JOURNAL OF PALLIATIVE MEDICINE
Volume 14, Number 1, 2011

DOI: 10.1089/jpm.2010.0191

An Approach to Diabetes Mellitus in Hospice and Palliative Medicine

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Abstract

Hospice and palliative medicine practitioners frequently encounter diabetes and associated complications as comorbidities in end-of-life patients. As the patient with diabetes approaches end-of-life, there comes a time when tight glycemic control can not only prove of questionable benefit, but has the potential to cause harm. The medical literature offers little guidance on managing these complications appropriately. This article identifies three distinct classifications of patients with diabetes approaching the ends of their lives due to advanced illnesses. The authors propose a specific framework to guide management in patients with diabetes and advanced disease who are relatively stable, experiencing impending death or organ failure, or actively dying. The authors provide comprehensive information on commonly used diabetic medications, with necessary considerations and dose adjustments for these populations. The goal of the approach is to address individual patient needs, provide guidance for patients and caregivers, and ultimately maximize outcomes for patients with diabetes in the palliative care setting.

Introduction

Practitioners have long been managing patients with diabetes who are at the end of life using guidelines based on the general population of patient with diabetes. As the patient with diabetes approaches the end of life (EOL), there comes a time when tight glycemic control can not only prove of questionable benefit, but has the potential to cause significant morbidity by causing symptomatic hypoglycemia. To date, there is no encompassing, evidence-based literature specifically looking at outcomes in patients with both diabetes and advanced disease, and a number of questions remain as how to best approach glucose management toward the end of life.

Current data from the Centers for Disease Control (CDC) suggest that 23.6 million people in the US over the age of 20 have diabetes. For people over the age of 60, the prevalence of diabetes is estimated at 12.2 million, or 23% of that population.[1] As patients approach EOL, the prevalence of multiple comorbidities increases, thereby increasing the likelihood that practitioners will encounter the dilemma of diabetes management in patients with advanced disease.

Current goals of therapy for patients with diabetes in the general population use hemoglobin A1C with a goal of less than 7 percent. This goal is associated with a significant reduction in long-term microvascular complications; however, the data comes from a general patient-with-diabetes population and may not be translatable to the end-of-life patient population.[2-4]

In patients with advanced life-limiting diseases, as seen by practitioners of hospice and palliative medicine, it is unclear whether tight glycemic control will demonstrate improved outcomes. In fact, tight glycemic control as patients advance throughout the stages of illness may be associated with increased morbidity.[5] This morbidity often manifests itself as typical symptoms of hypoglycemia, including diaphoresis, anxiety, tremors, weakness, palpitations, and, in extreme situations, seizure. At some point in the care of the palliative medicine patient, practitioners must shift their focus from prevention of long-term complications to patient comfort and individualized goals of care.

The Approach

Empiric evidence for the management of diabetes as a comorbidity in advanced disease remains fragmented; however, there is an approach to use with such patients, in the hope of maximizing patient outcomes and properly addressing individual needs. A firm knowledge of the pathophysiology

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Accepted September 2, 2010.

behind diabetes and glucose homeostasis is of paramount importance for developing an appropriate plan of action.

As happens in the care of many patients with life-limiting disease, a prognosis-based system of triage helps guide decision-making. Patients can be categorized into one of three groups (Table 1):

Advanced disease but relatively stable. Prognosis for this group may be anywhere from several months to more than a year. Examples may include advanced dementia or metastatic cancers without organ dysfunction. These patients often have fair calorie intakes, or their caretakers are able to modify an existing medication regimen based on declining function.

Impending death, or organ or system failure. Prognosis for this group is usually measured in weeks and is exemplified by the non-oliguric renal failure patient who declines hemodialysis, or of the patient with widespread multiple myeloma with bone marrow failure. These patients often demonstrate a diminished capacity for oral intake.

Actively dying. This group is typified by the presence of multiple organ failure, obtundation, agonal respirations, etc. This group usually has no capacity for enteral intake.

Management of patients from each of the groups group is unique and requires an individualized approach and care plan.

Managing the Stable Patient with Advanced Disease

Management of the patient with both advanced disease and diabetes can present a number of challenges. Often, this is the longest of the three stages above. Patients in this category may continue to feel as they have for the past several months, due to the insidious nature of their disease.

These patients are inclined to simply continue with their previous regimen, out of deference to their previous training about the importance of glycemic control. Practitioners must use this stage to begin a dialog with patients and caregivers about reducing the intensity of glycemic control. Instruction should focus on the acute prevention of hypoglycemia and maintenance of reasonable prevention of hyperglycemia with levels less than the renal threshold of glucose, which is generally agreed to be around 180mg/dL. There is very little role for A1C in these patients. Patients should be warned of the signs of hypoglycemia, but with the understanding that hypoglycemia unawareness occurs more frequently in the elderly and those with multiple co-morbidities.[6]

The acute risks of hyperglycemia, as experienced in this stage, center mainly on the presence of the hyperosmolar state and associated complications, such as osmotic diuresis, recurrent infection, and poor wound healing.

Type I patients with diabetes will continue to require insulin at this stage of their illness. Caution should be used when using long-acting insulin (NPH), due to the risk of prolonged hypoglycemia from its pharmacodynamic peak. In some cases, a dosage adjustment may be necessary. Rapid-acting insulin may be considered a safer alternative to ensure the patient is tolerating food, as this injection can be administered even after a meal has begun,.[7]

Often, Type I or Type II patients with diabetes can be instructed at this stage to continue with diabetes medications without change if they have demonstrated the ability to look for specific warning signs. If patients are not eating, or have nausea or vomiting, they should be instructed specifically on how to cut back their dosing. Medication dosing should be decreased in patients with worsening renal disease, given the failure to clear insulin. The presence of liver failure should, similarly, prompt the practitioner to cut back on dosing, given the failure of gluconeogenesis and the poor glycogen stores of the liver (Table 2). Patients who are losing weight should, equally, be prompted to discuss how to reduce their medications with their practitioners, as the risk of hypoglycemia will increase.

Mainly, a pleasure-based diet is prescribed to these patients, with a limit on highly concentrated carbohydrates. Finger-stick glucose tests should be used in only specific situations in Type II patients with diabetes, and Type I patients should likely continue their measurements if they are able.

Managing the Patient with Advancing Underlying Disease and Organ Failure

As patients move into this phase, the importance of glycemic control is less apparent and preventing hypoglycemia is of greater significance. Here, also, patient and caregiver education is of vital importance to prevent inappropriate action. The telltale signs of dehydration and hypoglycemia should be discussed, and an appropriate plan of action should be followed if these complications are encountered.

Type I patients with diabetes often have to decrease their insulin administration at this stage. Often, the presence of renal or hepatic failure becomes more evident at this stage and, for reasons listed above, insulin dosages must be reduced to prevent hypoglycemia.

Similarly, Type II patients with diabetes will also have to decrease their anti-diabetic regimens at this stage. Insulin and sulfonylurea agents should be decreased, given the risk of hypoglycemia if patients demonstrate poor calorie intake. If the presence of renal or hepatic failure is suspected, many oral hypoglycemic dosages must be discontinued or attenuated

Table 1. Patient Categories Based on Characteristics and Prognosis

Patient categories based on characteristics	*Prognosis*	*Enteral intake*	*Examples*
Active Disease but Relatively Stable	Several months to more than a year	Fair with sporadic improvements or worsening	Dementia, severe cardiomyopathy, metastatic cancers
Impending Death or Organ or System Failure	Several days to weeks	Declining calorie intake with anorexia	Fulminant liver failure due to hepatitis, bone marrow failure
Actively Dying	Several hours to days	None	Massive intracerebral hemorrhage, obtundation, or agonal respirations

Table 2. Commonly Prescribed Diabetes Medications

Drug class	*Examples*	*Comments*	*Dose considerations*
Insulin *Rapid-acting* *Long-acting*	glulisine, NPH insulin, glargine	Rapid-acting insulin may benefit patients who have erratic appetites or miss meals due to unforeseen nausea or vomiting. Long-acting insulin (glargine) may cause less hypoglycemia, due to "peakless" pharmacodynamics.	Dosage should be adjusted in patients with renal and/or liver dysfunction and stopped altogether in the presence of organ failure. Dose adjustments should be made based on food intake.
Sulfonylureas	glipizide, glimepiride, glyburide	Caution should be taken with agents with long half-lives and active metabolites. Patients may benefit from a shorter-acting agent (glipizide) with inactive metabolites.	Dose should be adjusted in patients with renal and/or liver dysfunction and stopped altogether in the presence of organ failure. Dose adjustments should be made based on food intake.
Meglitinides	repaglinide, nateglinide	May benefit patients who have erratic appetites or unexpectedly may miss meals due to rapid onset and preprandial dosing.	Dose should be adjusted in patients with renal and/or liver dysfunction and stopped altogether if organ failure. Dose adjustments should be made based on food intake but a lower risk of hypoglycemia exists in this class.
Biguanides	metformin	Very low risk of hypoglycemia, but patients may exhibit undesirable weight loss and GI distress. Caution must be taken in patients with compromised renal or liver function due to the risk of lactic acidosis.	Discontinue in patients with hepatic or renal failure. There is a high level of GI intolerability especially at higher doses.
Thiazolidinediones	pioglitazone, rosiglitazone (restricted access)	Very low risk of hypoglycemia, but undesirable fluid retention and edema may occur. Severe caution must be taken in patients with compromised cardiac function, as this class may worsen heart failure. Close monitoring is required.	Discontinue in patients with liver failure and significant cardiac compromise.
Alpha glucosidase inhibitors	acarbose, miglitol	May benefit patients who have erratic appetites or miss meals due to quick onset and dosed with meal. There is an undesirable incidence of GI distress.	Should not be given to patients who are not currently eating.
GLP-1 receptor agonist **Amylin analog**	exenatide, liraglutide, pramlintide,	Long-term data is lacking. Prescribed mostly for post-prandial hyperglycemia Nausea is a commonly encountered side effect. *Warning: Acute pancreatitis and renal failure*	Dose adjust GLP-1 drugs and possibly Amylin analog for renal failure
DPP-IV inhibitor	sitagliptin, saxagliptin	Long-term data is lacking. Prescribed mostly for postprandial hyperglycemia. Nausea is a commonly encountered side effect. *Warning: Acute pancreatitis and renal failure*	Dose must be adjusted for renal and liver failure

here as well. The DPP4 inhibitors and any other potentially nauseagenic medications should likely be purged from the patient's regimen. Table 2 provides a full description of the specific medications to address in the presence of organ failure.

In addition to addressing medication administration, the practitioner should be prompted by worsening anorexia and cachexia to fully liberalize patient diets to the extent that their underlying disease will tolerate.

Finger-stick glucose checks are generally eliminated in Type II patients with diabetes and used only where a decision needs to be made for management in Type I patients with diabetes. Some patients and/or caretakers may find

abandoning glucose monitoring to be distressing as either a marker of severity of underlying disease and life expectancy or loss of locus of control. This topic should act as a springboard for further discussion about goals of care and prognosis where appropriate.

Diabetes Management in the Actively Dying Patient

As in the previous two stages, a consensus on management is lacking for this stage. Most practitioners in this case would simply withdraw all oral hypoglycemics and stop insulin in most cases of Type I and Type II patients with diabetes.

At this point, care is focused on patient comfort and preparatory bereavement counseling for caretakers and patients, where appropriate.

Specific Medication Considerations (Table 2)

Insulin

Insulins are characterized and administered based on their pharmacodynamic actions. While effective in maintaining glucose control, they are limited by side effects, such as hypoglycemia and weight gain. When a Type I patient with diabetes continues to require insulin, the use of a rapid-acting analog (aspart, glulisine, and lispro) is advantageous to someone who has erratic appetites and meal schedules. They can be administered, based on meal-carbohydrate content, even after the patient starts a meal. In a Type I or Type II diabetes patient, a long-acting insulin analog (glargine or detemir), has the advantage of a virtually "peakless" pharmacodynamic profile, which offers an advantage over NPH insulins. The response should be monitored and dose adjusted as needed.[7] Long-acting insulins are adjusted based on fasting blood glucose.

Sulfonylureas

Sulfonylureas are generally effective, well-tolerated, and inexpensive, however, the duration of action and mode of metabolism make them precarious to use in palliative care patients. Sulfonylureas such as chlorpropamide and glyburide have long half-lives and are metabolized by the liver, which confers a high risk of hypoglycemia in this population. Glipizide, a short-acting sulfonylurea, which metabolizes to an inactive metabolite, or glimepiride, a sulfonyurea with dual renal/hepatic clearance, may be considered safer, due to potential lower incidences of hypoglycemia, although caution should still be taken.

Meglitinides

Repaglinide and nateglinide stimulate the pancreas to secrete insulin in a more rapid and shorter duration than sulfonylureas. These agents can be useful in patients with erratic appetites or those who miss multiple meals – they can be given at the first bite of each meal and withheld if the patient skips a meal. Because of their shorter duration of action, these items have a lower risk of hypoglycemia.[8]

Biguanides

Metformin is being widely used to treat Type II diabetes and is quite effective, without producing significant hypoglycemia. Gastrointestinal discomfort can occur in up to 30% of patients and can be managed with appropriate food intake. In patients who already have sporadic appetites and unwanted weight loss, metformin may be undesirable. In addition, a rare but serious side effect of lactic acidosis prohibits the use of metformin in patients with compromised liver or renal function.

Thiazolidinediones

Pioglitazone and rosiglitazone are used as second- or third-line oral agents in the treatment of Type II diabetes. These agents can cause considerable weight gain, mostly from fluid retention and edema. Rosiglitazone has also come under scrutiny as the cause of worsening heart failure, myocardial infarction, and death.

Alpha-glucosidase inhibitors

Acarbose and miglitol reduce the rate of carbohydrate digestion, thereby reducing post-prandial hyperglycemia. They do not cause hypoglycemia when used as monotherapy; however, they produce an unacceptably high incidence of GI distress (flatulence and diarrhea). Reports of liver dysfunction have been documented.

Newer therapies

There is limited data on long-term outcomes of GLP-1 analog (exenatide), amylin analog (pramlintide), and the Di-peptidylpeptidase-IV inhibitor (sitagliptin), which are associated with a significant incidence of nausea. They have the potential to cause hypoglycemia and, more recently, exenatide and sitagliptin have been associated with cases of acute pancreatitis and renal failure, making these agents less desirable for the end-of-life patient.[9]

The Use of Steroids in Patients with Diabetes

Corticosteroids, such as dexamethasone or prednisone, are commonly administered to the palliative care patient. This drug class has the tendency to unmask preexisting diabetes or cause diabetes in certain patient populations. Several mechanisms have been proposed, ranging from increased hepatic glucose production to decreasing tissue responsiveness to insulin. The onset of hyperglycemia varies and can occur as soon as a few hours after dosing to months or years for someone on chronic therapy. The effect is generally considered dose-dependent and clinicians should use the lowest effective dose for an individual patient.

It is important for the prescribing clinician to be aware of the hyperglycemic effects of corticosteroids, and anticipate the need to add or modify existing hyperglycemic therapy.[10] The presence of diabetes Type I or II is not an absolute contraindication for prescribing corticosteroids. Rather, practitioners should address the need for such medications based on patient comfort and goals of care. It is possible that corticosteroid administration may precipitate the need to increase antidiabetic therapy, especially in patients with Type II diabetes.

Conclusion

In conclusion, hospice and palliative medicine practitioners can expect to frequently encounter diabetes and associated complications as comorbidities in end-of-life patients. The medical literature offers little guidance, and is limited, on

appropriately managing these complications. Understanding the pathophysiology of diabetes and having a thorough knowledge of the medications appropriate for use in the end-of-life patient with diabetes should act as a framework for discussions with patients and caregivers and in formulating an appropriate plan of care.

Acknowledgments

The authors would like to acknowledge the support of the Cooper Foundation and Dr. Edward Viner, whose generous support has allowed us to write this manuscript.

Author Disclosure Statement

No competing financial interests exist.

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