days per week, and 65% report no leisure time physical activity (37). Increasing physical activity in older adults reduces insulin resistance (38), reduces the risk of developing diabetes (39), and improves glycemic control in people with diabetes (40).

Low-grade inflammation and stress-response changes associated with obesity and aging are likely to contribute to the increased risk of type 2 diabetes among older adults (41). Aging and obesity are both thought to be independently associated with the development of low-grade inflammation (42), and proinflammatory cytokines, such as C-reactive protein, interleukin 6, and tumor necrosis factor-α, have been found to inhibit insulin signaling and increase insulin resistance and risk of type 2 diabetes (41,43).

The role of mitochondrial function in aging and type 2 diabetes remains unclear. Older adults were found to have a decrease in mitochondrial function compared with younger adults (i.e., decreased ATP synthesis); however, older adults with normal glucose tolerance had similar ATP production level compared with older adults with impaired glucose tolerance (44). On the other hand, exercise reverses age-related declines in mitochondrial oxidative capacity and ATP production, which may be part of the underlying mechanism through which exercise improves insulin sensitivity (44,45).

As summarized in Fig. 1, there is a maladaptive response to insulin resistance in the setting of impaired β-cell function leading to further impairment of insulin secretion and progression to impaired glucose tolerance and type 2 diabetes. Hyperglycemia, in turn, contributes directly to insulin resistance and impairs pancreatic β-cell function, effects described as glucose toxicity (46). Such glucose toxicity sets up a vicious cycle of maladaptive mechanisms leading to further deterioration of β-cell function and more severe insulin resistance.

COMORBIDITIES AND THEIR EFFECT ON INSULIN SENSITIVITY AND SECRETION

Coexisting illness is another factor that can affect insulin sensitivity and insulin secretion in an older person. Hypertension, for example, is common in older people and has been associated with diminished insulin sensitivity (47). Furthermore, any acute illness can precipitate hyperglycemia because of effects of stress hormones to cause insulin resistance combined with the α-adrenergic effects of catecholamines released during stressful illness to inhibit insulin secretion.

Medications used in treating chronic medical conditions may induce or increase insulin resistance or worsening hyperglycemia among patients with diabetes. Glucocorticoids, for example, promote hepatic gluconeogenesis, thus increasing hyperglycemia, and contribute to insulin resistance by increasing visceral fat and promoting proteolysis, lipolysis, free fatty acid production, and fat accumulation in the liver (48).

Impaired glucose regulation over time leads to overt diabetes, which in turn leads to microvascular or macrovascular complications. Diabetes-associated complications, along with other comorbidities prevalent among older adults, such as arthritis, cognitive impairment, and depression, may contribute to decreased physical activity and disability (49). All of these changes can further impair glucose regulation and adversely affect glycemic management.

IMPLICATIONS FOR MANAGEMENT OF TYPE 2 DIABETES AMONG OLDER ADULTS

General Approach

The complexity of diabetes and its management requires a collaborative effort by a team of health care providers, which may include physicians, nurse practitioners, nurses, dietitians, pharmacists, social workers, and mental health professionals. Patients and family members must also assume an active role (50). When developing a treatment plan, in addition to targeting the various factors involved in the pathophysiologic pathways of type 2 diabetes, providers should address other relevant comorbid conditions that are common among older adults and can easily affect the ability of the patient to manage diabetes. Aging is associated with increasing risk of developing geriatric syndromes, such as visual impairment, cognitive impairment, and functional impairment, and diabetes is also associated with an increased risk of retinopathy (51) and deficits in cognitive and physical functioning (52). Geriatric syndromes will in turn affect the ability of older adults to manage their diabetes. Such limitations may affect a patient's ability to obtain food or medications, to exercise, or to see his or her health care providers.

Because older adults with diabetes are quite heterogeneous with respect to their health status and available care support, the goal for hyperglycemia management should be individualized based on their comorbidities and physical and cognitive function status. A comprehensive geriatric assessment (53) will help the providers to assess an older patient's ability to safely follow a complex diabetes treatment plan. Given that type 2 diabetes develops after years of metabolic abnormalities, a thorough medical evaluation in search for existing diabetes complications is warranted even when a new diagnosis is made in an older adult. The clinical assessment is used to recommend individualized glycemic, blood pressure, and lipid goals for older adults with diabetes. An interdisciplinary expert panel that included geriatricians, endocrinologists, and other diabetes health care providers was convened by the American Diabetes Association at a Consensus Development Conference on Diabetes and Older Adults in 2012. This group developed a framework to set diabetes treatment goals based on individual patients' comorbidities and physical and cognitive function status (54,55).

Lifestyle Interventions

Lifestyle interventions, including regular physical activity and mild-moderate weight loss, are the first-line intervention for diabetes prevention and for treatment of hyperglycemia in older people. Lifestyle interventions are particularly effective in reducing the risk of developing diabetes among older adults (39,56) and are also beneficial in improving diabetes management among older adults (57). Lifestyle interventions can reduce insulin resistance and thereby help reverse the vicious cycles in Fig. 1. However, there is no evidence that lifestyle interventions can reverse the effects of aging on β-cells; thus, such interventions may delay, but are not likely to completely prevent, the ultimate development of hyperglycemia.

Physical Activity

Regular physical activities for older adults with diabetes, particularly activities of moderate to vigorous intensity, can improve insulin sensitivity (38). Regular physical activities are a useful adjunct to drug therapy to manage glucose levels and may well contribute to enhanced effectiveness of glucose-lowering agents. Furthermore, increasing physical activity as part of a lifestyle intervention is effective in reducing physical functioning impairment among patients with diabetes, improving glucose, lipid, and blood pressure control, and enhancing weight loss (40,56,58–60).

Traditionally, aerobic training activities have been recommended for older adults, given their benefits in cardiorespiratory fitness. Evidence also supports regular whole-body resistance training for older adults with type 2 diabetes. As previously discussed, the pathophysiology of type 2 diabetes involves insulin resistance, and the main tissues in the body that are sensitive to insulin are muscles and adipose cells. Resistance training changes body composition (e.g., increases skeletal muscle mass), improves insulin sensitivity, and reduces HbA_{1c} (61,62).

In fact, physical activity programs that include both aerobic and resistance training improve glycemic levels more than aerobic or resistance training alone (63,64). Thus, the American Diabetes Association recommends that all adults with diabetes should perform at least 150 min/week of moderate-intensity aerobic physical activity, spread over at least 3 days/week with no more than 2 consecutive days without exercise. As part of the exercise routine, resistance training should be performed at least twice weekly (65).

Given the high prevalence of coronary artery disease in older patients with diabetes, which may be asymptomatic or atypical in symptoms, it is important for such patients to have medically supervised stress testing before entering any challenging exercise training program. Additional issues to consider in an older person participating in an exercise program include the potential for foot and joint injury with upright exercise, such as jogging, unstable comorbidities, autonomic neuropathy, peripheral neuropathy, or foot lesions that may predispose to injures, and the ability to promptly identify and treat hypoglycemia, which can be induced by exercise if the patient is on insulin or a sulfonylurea. Therefore, each patient's exercise prescription needs to be individualized based on his or her capability to safely participate in an exercise program.

Obesity and Diet

Even a modest to moderate body weight loss (5–10% of initial body weight) increases insulin sensitivity and improves glucose tolerance in obese individuals as well as in those with impaired glucose tolerance or type 2 diabetes (66). As part of diabetes management, the American Diabetes Association recommends that overweight adults with type 2 diabetes lose 2–8 kg weight through lifestyle changes (65). Recent studies have not substantiated previous concerns about the risks of weight loss among older adults, where older adults who intentionally lost weight by combining caloric restriction and exercise had minimal reduction in

lean muscle mass and actually had increased bone density and improvement in physical function compared with individuals who lost weight by caloric restriction alone or by exercise alone (67–69). Hence, weight loss programs for older adults with diabetes should incorporate caloric restriction with physical activity.

Caloric restriction is appropriate for healthier overweight and obese older diabetes patients as part of management of hyperglycemia but is not appropriate for some older patients who are at risk for undernutrition already. More pressing dietary issues for these patients are how to maintain adequate caloric intake and coordinate food intake with administration of glucose-lowering agents appropriately to avoid hypoglycemia. Older adults with mobility limitation or who lack transportation are likely to have limited access to healthy and fresh food (70). Social isolation (i.e., living alone, eating alone), poverty, and functional reliance on others to purchase food are all risk factors for decreased food intake. The presence of impaired cognitive function may make following a dietary prescription particularly difficult. Furthermore, dietary habits established for a lifetime and often with a cultural background may be particularly difficult to modify. Problems with taste and oral health, which are common in older people, may further limit adaptation to a prescribed diet (71). Oral health problems can be exacerbated by diabetes, which may increase the rate of periodontal disease. Xerostomia is also more common in older people owing to decreased salivary gland flow and is sometimes exacerbated by coexisting medication use.

MEDICATIONS IN THE MANAGEMENT OF HYPERGLYCEMIA

Most medications to treat hyperglycemia in older adults with type 2 diabetes target one or more of the pathophysiological impairments of age-related type 2 diabetes: reducing hepatic glucose production, increasing insulin secretion, increasing insulin sensitivity, decreasing glucagon secretion, increasing incretin levels, and decreasing satiety. Unfortunately, older patients are often underrepresented in large clinical trials; therefore, data on antihyperglycemic medications are often extrapolated from younger populations (72).

Treatment of older adults with diabetes needs to account for the progression of type 2 diabetes over time (73). Because of the age-related decline of β-cell function, maintaining target levels of glycemic control may necessitate escalation of drug doses or the addition of other antihyperglycemic agents (74). Thus, medications that target the β-cells, such as sulfonylureas or GLP-1–related drugs, are likely to become less effective over time. Medications such as metformin, thiazolidinediones (TZDs), and sodium glucose transporter 2 (SGLT2) inhibitors may help to reverse some of the vicious cycles contributing to hyperglycemia but do not directly address the effects of aging on β-cells.

A review of the pharmacologic treatment for hyperglycemia is beyond the scope of this article but has been extensively discussed elsewhere (75,76). Tables 1 and 2 list most of the currently available antihyperglycemic agents (noninsulin and insulin), including a brief description of the physiological action of the medication and the advantages and disadvantages of the agent when used by older patients. Treatment choices should be tailored to the specific situation of the individual patient, as determined in part by the initial comprehensive assessment of the patient's comorbidities, cognition, functional status, care support, and financial situation (55). Although it is common for an older adult to have multiple comorbidities, impairment in cognition or functional status, and limited financial support, a strong supportive care system may be sufficient to help the patient to safely implement a complex medical treatment plan.

The treatment plan should minimize risk for hypoglycemia, especially in frail, vulnerable older patients and when using agents with high risk for hypoglycemia such as insulin and sulfonylureas. Thus, emphasis on lifestyle interventions and classes of drugs that do not cause hypoglycemia can often result in safe achievement of lower A1C targets, especially early in the course of type 2 diabetes. As these safer interventions become less effective as a result of progressive β-cell failure with aging, insulin may be needed, and the A1C target may need to be higher to avoid hypoglycemia. Sulfonylurea drugs should be used only with extreme caution in any vulnerable older patient. Frequent follow-up should be provided to ensure that the treatment program is progressing smoothly and that hypoglycemia does not occur.

Biguanides

Metformin, a biguanide, is the first-line oral medication for hyperglycemia for older adults (76). Because metformin's mechanism of action predominately involves reducing hepatic glucose production, it rarely causes hypoglycemia when used alone. Some older patients may experience intolerable gastrointestinal discomfort, decreased appetite, and modest weight loss associated with metformin.

Metformin is contraindicated in patients with renal insufficiency, and the U.S. Food and Drug Administration recommends against the use of metformin in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2. Furthermore, metformin is recommended to be discontinued at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m^2, and can be restarted if the eGFR is stable 48 h after the imaging procedure.

Sulfonylureas

Sulfonylureas are probably overused in older adults with type 2 diabetes. These drugs are inexpensive, and their overall safety record is good. Their primary mechanism of action is to enhance insulin secretion by β-cells of the pancreas. Hypoglycemia is a serious risk, however, and conservative use is thus recommended for older people. Glyburide is associated with a high risk for hypoglycemia in older patients due to its long half-life so is not recommended in this population (77). Other sulfonylureas may be safer to use in older patients, but all have a hypoglycemia risk. Another concern about use of sulfonylurea drugs in older adults is a higher secondary failure rate than other drugs, probably related to progressive β-cell dysfunction (78).

TZDs

TZDs improve insulin sensitivity in skeletal muscle, reduce hepatic glucose production, and have the advantages of low risk for hypoglycemia. However, concerns over potential adverse effects associated with TZDs have been raised, including increased risks of bladder cancer, weight gain, fluid retention, and bone fractures (75). TZDS are usually

Table 1—Noninsulin antihyperglycemic agents (75,76)

Class	Primary physiological action	Advantages	Disadvantages
• Biguanide • Metformin	• ↓Hepatic glucose production, possible ↑insulin-mediated uptake of glucose in muscles	• No weight gain Minimal hypoglycemia Likely ↓in both microvascular and macrovascular events Extensive clinical experience	• Gastrointestinal side effects (diarrhea and abdominal discomfort) Lactic acidosis (rare) Contraindicated in renal insufficiency, liver, or cardiac failure
• Sulfonylureas • Glipizide • Glyburide • Glimepiride • Gliclazide[a]	• ↑Insulin secretion from pancreatic β-cells	• ↓Microvascular events Extensive clinical experience	• Hypoglycemia (esp. with longer half-life: glyburide) Weight gain Skin rash (including photosensitivity)
• Meglitinides • Repaglinide • Nateglinide	• ↑Insulin secretion from pancreatic β-cells	• ↓Postprandal glucose excursions Dosing flexibility (before meals)	• Hypoglycemia Weight gain Frequent dosing schedule
• TZDs • Pioglitazone • Rosiglitazone[b]	• ↑Insulin sensitivity	• Minimal hypoglycemia ↑HDL-C ↓Triglycerides (pioglitazone)	• Weight gain Edema/heart failure Bone fractures ↑LDL-C (rosiglitazone) ?↑MI
• DPP-4 inhibitors • Sitagliptin • Saxagliptin • Vildagliptin[a] • Linagliptin • Alogliptin[c]	• ↑Insulin secretion (glucose-dependent) ↓Glucagon secretion (glucose-dependent)	• Minimal hypoglycemia Well tolerated Once-daily dosing	• Urticaria/angioedema ?Increased risk of pancreatitis ?↑Heart failure hospitalization High cost
• GLP-1 receptor agonists • Exenatide (Byetta) • Exenatide extended release • Liraglutide • Dulaglutide • Albiglutide • Lixisenatide[a]	• ↑Insulin secretion (glucose-dependent) ↓Glucagon secretion (glucose-dependent) Slows gastric emptying ↑Satiety	• Minimal hypoglycemia Weight reduction ↓Postprandial glucose excursions	• Gastrointestinal adverse effects (nausea, vomiting) ↑Heart rate ?Acute pancreatitis C-cell hyperplasia/ medullary thyroid tumors in animals
• α-Glucosidase inhibitors • Acarbose • Miglitol	• Slows intestinal carbohydrate digestion or absorption	• Minimal hypoglycemia ↓Postprandial glucose excursions ?↓CVD events (STOP-NIDDM)	• Generally modest A1C reduction Flatulence Abdominal discomfort Contraindicated in cirrhosis Frequent dosing schedule (with meals)
• Bile acid sequestrant[d] • Colesevelam	• Unclear ?↓Hepatic glucose production ?↑Incretin levels	• Minimal hypoglycemia ↓LDL-C	• Generally modest A1C efficacy Constipation ↑Triglycerides Reduced absorption of fat-soluble vitamins High cost
• Dopamine-2 agonist • Bromocriptine, immediate release form[c]	• Modulates hypothalamic regulation of metabolism ↑Insulin sensitivity	• Minimal hypoglycemia	• Nausea, headache, orthostatic hypotension, potential exacerbation of psychosis High cost
• Amylin-like • Pramlintide[c]	• ↓Glucagon secretion Slows gastric emptying ↑Satiety	• ↓Postprandial glucose excursions Weight reduction	• GI adverse effects (nausea, vomiting) ↑Hypoglycemic risk of insulin Frequent dosing schedule High cost
• SGLT-2 inhibitors • Canagliflozin • Empagliflozin • Dapagliflozin	• ↓Glucose reabsorption by the kidney ↑Urinary glucose excretion	• Minimal hypoglycemia Weight reduction ↓Blood pressure Effective at all stages of T2D Once-daily dosing	• Caution in patients with renal insufficiency Genitourinary infections Genital yeast infections Polyuria Hyperkalemia Orthostatic hypotension Pancreatitis

CVD, cardiovascular disease; GI, gastrointestinal; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; MI, myocardial infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; T2D, type 2 diabetes. [a]Not licensed in the U.S. [b]Prescribing highly restricted in the U.S.; withdrawn in Europe. [c]Not licensed in Europe. [d]Limited use in the U.S. and Europe.

Table 2—Insulin for treatment of type 2 diabetes (75,76)

Insulin agents	Onset of action	Peak effect	Duration of action
• Long-acting			
Glargine 100	About 2 h	No peak	20 to >24 h
Detemir	About 2 h	3–9 h	6–24 h†
• Ultra-long-acting			
Degludec	About 2 h	No peak	>40 h
Glargine 300	About 6 h	No peak	28–36 h
• Intermediate-acting			
Human NPH	About 2 h	4–12 h	18–28 h
Neutral protamine lispro**	About 2 h	6 h	15 h
• Short-acting			
Human regular	About 30 min	2–4 h	5–8 h
• Rapid-acting Lispro Aspart Glulisine	5–15 min	45–75 min	2–4 h
• Inhalation powder Human insulin#	5–15 min	50 min (wide variation)	2–3 h

The insulin agents lead to increased glucose disposal and decreased hepatic glucose production. They are nearly universal responsive and likely lead to ↓microvascular risk (UK Prospective Diabetes Study [UKPDS]). Disadvantages are hypoglycemia risks, which varies based on the individual agent's dose and its course of the action **Only available in the U.S. in a premixed combination with insulin lispro. #Inhaled human insulin (Afrezza) is contraindicated in patients with chronic lung disease such as asthma or chronic obstructive pulmonary disease. †Duration of action is dose dependent; at ≥0.8 units/kg, mean duration of action is longer and less variable: 22 to 23 h).

not considered as first-line antihyperglycemic agents.

GLP-1 Agents

GLP-1 is an incretin, an intestinal hormone that is released as glucose levels increase with meals and cause glucose-dependent insulin secretion; therefore, GLP-1 agents are unlikely to cause hypoglycemia. Two classes of GLP-1 drugs are used clinically:

1. The injectable GLP-1 receptor agonists stimulate insulin section in a glucose-dependent fashion, suppress glucagon output, slow gastric emptying, and decrease appetite. These agents have the advantages of modest weight loss, but for some patients, the weight loss can be too much and there may be resistance against performing injections.
2. The oral dipeptidyl peptidase-4 (DPP-4) inhibitors enhance circulating concentrations of active GLP-1.

When used alone, both classes of GLP-1 agents rarely cause hypoglycemia, but high cost may be prohibitive for some older adults. Pilot studies of myocardial ischemia and animal studies suggested that GLP-1 agonists may improve cardiovascular outcomes, but the results from two recent large trials are mixed. Among patients with type 2 diabetes and high cardiovascular risk, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was lower with liraglutide than with placebo (79), but among patients with type 2 diabetes and recent acute coronary syndrome, no significant effect on the rate of major cardiovascular events was found with lixisenatide compared with placebo (80).

SGLT-2 Inhibitors

SGLT-2 inhibitors allow the kidneys to reabsorb most filtered glucose. SGLT-2 is found only in the proximal tubule of the kidney and accounts for 90% of the reabsorption of glucose. SGLT-2 inhibitors are oral agents that lower glucose levels by increasing urinary excretion of glucose. They are approved for use in both type 1 and type 2 diabetes. They are used once daily, result in modest lowering of A1C similar to DPP-4 inhibitors, and rarely cause hypoglycemia. They are contraindicated in chronic kidney disease. These agents increase urine volume and sodium excretion, so usually lower blood pressure modestly but may cause volume depletion. This volume effect may contribute to increased risk for diabetic ketoacidosis in people with type 1 diabetes. There is increased risk for genital yeast infection and urinary tract infection, likely resulting from the induced glycosuria. Because of these adverse effects, relatively high cost, and limited experience with these drugs in older adults, their use is usually reserved for situations in which other classes of drugs are not tolerated.

Insulin

Because β-cell dysfunction plays a major role in type 2 diabetes in older adults, insulin replacement therapy may be necessary to achieve the goal for hyperglycemia control, especially in patients with longer duration of type 2 diabetes with progressive β-cell dysfunction. The approach to use of insulin in older adults with type 2 diabetes is to start with a once-daily, long-acting insulin (basal insulin), with minimal peak or trough effect. Long-acting agents, such as insulin glargine 100 and detemir insulin, have a lower incidence of nocturnal hypoglycemia than shorter-acting insulin agents, even among older adults (81).

Premeal injections of a rapid-acting insulin analog can be added to the basal insulin, if necessary, in older patients in whom the physician has determined can safely administer insulin and monitor for hypoglycemia. Insulin aspart and insulin lispro have a very rapid onset and short duration of action and are used just before meals. They are less likely to result in postmeal hypoglycemia than human regular insulin (82). These rapid-acting insulin agents can be given within 20 min after starting a meal, and hence, are particularly useful in older patients who may not eat regularly.

Combination Therapy

Use of combination antihyperglycemic agents in older patients may be necessary with the progression of the disease. Combinations of different classes of drugs are theoretically attractive because their different modes of action address various aspects of the pathophysiology of hyperglycemia. For older patients who have persistent hyperglycemia (above their individualized A1C target) with lifestyle intervention and metformin (if not contraindicated), adding another agent would be recommended. The options include adding an oral agent such as short-acting

sulfonylurea (i.e., glipizide), DPP-4 inhibitors (83), or SGLT2 inhibitors (75). Alternatively, a basal insulin, such as glargine, may be added (75). If a sulfonylurea is already being used, we would recommend tapering it to discontinue because a combination of sulfonylurea and insulin greatly increases the risk of hypoglycemia (84).

CONCLUSIONS

Older adults are at high risk for the development of type 2 diabetes as a result of the combined effects of genetic, lifestyle, and aging influences. Despite the advancement in understanding the pathophysiology of type 2 diabetes, more research is needed to elucidate the underlying molecular mechanisms of how aging is related to type 2 diabetes and to diabetes-related complications (45). Prevention of type 2 diabetes and treatment of hyperglycemia in older adults should emphasize lifestyle interventions based on the pathophysiology of the development of type 2 diabetes and their numerous benefits on the overall health of older adults. With the aging of β-cell function, the addition of one or more medications to achieve glycemic control targets may be needed. However, the overall management of hyperglycemia needs to be individualized for older adults based on individuals' likelihood of benefiting from tight control versus the risks associated with implementing complex management regimens, especially when insulin or a sulfonylurea drug is included. A comprehensive assessment involving the individual's comorbidities and geriatric syndromes, including cognitive and functional status, can help tailor the treatment plan.

Funding. P.G.L. was supported by the VA Career Development Award 1IK2RX001190-01A2. The contents do not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.

Conflict of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. P.G.L. and J.B.H. researched the data, wrote the manuscript, and reviewed and edited the manuscript.

References

1. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA, U.S. Department of Health and Human Services, 2014
2. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev 2013;93:137–188
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006;29(Suppl. 1):S43–S48
4. Medici F, Hawa M, Ianari A, Pyke DA, Leslie RD. Concordance rate for type II diabetes mellitus in monozygotic twins: actuarial analysis. Diabetologia 1999;42:146–150
5. Billings LK, Florez JC. The genetics of type 2 diabetes: what have we learned from GWAS? Ann N Y Acad Sci 2010;1212:59–77
6. Zeggini E, Weedon MN, Lindgren CM, et al.; Wellcome Trust Case Control Consortium (WTCCC). Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007;316:1336–1341
7. Krishnamurthy J, Torrice C, Ramsey MR, et al. Ink4a/Arf expression is a biomarker of aging. J Clin Invest 2004;114:1299–1307
8. Krishnamurthy J, Ramsey MR, Ligon KL, et al. p16INK4a induces an age-dependent decline in islet regenerative potential. Nature 2006;443:453–457
9. Chang AM, Smith MJ, Galecki AT, Bloem CJ, Halter JB. Impaired beta-cell function in human aging: response to nicotinic acid-induced insulin resistance. J Clin Endocrinol Metab 2006;91:3303–3309
10. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999;104:787–794
11. Basu R, Breda E, Oberg AL, et al. Mechanisms of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. Diabetes 2003;52:1738–1748
12. Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab 2003;284:E7–E12
13. Teta M, Long SY, Wartschow LM, Rankin MM, Kushner JA. Very slow turnover of beta-cells in aged adult mice. Diabetes 2005;54:2557–2567
14. Rankin MM, Kushner JA. Adaptive beta-cell proliferation is severely restricted with advanced age. Diabetes 2009;58:1365–1372
15. Tschen SI, Dhawan S, Gurlo T, Bhushan A. Age-dependent decline in beta-cell proliferation restricts the capacity of beta-cell regeneration in mice. Diabetes 2009;58:1312–1320
16. Saisho Y, Butler AE, Manesso E, Elashoff D, Rizza RA, Butler PC. β-Cell mass and turnover in humans: effects of obesity and aging. Diabetes Care 2013;36:111–117
17. Perl S, Kushner JA, Buchholz BA, et al. Significant human beta-cell turnover is limited to the first three decades of life as determined by in vivo thymidine analog incorporation and radiocarbon dating. J Clin Endocrinol Metab 2010;95:E234–E239
18. Menge BA, Tannapfel A, Belyaev O, et al. Partial pancreatectomy in adult humans does not provoke beta-cell regeneration. Diabetes 2008;57:142–149
19. Saisho Y, Manesso E, Butler AE, et al. Ongoing beta-cell turnover in adult nonhuman primates is not adaptively increased in streptozotocin-induced diabetes. Diabetes 2011;60:848–856
20. Wang Y, Perfetti R, Greig NH, et al. Glucagon-like peptide-1 can reverse the age-related decline in glucose tolerance in rats. J Clin Invest 1997;99:2883–2889
21. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. Diabetes 1999;48:2270–2276
22. Gregg BE, Moore PC, Demozay D, et al. Formation of a human β-cell population within pancreatic islets is set early in life. J Clin Endocrinol Metab 2012;97:3197–3206
23. Meier JJ, Butler AE, Saisho Y, et al. Beta-cell replication is the primary mechanism subserving the postnatal expansion of beta-cell mass in humans. Diabetes 2008;57:1584–1594
24. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102–110
25. Reers C, Erbel S, Esposito I, et al. Impaired islet turnover in human donor pancreata with aging. Eur J Endocrinol 2009;160:185–191
26. Gunasekaran U, Gannon M. Type 2 diabetes and the aging pancreatic beta cell. Aging (Albany, NY) 2011;3:565–575
27. Kushner JA. The role of aging upon β cell turnover. J Clin Invest 2013;123:990–995
28. Salpeter SJ, Klein AM, Huangfu D, Grimsby J, Dor Y. Glucose and aging control the quiescence period that follows pancreatic beta cell replication. Development 2010;137:3205–3213
29. Chen M, Bergman RN, Pacini G, Porte D Jr. Pathogenesis of age-related glucose intolerance in man: insulin resistance and decreased beta-cell function. J Clin Endocrinol Metab 1985;60:13–20
30. Ferrannini E, Vichi S, Beck-Nielsen H, Laakso M, Paolisso G, Smith U; European Group for the Study of Insulin Resistance (EGIR). Insulin action and age. Diabetes 1996;45:947–953
31. Karakelides H, Irving BA, Short KR, O'Brien P, Nair KS. Age, obesity, and sex effects on insulin sensitivity and skeletal muscle mitochondrial function. Diabetes 2010;59:89–97
32. Petersen KF, Shulman GI. Etiology of insulin resistance. Am J Med 2006;119(Suppl. 1):S10–S16
33. Kanaya AM, Harris T, Goodpaster BH, Tylavsky F, Cummings SR; Health, Aging, and Body Composition (ABC) Study. Adipocytokines attenuate the association between visceral adiposity and diabetes in older adults. Diabetes Care 2004;27:1375–1380
34. Cefalu WT, Wang ZQ, Werbel S, et al. Contribution of visceral fat mass to the insulin resistance of aging. Metabolism 1995;44:954–959
35. Coon PJ, Rogus EM, Drinkwater D, Muller DC, Goldberg AP. Role of body fat distribution in the decline in insulin sensitivity and glucose tolerance with age. J Clin Endocrinol Metab 1992;75:1125–1132
36. Kohrt WM, Kirwan JP, Staten MA, Bourey RE, King DS, Holloszy JO. Insulin resistance in aging is related to abdominal obesity. Diabetes 1993;42:273–281
37. Conn VS, Minor MA, Burks KJ, Rantz MJ, Pomeroy SH. Integrative review of physical activity intervention research with aging adults. J Am Geriatr Soc 2003;51:1159–1168
38. Kahn SE, Larson VG, Beard JC, et al. Effect of exercise on insulin action, glucose tolerance, and insulin secretion in aging. Am J Physiol 1990;258:E937–E943

39. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
40. Armstrong MJ, Colberg SR, Sigal RJ. Moving beyond cardio: the value of resistance training, balance training, and other forms of exercise in the management of diabetes. Diabetes Spectr 2015;28:14–23
41. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444:860–867
42. de Rekeneire N, Peila R, Ding J, et al. Diabetes, hyperglycemia, and inflammation in older individuals: the Health, Aging and Body Composition Study. Diabetes Care 2006;29:1902–1908
43. Snijder MB, Heine RJ, Seidell JC, et al. Associations of adiponectin levels with incident impaired glucose metabolism and type 2 diabetes in older men and women: the Hoorn Study. Diabetes Care 2006;29:2498–2503
44. Ghosh S, Lertwattanarak R, Lefort N, et al. Reduction in reactive oxygen species production by mitochondria from elderly subjects with normal and impaired glucose tolerance. Diabetes 2011;60:2051–2060
45. Halter JB, Musi N, McFarland Horne F, et al. Diabetes and cardiovascular disease in older adults: current status and future directions. Diabetes 2014;63:2578–2589
46. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54:1615–1625
47. Ferrannini E, Buzzigoli G, Bonadonna R, et al. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350–357
48. Mazziotti G, Gazzaruso C, Giustina A. Diabetes in Cushing syndrome: basic and clinical aspects. Trends Endocrinol Metab 2011;22:499–506
49. Fried LP, Bandeen-Roche K, Kasper JD, Guralnik JM. Association of comorbidity with disability in older women: the Women's Health and Aging Study. J Clin Epidemiol 1999;52:27–37
50. Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51(5 Suppl. Guidelines):S265–280
51. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
52. Lee PG, Cigolle CT, Ha J, et al. Physical function limitations among middle-aged and older adults with prediabetes: one exercise prescription may not fit all. Diabetes Care 2013;36:3076–3083
53. Elsawy B, Higgins KE. The geriatric assessment. Am Fam Physician 2011;83:48–56
54. Blaum C, Cigolle CT, Boyd C, et al. Clinical complexity in middle-aged and older adults with diabetes: the Health and Retirement Study. Med Care 2010;48:327–334
55. Kirkman MS, Briscoe VJ, Clark N, et al.; Consensus Development Conference on Diabetes and Older Adults. Diabetes in older adults: a consensus report. J Am Geriatr Soc 2012;60:2342–2356
56. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–1686
57. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:543–551
58. Colberg SR, Albright AL, Blissmer BJ, et al.; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Med Sci Sports Exerc 2010;42:2282–2303
59. Diabetes Prevention Program Research Group, Crandall J, Schade D, Ma Y, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. J Gerontol A Biol Sci Med Sci 2006;61:1075–1081
60. Rejeski WJ, Ip EH, Bertoni AG, et al.; Look AHEAD Research Group. Lifestyle change and mobility in obese adults with type 2 diabetes. N Engl J Med 2012;366:1209–1217
61. Hovanec N, Sawant A, Overend TJ, Petrella RJ, Vandervoort AA. Resistance training and older adults with type 2 diabetes mellitus: strength of the evidence. J Aging Res 2012;2012:284635
62. Mavros Y, Kay S, Anderberg KA, et al. Changes in insulin resistance and HbA1c are related to exercise-mediated changes in body composition in older adults with type 2 diabetes: interim outcomes from the GREAT2DO trial. Diabetes Care 2013;36:2372–2379
63. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA 2010;304:2253–2262
64. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med 2007;147:357–369
65. American Diabetes Association. Foundations of care and comprehensive medical evaluation. Sec. 3. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S23–S35
66. Ryan AS. Insulin resistance with aging: effects of diet and exercise. Sports Med 2000;30:327–346
67. Waters DL, Ward AL, Villareal DT. Weight loss in obese adults 65 years and older: a review of the controversy. Exp Gerontol 2013;48:1054–1061
68. Nicklas BJ, Chmelo E, Delbono O, Carr JJ, Lyles MF, Marsh AP. Effects of resistance training with and without caloric restriction on physical function and mobility in overweight and obese older adults: a randomized controlled trial. Am J Clin Nutr 2015;101:991–999
69. Houston DK, Leng X, Bray GA, et al.; Action for Health In Diabetes (Look AHEAD) Movement and Memory Ancillary Study Research Group. A long-term intensive lifestyle intervention and physical function: the Look AHEAD Movement and Memory Study. Obesity (Silver Spring) 2015;23:77–84
70. Huang DL, Rosenberg DE, Simonovich SD, Belza B. Food access patterns and barriers among midlife and older adults with mobility disabilities. J Aging Res 2012;2012:231489
71. Institute of Medicine, Food and Nutrition Board, Food Forum. Pillsbury L, Miller EA, Boon C, Pray L, Eds. *Providing Healthy and Safe Foods As We Age: Workshop Summary*. Washington, D.C., National Academies Press, 2010
72. Saunders C, Byrne CD, Guthrie B, et al.; Scottish Diabetes Research Network Epidemiology Group. External validity of randomized controlled trials of glycaemic control and vascular disease: how representative are participants? Diabet Med 2013;30:300–308
73. U.K. Prospective Diabetes Study Group. U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249–1258
74. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005–2012
75. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
76. American Diabetes Association. Approaches to glycemic treatment. Sec. 7. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S52–S59
77. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–2246
78. Kahn SE, Haffner SM, Heise MA, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443
79. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
80. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257
81. Lee P, Chang A, Blaum C, Vlajnic A, Gao L, Halter J. Comparison of safety and efficacy of insulin glargine and neutral protamine hagedorn insulin in older adults with type 2 diabetes mellitus: results from a pooled analysis. J Am Geriatr Soc 2012;60:51–59
82. Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. Diabetes Obes Metab 2012;14:780–788
83. Wu D, Li L, Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Obes Metab 2014;16:30–37
84. Mogensen UM, Andersson C, Fosbøl EL, et al. Sulfonylurea in combination with insulin is associated with increased mortality compared with a combination of insulin and metformin in a retrospective Danish nationwide study. Diabetologia 2015;58:50–58