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REVIEW

Optimal management of type 2 diabetes in patients with increased risk of hypoglycemia

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Abstract: With the number of individuals diagnosed with type 2 diabetes on the rise, it has become more important to ensure these patients are effectively treated. The Centers for Disease Control and Prevention estimated that 8.3% of all Americans were diagnosed with diabetes in 2011 and this number will likely continue to rise. With lifestyle interventions, such as proper diet and exercise, continuing to be an essential component of diabetes treatment, more patients are requiring medication therapy to help them reach their therapeutic goals. It is important for the clinician, when determining the treatment strategy for these individuals, to find a balance between reaching treatment goals and limiting the adverse effects of the treatments themselves. Of all the adverse events associated with treatment of diabetes, the risk of hypoglycemia is one that most therapies have in common. This risk is often a limiting factor when attempting to aggressively treat diabetic patients. This manuscript will review how hypoglycemia is defined and categorized, as well as discuss the prevalence of hypoglycemia among the many different treatment options.

Keywords: type 2 diabetes, hypoglycemia

Introduction

In 2011, approximately 8.3% of all Americans were diagnosed with diabetes and diabetes reported as the seventh leading cause of death and disability in the US.[1,2] The prevalence of diabetes is projected to increase to nearly one-third of the population by 2050.[3] Long-term complications of poorly controlled diabetes (glycated hemoglobin [A1C] >7%) include microvascular complications (retinopathy, neuropathy, and nephropathy) and macrovascular complications (cardiovascular, cerebrovascular, and peripheral vascular diseases). These complications have been associated with a 2.0–4.0 fold increase in premature cardiac disease and death versus non-diabetics.[1] Intensive treatment to improve glycemic control has been shown to prevent or delay disease onset and help mitigate progression of these lifelong complications.[4,5] The leading limitation to intensive glucose lowering is the increased risk for hypoglycemia. Individuals with diabetes need their treatment optimized to achieve and maintain euglycemia safely.[6] This manuscript will discuss treatment options available in the US for type 2 diabetes and their potential likelihood for hypoglycemia.

Hypoglycemia

According to the American Diabetes Association (ADA), hypoglycemia is defined as a plasma glucose value of less than 70 mg/dL. These guidelines further define mild hypoglycemia as when the patient has the ability to self-treat the condition by ingesting

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glucose- or carbohydrate-containing foods. Severe hypoglycemia is defined as a life-threatening emergency when the patient needs assistance of another person to administer therapy due to confusion or unconsciousness; in these cases in which the patient is not able to be treated with oral carbohydrates, they should be treated using intravenous glucose or emergency glucagon kits.[7]

Incidence

Event rates for severe hypoglycemia during aggressive insulin therapy in type 2 diabetes vary greatly and it is difficult to derive comparable data due to differing study designs, populations, and definitions of hypoglycemia. Some studies indicate a range from 3% to 10%, but other cases demonstrate 73 episodes per 100 patient years.[8–10] Most episodes of hypoglycemia in type 2 diabetes are considered mild to moderate.[11] In addition to hypoglycemia with insulin therapy, the rate of hypoglycemic events has been reported to be as high as 20% with some oral agents, such as glyburide, which may even compromise initiation of or titration to intensive oral therapy.[12]

Symptoms and consequences of hypoglycemia

Acute symptoms of hypoglycemia derive from the activation of the autonomic central nervous system (neurogenic) and commonly present as shakiness, palpitations, sweating, and anxiety (Table 1). Neuroglycopenic symptoms are derived from the brain's deficiency of glucose and present as blurred vision, dizziness, confusion, and can lead to seizures and loss of consciousness.[13]

Hypoglycemia has also been shown to be associated with long term complications, such as provoking major cardiovascular and cerebrovascular events including myocardial infarction, acute heart failure, ventricular arrhythmias, and stroke.[14–16] Another hypoglycemia-related consequence is weight gain. As reported by the Diabetes Control and Complications Trial (DCCT), it appears that more weight gain is seen in intensively treated type 1 diabetics who experienced at least one severe hypoglycemic episode than in diabetics without a severe hypoglycemic episode.[17] This occurrence may be secondary to patients increasing their food intake to prevent a hypoglycemic episode. Severe hypoglycemia has also been associated with an increased risk of mortality, as shown in Campbell et al, who found that sulfonylurea-induced severe hypoglycemia increases mortality by 9%.[18]

Table 1 Hypoglycemia signs and symptoms[13,19]

Early neurogenic symptoms	Neuroglycopenic signs
Shakiness	Confusion
Irritability	Difficulty speaking
Sweating	Disorientation
Palpitations	Dizziness
Pallor	Seizures
Hunger	Loss of consciousness
Anxiety	Coma

Risk factors for hypoglycemia

Many factors can put type 2 diabetics at increased risk of experiencing hypoglycemia. These factors include administering too much insulin or insulin-producing medications, delayed or missed meal intake or eating a smaller meal than planned, unplanned strenuous exercise, alcohol consumption, and interactions with other drugs. Patient-specific risk factors are also recognized to increase the risk of hypoglycemia, including advanced age, nutritional status, long duration of diabetes, renal or hepatic disease (may alter the metabolism or excretion of medications), and a history of previous hypoglycemic episodes.[20–24]

Hypoglycemia and special populations

There are many special populations who are at increased risk for episodes of hypoglycemia. Those with mental illness and cognitive impairment have been shown to be at greater risk making it important for health care providers to seek treatment regimens that will help reduce this concern.[25] The elderly may suffer from treatment related hypoglycemia, which may be more severe in those patients who are hospitalized and have a poor prognosis.[26] Minority populations may also suffer from the effects of hypoglycemia secondary to poverty and low literacy levels directly affecting medication access and compliance.[27] In addition, glycemic control in pregnancy is a known concern and is assessed between the 24th and 28th week of gestation. Even though the effects of hypoglycemia in pregnancy have not been well defined in the literature, patients more prone to hypoglycemia were found to be younger and have more comorbidities.[28]

Hypoglycemia treatment

Mild hypoglycemia (patient can self-treat) is managed with the oral administration of 15–20 grams of carbohydrates (four teaspoons of sugar or glucose).[29] It is important to recognize that the ingestion of added fat may slow the glycemic response. After ingesting carbohydrates, it is recommended to check blood glucose in 15 minutes before determining if treatment needs to be repeated. Once glucose is restored and

symptoms are resolved, it is recommended to consume a meal or snack to help avoid hypoglycemia recurrence.[7] If severe hypoglycemia occurs, as defined previously, rapid treatment is necessary. Treatment with glucagon intramuscularly may be administered by a family member at home followed by replenishment of glucose once the patient is able to eat. If the patient does not respond to glucagon therapy then intravenous glucose will likely be needed.[30]

Pharmacologic treatments for diabetes and their associated risk of hypoglycemia

Biguanides

Metformin

The American Association of Clinical Endocrinologists (AACE) and the ADA recommend metformin as initial therapy after lifestyle modification for type 2 diabetes in appropriate patients (Table 2). Metformin inhibits hepatic glycogenolysis, gluconeogenesis, and enhances insulin sensitivity in muscle and adipose tissue.[23,50,51] An A1C decrease of between 1% to 1.5% may be seen with this agent.[28] When used as monotherapy, it has a minimal risk for hypoglycemia. When compared with placebo, hypoglycemia was reported in less than 5% of patients taking metformin alone. Since metformin enhances insulin sensitivity, when combined with other medications that increase circulating levels of insulin, the risk of hypoglycemia increases.[34] Metformin does not induce weight gain, making it an optimal agent in obese patients. A modest decrease (10%–30%) in triglyceride levels is also seen.[52–55] Common side effects include diarrhea, bloating, and nausea. An extremely rare but serious side effect of metformin therapy is lactic acidosis (0.03 cases per 1,000 patient years).[56] Because of this risk, metformin should not be used in patients with renal or hepatic diseases, alcoholism, or in unstable or hospitalized patients with congestive heart failure (CHF).

Thiazolidinediones (TZDs)

Pioglitazone and rosiglitazone

Pioglitazone is considered as second-line therapy to be added to metformin if target A1C is not met, or may be used as first-line therapy in patients who cannot take metformin by AACE/ADA guidelines.[23] TZDs increase glucose transporter expression on the cell surface of muscle, liver, and adipose tissues, causing enhanced insulin sensitivity and glucose uptake into these tissues.[23,50,51] These medications reduce A1C by 1% to 1.5% and, similar to metformin, these agents carry a low risk of hypoglycemia when used in monotherapy.[51] Pioglitazone has been associated with significant improvements in plasma lipids independent of glycemic control, but also causes an increase in weight.[57,58] Other adverse effects include fluid retention, CHF, and bone fractures.[59] Concerns over an increased risk of a heart attack with rosiglitazone led to its restricted use through the Avandia-Rosiglitazone Medicines Access Program (REMS).[57]

Dipeptidyl peptidase-4 (DDP-4) inhibitors

Sitagliptin, saxagliptin, linagliptin, and alogliptin

Agents in this class may be used as first-line therapy in patients who cannot take metformin, but are otherwise second line agents.[23] The DDP-4 enzyme is responsible for the breakdown of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucagon-dependent insulinotropic polypeptide (GIP). DDP-4 inhibitors therefore enhance circulating concentrations of active GLP-1 and GIP, indirectly doing some of the same actions as the GLP-1 agonists.[60] In addition, slightly lower rates of A1C reductions are seen with these agents between 0.5% to 1%.[51] DDP-4 inhibitors generally do not cause hypoglycemia when used as monotherapy, are weight neutral, and relatively well tolerated.[61]

Alpha-glucosidase inhibitors

Acarbose and miglitol

These agents are third-line therapies because of their lower or equivalent overall glucose lowering effectiveness compared to other therapies and/or their limited clinical data or relative expense.[23] This class of medications competitively block the brush border alpha-glucosidase enzymes necessary for the breakdown of complex carbohydrates and thus slows glucose absorption after meal ingestion.[23] Moderate reductions in A1C of 0.5% to 1% are expected.[62] Since the mechanism of these agents does not increase circulating insulin levels, the risk of hypoglycemia is very low.[63] However, should a patient experience hypoglycemia, it cannot be treated with sucrose, or table sugar (which is hydrolyzed to glucose and fructose), since the absorption is inhibited by the mechanism of these medications. Hypoglycemic episodes must be treated with simple sugars, such as oral glucose (dextrose).[31] Other common adverse effects include bloating, abdominal pain, and flatulence.[23]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Canagliflozin

The ADA guidelines do not mention this agent, as these guidelines were published before the approval of SGLT2 inhibitors.

Table 2 Glucose lowering medications for type 2 diabetes mellitus[23,28,31–49]

Class	Specific agents	Expected A1C reduction	Principal mechanisms of action	Doses*	Notable adverse effects	Monitoring	Weight and lipid effects	Hypoglycemia risk
Oral agents that do not induce hypoglycemia								
Biguanides	Metformin (Glucophage)	1% to 1.5%	Decreases hepatic glucose production (major); increase uptake of glucose from blood into tissues (minor)	Initial: 500 mg PO BID or 850 mg once daily Max: 2,550 mg/day	GI side effects (diarrhea, bloating, nausea) Lactic acidosis (rare)	Renal and hepatic function	Weight loss; slight decrease in triglycerides	Low
Thiazolidinediones	Pioglitazone (Actos)	1% to 1.5%	Increases insulin-mediated glucose uptake into adipose tissues and skeletal muscles (major); decreases hepatic glucose production (minor)	Initial: 15 mg PO once daily Max: 45 mg/day	Volume retention, heart failure, fracture risk Pioglitazone: possible increase in bladder cancer risk	Hepatic function	Weight gain Pioglitazone: may decrease triglycerides and increase HDL-C	Low
	Rosiglitazone*** (Avandia)			Initial: 4 mg PO once daily Max: 8 mg/day	Rosiglitazone: increased risk of heart attack			
Dipeptidyl peptidase-4 Inhibitors	Sitagliptin (Januvia)	0.5% to 1%	Increases incretin hormones, enhances glucose-dependent insulin secretion, and decreases glucagon release	Initial: 25 mg PO once daily Max: 100 mg/day	Well tolerated	Renal function	Weight neutral	Low
	Saxagliptin (Onglyza)			Initial: 2.5 or 5 mg PO once daily Max: 5 mg/day				
	Linagliptin (Tradjenta)			Initial: 5 mg PO once daily Max: 5 mg/day				
	Alogliptin (Nesina)			Initial: 25 mg PO once daily Max: 25 mg/day				
Alpha-glucosidase inhibitors	Acarbose (Precose)	0.5% to 1%	Reduces intestinal carbohydrate digestion/ absorption	Initial: 25 mg PO TID Max: 300 mg/day	GI symptoms (gas, bloating, diarrhea)	Hepatic function	Weight neutral	Low
	Miglitol (Glyset)							
Sodium-glucose co-transporter 2 inhibitors	Canagliflozin (Invokana)	0.7% to 1%	Reduces reabsorption of filtered glucose, lowers renal threshold for glucose, and increases urinary glucose excretion	Initial: 100 mg PO once daily Max: 300 mg/day	Urinary tract infections, genital fungal infections, slight systolic BP reduction	Renal function	Weight loss; may increase LDL and risk of stroke	Low
Oral agents that may induce hypoglycemia								
Meglitinides	Repaglinide (Prandin)	0.5% to 1% (repaglinide is more effective for lowering A1C than nateglinide)	Increases insulin secretion	Initial: 0.5 mg PO TID with meals if A1C <8%, 1 or 2 mg TID with meals if A1C ≥8% Max: 16 mg/day	Hypoglycemia (less than sulfonylureas)		Weight gain	Moderate (may be less frequent with nateglinide)

	Nateglinide (Starlix)			Initial: 60–120 mg PO TID with meals Max: 120 mg/day				
Oral agents that induce hypoglycemia								
Sulfonylureas**	Glyburide (Diabeta)	1% to 1.5%	Not clearly defined; appears to stimulate release of insulin from the pancreas	Initial: 2.5 mg PO once daily Max: 20 mg/day	Hypoglycemia	Renal function	Weight gain	Highest
	Glipizide (Glucotrol)			Initial: 5 mg PO once daily Max: 40 mg/day				High
	Glimepiride (Amaryl)			Initial: 1 mg PO once daily Max: 8 mg/day				High
Injectable agents that do not induce hypoglycemia								
Glucagon-like peptide-1 receptor agonist	Exenatide (Byetta)	1% to 1.5%	Mimics natural incretin hormones, which enhances glucose-dependent insulin secretion, decreases glucagon release after meals, slows nutrient absorption, increases satiety	Initial: 5 mcg SC BID Max: 10 mcg SC BID	GI symptoms (nausea, vomiting, diarrhea) Possible pancreatitis risk Liraglutide: may be associated with thyroid cancer in rodents	Renal function	Weight loss	Low
	Exenatide extended-release (Bydureon)			Initial: 2 mcg SC once weekly Max: 2 mcg SC once weekly				
	Liraglutide (Victoza)			Initial: 0.6 mg SC once daily for 1 week (to reduce GI symptoms), then 1.2 mg SC once daily Max: 1.8 mg/day				
Injectable agents that cause hypoglycemia								
Amylin analogs	Pramlintide (Symlin)	0.5% to 1%	Analog of natural amylin hormone co-secreted by the pancreas along with insulin	Initial: 60 mcg SC prior to major meals (≥250 kcal or containing ≥30 g carbohydrate) Max: 120 mcg/meal	Nausea; hypoglycemia		Weight loss	High
Insulins	Various types	1.5% to 3.5%	Insulin replacement therapy	Individualized	Hypoglycemia		Weight gain	High

Notes: *Doses (for patients with normal renal/hepatic function) based on most current US product information inserts: **sulfonylureas refers to only the second generation agents and not the older agents (chlorpropamide, tolazamide, tolbutamide), which are rarely used in current practice; ***rosiglitazone is on restricted access by the US Food and Drug Administration.

Abbreviations: BID, twice a day; BP, blood pressure; GI, gastrointestinal; HDL-c, high density lipoprotein cholesterol; LDL, low density lipoprotein; max, maximum; PO, oral administration; sc, subcutaneous; TID, three times daily.

The AACE guidelines base their recommendations on the Phase III clinical trials data for this agent as a second-line therapy to be added to metformin if target A1C is not met, or as first-line therapy in patients who cannot take metformin.[64] These agents decrease plasma glucose by reducing the reabsorption of filtered glucose, lowering the renal threshold for glucose, and increasing urinary glucose excretion. SGLT2 inhibitors have been associated with a decrease in A1C by 0.7% to 1%, weight loss, a slight reduction of systolic blood pressure, and a low risk of hypoglycemia with monotherapy. Canagliflozin may also increase low-density lipoprotein (LDL) and increase risk of stroke. Other adverse effects include urinary tract infections (UTIs) and genital fungal infections.[65,66]

Meglitinides

Repaglinide and nateglinide

These agents are mainly reserved as a second-line therapy to be added to metformin if target A1C is not met, or may be used as first-line therapy in patients who cannot take metformin.[23] Similar to sulfonylureas, meglitinides are insulin secretagogues that work by stimulating rapid insulin release from the pancreatic beta-cells in response to glucose. A decrease in A1C of 0.5% to 1% may be seen when using these medications.[51] Varghese et al reviewed the use of meglitinides in 2,174 patients on antihyperglycemic agents (with or without insulin) over 3 months. They reported 7.1% (1/14) and 7.0% (4/57) of those on nateglinide and repaglinide, respectively, experienced a hypoglycemic occurrence.[67] Compared with sulfonylureas, these agents cause less occurrences of hypoglycemia; however, they pose a similar risk of weight gain.[68] This lower hypoglycemia risk is also thought to be secondary to the rapid onset and short duration of these medications, which also contributes to its more frequent dosing schedule.[69]

Sulfonylureas

Glyburide, glipizide, and glimepiride

The AACE and ADA consider these as second-line therapies to be added to metformin if target A1C is not met, or may be used as first-line therapy in patients who cannot take metformin. Sulfonylureas are insulin secretagogues that appear to work by stimulating insulin secretion from beta cells of the pancreas.[50,51] Typically, monotherapy reduces A1C by 1% to 1.5%.[51] Although these medications are efficacious, hypoglycemia is a very common adverse effect even when administered as monotherapy and the rate of hypoglycemia differs with each sulfonylurea based on each agent's pharmacokinetic properties.[51,70,71] Glyburide has been associated with a higher incidence of hypoglycemia when compared to glipizide (1.9 adjusted relative risk [ARR]), likely due to the accumulation of active metabolites.[72] To help avoid this accumulation, glyburide should be avoided in patients with a creatinine clearance of <50 mL/minute.[73] Glimepiride and glipizide are thought to be better options for patients at increased risk of hypoglycemia; however, they are not risk-free. Inzucchi et al conducted a study to assess hypoglycemia incidence in 2,174 patients receiving antihyperglycemic agents (with or without insulin) over a period of 3 months.[51] They found the incidence of a single episode of hypoglycemia to be 13.6% (8/59), 10.0% (19/190), and 19.1% (18/94) in those taking glimepiride, glipizide, and glyburide, respectively.[51] In addition to hypoglycemia, sulfonylureas also cause significant weight gain, secondary to the increased amount of circulating endogenous insulin.

GLP-1 agonists

Exenatide and liraglutide

The AACE and ADA consider these as second-line therapy to be added to metformin if target A1C levels are not met, or may be used as first-line therapy in patients who cannot take metformin.[23] GLP is a gut derived hormone secreted in response to food ingestion. These agents stimulate the production of insulin in response to high glucose concentrations, inhibit the release of glucagon after meals, slow the rate of gastric emptying, and decrease appetite.[51] This class of medications can decrease A1C between 1% to 1.5%.[74] GLP-1 agonists are associated with a low risk of hypoglycemia and modest weight loss, but cause a relatively high incidence of gastrointestinal disturbances, including nausea, vomiting, and diarrhea.[23] Concerns over the association with liraglutide and thyroid cancer in rodents and the risk of pancreatitis with these agents remains unsettled.[51]

Amylin analogs

Pramlintide

This agent is considered as a third-line therapy because of its lower or equivalent overall glucose lowering effectiveness compared to other therapies and/or their limited clinical data or relative expense.[23] Amylin is a human neuroendocrine hormone that is co-released with insulin from pancreatic beta-cells in a molar ratio of 100:1 (insulin:amylin). Pramlintide is a synthetic analog of amylin and works by slowing gastric emptying, leading to feelings of early satiety, and suppresses postprandial glucagon secretion.[75,76] This agent decreases A1C by 0.5% to 1%, but is associated with a high risk of

hypoglycemia when it is combined with insulin therapy, as US Food and Drug Administration (FDA) indicated.[51] Pramlintide carries a black box warning that when adding pramlintide to insulin, the prandial insulin dose must be reduced by 50% and titrated up to avoid severe hypoglycemia. Other common adverse effects of pramlintide include nausea and vomiting.[23,51]

Insulin

The AACE and ADA guidelines consider insulin, usually basal, as second-line therapy to be added on to metformin or other antidiabetic agents mentioned previously if target A1C is not met, or may be used as first-line therapy in patients who are unlikely to reach their target A1C with additional antidiabetic medications.[23] Insulin therapy mimics physiologic glucose control and is associated with a 1.5% to 3.5% A1C reduction. All insulin analogs are associated with some amount of weight gain and hypoglycemia. Long acting basal insulins, such as insulin glargine and insulin detemir, have a lower risk of hypoglycemia when compared to intermediate-acting neutral protamine Hagedorn (NPH) insulin.[66] In addition, insulin glargine was also associated with a lower hypoglycemia risk when compared to premixed insulin.[77] This lower hypoglycemia risk with long acting insulin is most likely due to the lack of peaks in their pharmacokinetic profiles. In a systematic review of randomized control trials, they looked at insulin monotherapy versus combination therapy with oral agents, and 13 of the 14 studies showed no significant difference in the rates of hypoglycemia between the regimens.[78]

In some cases, patients require the addition of a rapid acting insulin (basal-bolus regimen), which mimics the mealtime insulin response, to achieve optimal glycemic control. Rapid acting insulins include insulin lispro, insulin aspart, and insulin glulisine. These agents are quickly absorbed into the system, and have a rapid onset and shorter duration of action. Based on their pharmacokinetic properties, they reduce postprandial blood glucose excursions and help lower the risk of hypoglycemia between mealtimes. It is imperative that patients eat a meal when they take a dose of rapid-acting insulin to avoid experiencing severe hypoglycemia due to the excess insulin. However, these rapid acting agents are associated with a lower risk of hypoglycemia than for those patients on short-acting regular human insulin. A systematic review found a median 0.3 episodes per 100 person-years in type 2 diabetics for rapid-acting insulins, compared with 4.1 episodes per 100 person-years in type 2 diabetics for short-acting regular insulin.[79] It is also suggested that rapid-acting insulins reduce the risk of nocturnal hypoglycemia. This is based off a study which found that 1.3% of patients experienced major nocturnal hypoglycemic events with insulin aspart versus 3.4% of patients with short-acting regular insulin.[80]

Summary and comparison of hypoglycemia risks with the pharmacotherapy treatment options for diabetes

The highest risks of hypoglycemia have been associated with sulfonylureas and meglitinides, both secondary to increasing the amount of circulating insulin in the body. Both classes of medications have increased the absolute risk of hypoglycemia by 4%–9% compared to placebo or other agents.[81] Sulfonylureas have an 11% higher risk of hypoglycemia than metformin, and a 9% higher risk than TZDs.[82] The risk of hypoglycemia with meglitinides is 6% higher than with metformin.[82]

The rate of hypoglycemia in type 2 diabetics on pramlintide therapy was shown to be two to four times greater than that of placebo.[83,84] To minimize the risk of hypoglycemia, the manufacturer recommends reducing the dose of short-acting insulin by 50% when starting pramlintide.

Metformin, TZDs, GLP-1 inhibitors, DPP-4 inhibitors, alpha-glucosidase inhibitors, and canagliflozin have not been shown to significantly increase the risk of hypoglycemia compared to placebo.[85–89]

Glucose monitoring/goals of therapy

Two essential principles of optimal and safe management of patients at high risk of hypoglycemia are frequently monitoring blood glucose values and individualizing glycemic goals.[90] The ADA recommends the frequency and timing of self-monitoring of blood glucose be individualized and determined by the specific needs of each patient.[7] Frequent self-testing helps recognize the relationship between symptoms with decreases in blood glucose and detects developing episodes, which allows patients to act promptly to help avoid major hypoglycemic events.[91–93]

Longitudinal studies have demonstrated a strong correlation between improved blood glucose control in early disease stages and a reduction in complications.[94] The ADA recommends an A1C goal for most non-pregnant adults to be $<7\%$ to reduce the occurrence of microvascular complications.[7] Selected individuals, such as patients with short duration of diabetes, long life expectancy, and no significant cardiovascular disease (CVD), are appropriate patients to suggest a more stringent A1C goal (such as $<6.5\%$) if this can be achieved without significant hypoglycemia.[7]

However, this benefit does not apply to all patients, in terms of preventing complications and mortality.[94] Other trials demonstrated risks and uncertain safety margins associated with restoring normal blood glucose control with narrow targets in certain specific patient populations with type 2 diabetes.[95–97] Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular diseases, extensive comorbid conditions, and those with a long duration of diabetes in whom achieving the general goal is problematic.[7]

Conclusion

It appears that the diagnosis of diabetes is on the rise in the US and the need for medication treatment for this disease is increasing. The ADA has set specific treatment goals for diabetics, and the aggressive treatment to reach these goals may lead to increased incidences of hypoglycemia. Some medications, such as metformin and DDP-4 inhibitors, do not generally cause hypoglycemia when used as monotherapies; however, many diabetics require additional agents added on to these medications to reach their therapeutic goals. Many other medications, such as sulfonylureas, meglitinides and others, may cause hypoglycemia when used alone to treat diabetes. Insulin therapy will continue to have the highest incidences of hypoglycemia; however, with the use of the new long acting insulins, such as glargine and detemir, these incidences can be reduced. The need for multiple therapies, comorbidities, and lack of patient education will continue to play a role in hypoglycemic incidences. Hypoglycemia will always be a risk when treating diabetes; however, it is important to individualize the treatment strategy for each diabetic to help them achieve their individual treatment goals while minimizing their risk for hypoglycemia.

Disclosure

The authors report no conflicts of interest in this work.

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