INITIAL MANAGEMENT OF SEVERE HYPERGLYCEMIA IN TYPE 2 DIABETES

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CLINICAL RECOGNITION

Type 2 diabetes mellitus (DM) is a common disease affecting 26 million people, 8.3% of the US population. Of these, an estimated 7 million people are undiagnosed.

Type 2 DM typically has two pathophysiologic defects: an insulin secretory defect and insulin resistance. Symptoms of uncontrolled hyperglycemia include polyuria, polydipsia, blurry vision, and possibly dehydration and weight loss. Patients may complain of thirst, sweet cravings, generalized fatigue, abdominal discomfort, and muscle cramps. They may have a history of poor wound healing and/or frequent infections. Basic metabolic laboratory tests may reveal a random blood glucose level over 200 mg/dL [11.1 mmol/L], hyper- or hyponatremia, hypokalemia, metabolic acid-base derangements, and acute renal or prerenal insufficiency. Historical clues for the diagnosis of type 2 DM might include pre-existing history of pre-diabetes, a family history of type 2 diabetes, an ethnicity at higher risk for DM (African-American, Hispanic, Native American, Pacific Islander), a history of gestational diabetes, obesity, and sedentary lifestyle.

PATHOPHYSIOLOGY

Table 1. Clinical Features of the Acute Presentation of Type 2 Diabetes and Pathophysiology	
Hyperglycemia	Insulin resistance, insulin deficiency (pancreatic beta cell failure), increased gluconeogenesis, glycogenolysis
Dehydration, polyuria, polydipsia	Osmotic diuresis, compensatory thirst
Weight loss, sweet cravings	Glycosuric calorie loss and inadequate glucose utilization
Muscle pain and abdominal discomfort	Lactic acid accumulation, hypokalemia, electrolyte /acid-base derangements
Metabolic alkalosis and/or acidosis, electrolyte disturbances	Dehydration and ketogenesis
Ketogenesis	Insulin deficiency resulting in lipolysis yielding free fatty acids, substrate for formation of ketone bodies

DIAGNOSIS AND DIFFERENTIAL

Diabetes can be diagnosed in several ways: 1) Presence of symptoms of hyperglycemia with a random blood glucose of 200 mg/dL [11.1 mmol/L]; 2) fasting blood glucose > 126 mg/dL [7.0 mmol/L; 3) the 75-gram oral glucose tolerance test with a blood glucose > 200 mg/dL [11.1 mmol/L] at 2 hours; 4) hemoglobin A1C value > 6.5%. If asymptomatic, the diagnosis of diabetes is confirmed with two consecutive day abnormal results from the same test or a different test or with two different tests on the same day. If using the hemoglobin A1C for diagnosis, one should be aware of several conditions (some common) making this measure un-interpretable

Adult patients with type 1 and type 2 DM can sometimes present similarly. If a patient presents with hyperglycemia, ketonemia, and metabolic acidosis, distinguishing between types of diabetes is not necessary in this acute setting because initially, both type 1 and type 2 DM are treated with insulin. Later the two diseases may be distinguished with antibody testing although this is neither completely sensitive nor specific. Type 2 DM can also present acutely with a hyperglycemic hyperosmolar state (HHS) with dehydration, altered level of consciousness, and a lesser degree of clinical ketosis than seen in diabetic ketoacidosis (DKA). Consideration for genetic syndromes and concomitant rare conditions of endocrine hormone excess (cortisol, growth hormone, epinephrine, glucagon) leading to hyperglycemia should be in the non-urgent setting for patients with new diagnoses of diabetes.

DIAGNOSTIC TESTS NEEDED AND SUGGESTED

For an acute presentation of diabetes with hyperglycemic symptoms, the patient should have a basic metabolic panel of laboratory tests including glucose, electrolytes, blood urea nitrogen, creatinine, blood and or urinary ketones, liver function tests, and urinalysis. Other testing should be guided by a patient's history and physical exam and might include evaluation for infection or cardiac dysfunction. A hemoglobin A1C reflects the average blood glucose over the last 90 days and is a helpful test. Distinguishing type 1 from type 2 DM can on occasions be difficult but can be assisted with autoantibody testing [tyrosine phosphatase antibody (IA-2) or glutamic acid decarboxylase (GAD) 65 antibody]. The presence of antibody suggests an autoimmune lesion as seen in type 1 DM. In type 1 DM insulin and C-peptide levels are characteristically low, whereas they may be normal or elevated at the onset of type 2 DM.

TREATMENT

Insulin therapy is the initial management choice for patients presenting with hyperglycemia and catabolic symptoms including weight loss. If laboratory abnormalities suggest concurrent DKA or HHS, these must be treated emergently with aggressive saline rehydration, intravenous insulin, potassium and other electrolyte replacement.

For a severely hyperglycemic patient, with a catabolic presentation that usually includes moderate to severe volume depletion, the first therapeutic step is rehydration, usually with intravenous saline. After adequate hydration, therapy with physiologic doses of insulin (0.3-0.4 units per kilogram body weight daily) is recommended. The ideal treatment regimen would be a combination of a long-acting basal insulin plus multiple premeal prandial "bolus" injections to manage meal-related insulin requirements and correction of pre-meal hyperglycemia, referred to as basal-bolus insulin therapy. A good starting place is to prescribe half the total daily insulin dose as basal and the other half as bolus. The combination of long-acting insulin and a rapid acting analogue are good options for basal-bolus therapy. The basal dose is given as a separate injection from the bolus injection.

The premeal "bolus" dose is calculated by summing the dose required to cover the carbohydrate load plus

the dose to correct premeal hyperglycemia and is given as one injection 10-15 minutes before the meal. Particularly with premeal hyperglycemia but even with mealtime glucose levels within target, today's rapid-acting analogues require time for absorption to avoid more severe postprandial hyperglycemia (this is typically called the "lag time"). In an acute setting, and in a less sophisticated patient, it might be more appropriate to begin therapy with a twice-daily pre-mixed insulin. Even though this regimen is not ideal for many for the long-term because it does not allow for sufficient dose titration, this regimen allows approximate physiologic basal-bolus insulin coverage with fewer injections. Nevertheless, if starting with basal-bolus or premixed insulin, it is best to teach the patient to use the strategy of correcting pre-meal hyperglycemia with an additional dose of rapid acting insulin analogue, given 10-15 minutes before the meal. This adds tremendous flexibility to an otherwise rigid regimen.

Until more education is possible, the need to limit high glycemic-load carbohydrate intake (such as with sweetened beverages and juice) should be strongly reinforced with counseling. Certainly, arrangements for general and dietary diabetes education should be made for a newly diagnosed diabetic patient or for a patient new to insulin therapy.

FOLLOW-UP

The patient will use a glucose meter to check his/her fasting and premeal blood glucose levels. For the patient on basal-bolus insulin therapy, he/she will increase bedtime basal insulin doses by 1-2 units every 3 days until fasting blood glucose falls into target range of 90 -130 mg/d [5 – 7.2 mmol/L]. Ideally, bedtime and fasting glucose levels are about the same at the end of the basal insulin titration. If there is a consistent reduction in bedtime to fasting glucose by more than 50 mg/dL [2.8 mmol/L], basal insulin dose is too high.

Adjustments for pre-meal insulin doses are most easily made with an algorithm written clearly for the patient to reference. The importance of injecting the mealtime insulin 10 -15 minutes before eating needs to be emphasized. In contrast to type 1 diabetes where carbohydrate counting is standard, most type 2 patients do well by taking the same mealtime dose or altering up or down based on the size of the meal. For example, one might take 8 units for a smaller meal and 12 units for a large one. If patients feel hypoglycemic symptoms (sweating, shaking, mental fogginess, hunger) despite concurrent blood glucoses levels in the normal range, one could use smaller insulin dose increments to lower blood glucose into the target range more gradually. Generally, increases of insulin dose by10% are well tolerated by patients. Late night snacks without insulin coverage may lead to morning hyperglycemia and interfere with the assessment of the adequacy of the bedtime insulin doses. Correction doses are "trial and error" but most patients with type 2 diabetes require an "insulin sensitivity factor" of 30 (i.e., 30 mg/dL glucose reduction expected from one unit of insulin injected). For example, if additional insulin is provided for premeal glucose levels above 150 mg/dL, 1 extra unit would be given for 150-180 mg/dL, 2 units for 181-210 mg/dL, etc. When starting insulin, it may be appropriate to use a more conservative insulin sensitivity factor such as 40 or 50.

Table 2. Premeal Bolus Dose Calculation Using Rapid-Acting Insulin Analogue

Total premeal insulin dose is sum of:	**Suggested Units**
Meal coverage	5-8 units for smaller meal, 9-12 units for larger meal

Pre meal hyperglycemia correction	1 unit per 30-50 mg/dL above150 mg/dL

Initial diabetes therapy includes counseling for lifestyle and diabetic nutritional interventions. Starting therapy with metformin could also be considered as an adjunctive therapy with insulin to reduce insulin requirements and minimize weight gain. Overtime with lifestyle changes, a decrease in glucose toxicity, and the addition of other hypoglycemic agents some patients who present with very high glucose levels may be able discontinue insulin therapy.

GUIDELINES

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