D.M.

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The term diabetes mellitus describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia.

It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin.

Type 2 diabetes accounts for over 90 percent of cases of diabetes.

type 1 diabetes accounts for another 5 to 10 percent, with the remainder due to other causes.

- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
- Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

- **TYPE 1 DIABETES — Type 1 diabetes is characterized by destruction of the pancreatic beta cells, leading to absolute insulin deficiency. This is usually due to autoimmune destruction of the beta cells (type 1A). Testing for islet cell antibodies (ICA) or other islet autoantibodies (antibodies to glutamic acid decarboxylase [GAD65], insulin, and to the tyrosine phosphatases, IA-2 and IA-2β, and zinc transporter ZnT8) in serum may be helpful if establishing the diagnosis is important; a positive result is indicative of immune-mediated or type 1A diabetes .**
- **However, some patients with absolute insulin deficiency have no evidence of autoimmunity and have no other known cause for beta-cell destruction. They are said to have idiopathic or type 1B diabetes mellitus.**

- **TYPE 2 DIABETES — Type 2 diabetes is by far the most common type of diabetes in adults and is characterized by hyperglycemia and variable degrees of insulin deficiency and resistance. It is a common disorder whose prevalence rises markedly with increasing degrees of obesity. Insulin resistance and insulin deficiency can arise through genetic or environmental influences, making it difficult to determine the exact cause in an individual patient. In addition, hyperglycemia itself can impair pancreatic beta cell function and exacerbate insulin resistance.**

- **DISTINGUISHING TYPE 1 FROM TYPE 2 DIABETES — Patients with type 1 diabetes have an absolute requirement for insulin therapy. However, many patients with type 2 diabetes lose beta cell function over time and require insulin for glucose control. Thus, need for insulin per se does not distinguish between type 1 and type 2 diabetes.**
- **While it is known that diabetic ketoacidosis (DKA) can occur in the presence of complete insulin deficiency, and it is not a typical feature of type 2 diabetes, some patients with type 2 diabetes develop diabetic ketoacidosis under certain circumstances (usually severe infection or other illness). Thus, ketoacidosis cannot be relied upon as an absolute indicator that the patient has type 1 diabetes or that long-term insulin therapy will be required.**

- In addition, patients with type 1 diabetes may coincidentally have pathophysiologic elements of type 2 diabetes. In the past, poor metabolic control of type 1 diabetes prevented most of these patients from gaining weight. Intensive therapy now commonly used to manage type 1 diabetes has resulted in approximately 20 to 30 percent of type 1 diabetic patients becoming overweight or obese. Insulin resistance and other features of type 2 diabetes may be exhibited in overweight patients with type 1 diabetes, especially those who also have a family history of type 2 diabetes.

- Measure autoantibodies (GAD65, insulin, tyrosine phosphatases [IA-2 and IA-2β], islet cell) when the diagnosis of type 1 or type 2 diabetes is uncertain by clinical presentation (ie, thin patient with poor response to initial therapy with sulfonylureas or metformin, personal or family history of autoimmune disease).
- If one or more of the antibodies is present, and especially if two or more are positive, the patient should be presumed to have type 1 diabetes and should be treated with insulin replacement therapy, as these patients respond poorly to diet and oral hypoglycemic drug therapy.

- Given the risk of ketoacidosis, insulin should also be started in any patient, regardless of whether they are thought to have type 1 or type 2 diabetes, who is catabolic (weight loss or dehydration in the setting of hyperglycemia) or who has evidence of increased ketogenesis (ketonuria or acidosis).

- Maturity onset diabetes of the young — Maturity onset diabetes of the young (MODY) is a clinically heterogeneous disorder characterized by non-insulin dependent diabetes diagnosed at a young age (<25 years) with autosomal dominant transmission and lack of autoantibodies .
- MODY is the most common form of monogenic diabetes, accounting for 2 to 5 percent of diabetes Many patients are misclassified as having either type 1 or 2 diabetes.

- Mutations in hepatocyte nuclear factor-1-alpha (HNF1A) and the glucokinase (GCK) gene are most commonly identified, occurring in 52 to 65 and 15 to 32 percent of MODY cases, respectively .Mutations in HNF4A account for approximately 10 percent of cases.
- Some members of a family have the genetic defect but do not develop diabetes; the reason for this is unclear. Other patients may have the classic MODY phenotype but do not have an identifiable mutation in any of the MODY genes .
- The diagnosis of MODY is made by performing diagnostic genetic testing by direct sequencing of the gene.

- Indications for genetic testing — It is important to distinguish MODY from type 1 and type 2 diabetes because the optimal treatment and risk for diabetes complications varies with the underlying genetic defect.
- Genetic testing for MODY when there is a high index of suspicion (familial diabetes with autosomal dominant pattern of inheritance (>2 generations), onset <25 years, non-obese, negative islet autoantibodies) .
- In all patients, therefore, it is important to obtain a detailed history of diabetes at diagnosis, including age, body mass index, and presenting symptoms . It is also important to ascertain insulin dependency and the presence or absence of family history of diabetes.

- In a patient with presumed type 1 diabetes, measurement of serum autoantibodies (islet-cell antibodies [ICA], glutamic acid decarboxylase [GAD65], insulin, tyrosine phosphatases, IA-2 and IA-2β) should be performed prior to consideration of genetic testing for MODY. The presence of autoantibodies makes MODY very unlikely .
- It is more difficult to differentiate between MODY and type 2 diabetes mellitus. For patients with presumed type 2 diabetes, the presence of a simple (non-multigenerational) family history does not discriminate between MODY and type 2 diabetes.

- Insulin resistance is not a feature of MODY. Thus, diabetes in the absence of obesity is suspicious for MODY, particularly in adolescents with presumed type 2 diabetes. However, the absence of obesity or surrogate markers of insulin resistance is, in general, a poor discriminator of MODY and type 2 diabetes in adults . There are currently no biochemical tests that reliably differentiate between the two diseases.
- For family members of mutation carriers, biochemical testing to confirm diabetes should be performed before genetic testing is considered . If the biochemical tests are consistent with a diagnosis of diabetes, genetic testing can be performed to confirm the diagnosis of a MODY mutation.

- Other beta-cell gene defects — There are other rare genetic defects in beta-cell function that are not considered part of the MODY spectrum. One type results from a dominantly inherited missense mutation in the sulfonylurea 1 receptor subunit (SUR1) that causes hyperinsulinemia in childhood, but beta-cell dysfunction and diabetes in adulthood
- Genetic defects in insulin action — There are a series of rare abnormalities in the insulin receptor (due to a genetic defect or the polycystic ovary syndrome) or in the structure of insulin itself.
- Genetic defects in mitochondrial DNA — Maternally inherited diabetes and deafness (MIDD) is a rare mitochondrial disorder caused by a genetic mutation at position 3243 in transfer RNA
- Wolfram syndrome — or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) . This disorder is inherited as an autosomal recessive trait with incomplete penetrance.

- **DISEASES OF THE EXOCRINE PANCREAS — Any disease that damages the pancreas, or removal of pancreatic tissue, can result in diabetes.**
- **Cystic fibrosis .**
- **Hereditary hemochromatosis.**

- **ENDOCRINOPATHIES :**
- **Cushing's syndrome**
- **Acromegaly**
- **Catecholamine excess in pheochromocytoma**
- **Glucagon-secreting tumors (glucagonomas), associated with an unusual constellation of other clinical features, including skin rash, weight loss, anemia, and thromboembolic problems**
- **Somatostatin-secreting tumors (somatostatinomas), typically associated with the triad of diabetes mellitus, cholelithiasis, and diarrhea with steatorrhea**
- **Hyperthyroidism, which can interfere with glucose metabolism, although overt diabetes is unusual**

- DRUG-INDUCED DIABETES — A large number of drugs can impair glucose tolerance; they act by decreasing insulin secretion, increasing hepatic glucose production, or causing resistance to the action of insulin(Glucocorticoids,Oral contraceptives,Tacrolimus, sirolimus, and cyclosporine,Nicotinic acid (niacin).HIV protease inhibitors.Thiazide diuretics (primarily at doses above 25 mg/day of hydrochlorothiazide or its equivalent).Atypical antipsychotics (clozapine, and some conventional antipsychotics),Gonadotropin releasing hormone agonists,OtherBeta blockers,Clonidine,Pentamidine,Alcohol
- VIRAL INFECTIONS — Certain viruses can cause diabetes, either through direct beta-cell destruction or, hypothetically, by inducing autoimmune damage.Chronic hepatitis C virus infection has been associated with an increased incidence of diabetes, but it is uncertain if there is a cause-and-effect relationship.

- **GESTATIONAL DIABETES MELLITUS — Gestational diabetes occurs when a woman's pancreatic function is not sufficient to overcome both the insulin resistance created by the anti-insulin hormones secreted by the placenta during pregnancy (eg, estrogen, prolactin, human chorionic somatomammotropin, cortisol, and progesterone) and the increased fuel consumption necessary to provide for the growing mother and fetus. It is estimated to occur in approximately 2.1 percent of pregnant women in the United States, usually developing in the second or third trimester.**

- Test for undiagnosed prediabetes and diabetes at the first prenatal visit in those with risk factors using standard diagnostic criteria.
- Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously found to have diabetes.
- Test women with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria.
- Women with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years.
- Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes.

Risk factors — The following factors are associated with an increased risk for childhood onset type 2 diabetes:

- Obesity
- Positive family history
- Specific ethnic groups
- Female gender
- Conditions with insulin resistance

Symptoms

- are due to hyperglycemia and commonly include polyuria, polydipsia, and nocturia similar to that seen in patients with type 1 diabetes. Recent weight loss .
- In adolescent girls, vaginal discharge or vulvovaginitis due to monilial infection can be the initial chief complaint .
- Asymptomatic —
- Many patients with type 2 diabetes are identified by screening and are asymptomatic at presentation. This occurs as a result of screening specifically for type 2 diabetes or because of a positive urinalysis test for glycosuria obtained as part of a routine physical examination.

Prediabetes and Type 2 Diabetes

Recommendations

- Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults.
- Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for diabetes
- Testing for prediabetes and/or type 2 diabetes should be considered in women with overweight or obesity planning pregnancy and/or who have one or more additional risk factor for diabetes
- For all people, testing should begin at age 45 years.
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable, sooner with symptoms.

- To test for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are equally appropriate
- In patients with prediabetes and type 2 diabetes, identify and treat other cardiovascular disease risk factors.
- Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factor for diabetes.
- for evidence grading of risk factors.) Patients with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually.

Test — Screening for diabetes can be done by measuring hemoglobin A1C (A1C), fasting plasma glucose (FPG), or performing an oral glucose tolerance test (OGTT).

WHO criteria — The 2006 WHO criteria define:

- Diabetes as a fasting glucose ≥126 mg/dL (7.0 mmol/L) or a two-hour post glucose challenge value ≥200 mg/dL (11.1 mmol/L).
- Impaired glucose tolerance (IGT) is defined as a fasting glucose <126 (7.0 mmol/L), and a two-hour glucose ≥140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.05 mmol/L) .
- Impaired fasting glucose (IFG) is defined as a fasting glucose of 100 to 125 mg/dL (6.1 to 6.9 mmol/L).
- In 2011, the WHO concluded that an A1C value of ≥6.5 percent (48 mmol/mol) can be used as a diagnostic test for diabetes .
- A value of <6.5 percent does not exclude diabetes diagnosed using glucose levels.

The American Diabetes Association (ADA) issued diagnostic criteria for diabetes mellitus in 1997, with follow-up in 2003 and 2010 .

The diagnosis is based on one of four abnormalities:

1) Hemoglobin A1C (A1C).
2) Fasting plasma glucose (FPG).
3) Random elevated glucose with symptoms.
4) Abnormal oral glucose tolerance test (OGTT) .

- Patients with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are referred to as having increased risk for diabetes .

Criteria for the diagnosis of diabetes

- 1. A1C ≥6.5 percent. The test should be performed in a laboratory using a method that is NGSP(national glycohemoglobin standardization program) certified and standardized to the DCCT assay(diabetes control and complications trial).*

OR

- 2. FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

- 3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

- 4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

- In the absence of unequivocal symptomatic hyperglycemia, the diagnosis of diabetes must be confirmed on a subsequent day by repeat measurement, repeating the same test for confirmation. However, if two different tests (eg, FPG and A1C) are available and are concordant for the diagnosis of diabetes, additional testing is not needed. If two different tests are discordant, the test that is diagnostic of diabetes should be repeated to confirm the diagnosis

Normal —

1) Fasting plasma glucose (FPG) <100 mg/dL (5.6 mmol/L).
2) Two-hour glucose during OGTT <140 mg/dL (7.8 mmol/L).

Categories of increased risk for diabetes (prediabetes)*

1) FPG 100-125 mg/dL (5.6-6.9 mmol/L) [IFG]
2) 2-h PG on the 75-g OGTT 140-199 mg/dL (7.8-11.0 mmol/L) [IGT]
3) A1C 5.7-6.4 percent

The adult patient with brittle diabetes mellitus

- Almost all diabetic patients experience swings in blood glucose levels, which are larger and less predictable than in nondiabetics. When these swings become intolerable and cause disruption to the person's daily life and/or prolonged hospitalization, the person is labeled as having "labile" or "brittle" diabetes. Although brittle diabetes is uncommon (less than 1 percent of insulin-taking diabetic patients) .
- Severe instability of blood glucose levels with frequent and unpredictable episodes of hypoglycemia and/or ketoacidosis that disrupt quality of life.
- Thus, brittle diabetic patients virtually always have type 1 diabetes.

- Three clinical presentations of brittle diabetes have been described: (1) predominant hyperglycemia with recurrent ketoacidosis, (2) predominant hypoglycemia, and (3) mixed hyper- and hypoglycemia .
- Patients with brittle diabetes have wide swings in their blood sugar levels and report differing blood sugar responses to the same dose and type of insulin. Historically, glycated hemoglobin (A1C) levels are typically elevated (10 to 14 percent), and acute (ketoacidosis, severe hypoglycemia) and chronic (neuropathy, nephropathy, retinopathy) diabetes complications are common .
- Most patients are in their twenties and thirties, although the elderly may also have brittle diabetes .

- The overall mortality rate for patients with brittle diabetes is high, ranging from 20 to 50 percent in series from specialist centers .
- The age at death ranged from 27 to 45 years.
- A predominance of young women, and one noted a significant increase in microvascular diabetic complications (67 versus 25 percent in stable diabetic controls) and pregnancy complications (46 versus 7 percent) .

DIAGNOSIS —

- **Brittle diabetes is labile or unstable diabetes, which requires frequent and/or prolonged hospitalizations for ketoacidosis or severe hypoglycemia . Thus, the diagnosis of brittle diabetes is established when a patient with absolute insulin deficiency (type 1 or rarely long-standing type 2 diabetes mellitus) has frequent episodes of severe hyper and/or hypoglycemia, requiring frequent hospitalizations and preventing a normal lifestyle.**

- **ETIOLOGY — There are multiple causes of brittle diabetes. The major cause of brittle diabetes is non-physiologic matching of meals/exercise and insulin administration either by clinicians or patients.**
- **Potential physiological causes include malabsorption, delayed gastric emptying due to autonomic neuropathy, impairment of behavioral and counterregulatory responses to falling plasma glucose concentrations, use of certain drugs (alcohol, antipsychotics), systemic insulin resistance, and abnormal insulin absorption or degradation .**

- However, the vast majority of cases appear to be due to psychological factors, with patient-centered behavioral issues often underlying the poor glycemic control . When “brittle” diabetic patients were studied in a controlled environment with regimented meals and exercise and insulin dosing choices made by and administered by the health care team, their labile glycemic state often improved and they were no longer brittle.
- After eliminating the behavioral aspects of brittle diabetes and improving the physiologic match between insulin delivery and insulin requirements, there are still a small number of patients with type 1 diabetes who will remain inexplicably brittle.

MANAGEMENT —

The approach to management will obviously vary depending on the specific etiology in each case. However, regardless of the cause, brittle diabetes is difficult to treat.

- General principles — Diabetes education is important for the patient who is struggling with insulin dosing and dietary prescriptions. Patients need to be instructed on how to match the insulin dose to the amount of carbohydrates ingested at each meal. In addition, insulin regimens must be individually tailored to reduce the risk of hypoglycemia, while maintaining or improving glycemic control. Health care professionals who treat patients with insulin dependent diabetes should have expertise in the principles of insulin management.

- Patient education and empowerment, frequent self-monitoring of blood glucose (SMBG), flexible and rational insulin (and other drug) regimens, individualized glycemic goals, and ongoing professional guidance and support are required to meet these goals. Carbohydrate counting, insulin therapy (multiple daily injections or continuous subcutaneous insulin infusion [insulin pump]), and strategies to prevent hypoglycemia.

- Gastroparesis
- Psychosocial — In patients with a clear psychosocial component to diabetes instability, a psychological evaluation is warranted, since psychotherapy has been shown to be effective in selected patients

Complications

- **HYPOGLYCEMIA — Hypoglycemia is the most common complication of type 1 diabetes in childhood. Hypoglycemia is usually defined as a blood glucose level <70 mg/dL (3.9 mmol/L) . It can occur in any child in whom the dose of administered insulin exceeds insulin requirement. Responses to hypoglycemia include release of counterregulatory hormones such as glucagon, epinephrine, cortisol, and growth hormone. However, over time, the glucagon response usually is impaired and the epinephrine surge may be attenuated, increasing the risk of persistent hypoglycemia. This is especially likely to occur in tightly controlled patients with frequent biochemical hypoglycemia.**

- Symptoms — Hypoglycemic symptoms may be adrenergic due to sympathetic neural activation and epinephrine release , and neuroglycopenic, resulting from direct effects of hypoglycemia on the central nervous system.
- Adrenergic symptoms — Tremor, pallor, rapid heart rate, palpitations, and diaphoresis.
- Neuroglycopenic symptoms — Fatigue, lethargy, headaches, behavior changes, drowsiness, unconsciousness, seizures, or coma.
- The severity of the neuroglycopenic symptoms increases with the severity of hypoglycemia and resultant central nervous system energy deprivation.

Hypoglycemia unawareness is a condition characterized by a lack of warning symptoms of hypoglycemia, due to blunting of the autonomic epinephrine response.

- This is more commonly seen in children with long duration of diabetes, and increases the risk of severe and/or recurrent hypoglycemia.
- Prevention of hypoglycemia for a few weeks can restore hypoglycemia awareness.
- Impairment of the epinephrine response occurs in 30 percent or more of children and adolescents whose diabetes is well controlled .

- In children, nocturnal hypoglycemia is common with reported incidences of 14 to 47 percent . Symptoms can be subtle and include nightmares, restless sleep, and upon awakening, headache, confusion, or behavior changes.
- Decreased release of counter-regulatory hormones during the night may contribute to nocturnal hypoglycemia .

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS, also called nonketotic hyperglycemia)

- are two of the most serious acute complications of diabetes. They are part of the spectrum of hyperglycemia and each represents an extreme in the spectrum.

EPIDEMIOLOGY — Diabetic ketoacidosis is characteristically associated with type 1 diabetes. It also occurs in type 2 diabetes under conditions of extreme stress such as serious infection, trauma, cardiovascular or other emergencies, and, less often, as a presenting manifestation of type 2 diabetes, a disorder called ketosis-prone diabetes mellitus.

- DKA is more common in young (<65 years) diabetic patients and in women compared to men.

- Mortality in DKA is primarily due to the underlying precipitating illness and only rarely to the metabolic complications of hyperglycemia or ketoacidosis . The prognosis of DKA is substantially worse at the extremes of age and in the presence of coma and hypotension.
- the rate of hospital admissions for HHS is lower than the rate for DKA, and accounts for less than 1 percent of all primary diabetic admissions . HHS is most commonly seen in individuals older than 65 years with type 2 diabetes . Mortality attributed to HHS is higher than that of DKA, with rates ranging from 5 to 20 percent; as in DKA, mortality is most often due to the underlying illness or comorbidity .

PATHOGENESIS —

- Two hormonal abnormalities are largely responsible for the development of hyperglycemia and ketoacidosis in patients with uncontrolled diabetes :
- Insulin deficiency and/or resistance.
- Glucagon excess, which may result from removal of the normal suppressive effect of insulin .
- Although glucagon excess contributes to the development of DKA, it is not required. As an example, patients with complete pancreatectomies and who have no pancreatic glucagon will develop DKA if insulin is withheld; however, it takes longer for DKA to develop compared with patients with type 1 diabetes.

- In addition to these primary factors, increased secretion of catecholamines and cortisol can contribute to the increases in glucose and ketoacid production.
- Normal response to hyperglycemia- the extracellular supply of glucose is primarily regulated by two hormones: insulin and glucagon. As the serum glucose concentration rises after a glucose meal, glucose enters the pancreatic beta cells, initiating a sequence of events leading to insulin release.
- Insulin acts to restore normoglycemia by diminishing hepatic glucose production, via reductions in both glycogenolysis and gluconeogenesis, and by increasing glucose uptake by skeletal muscle and adipose tissue. Insulin-induced inhibition of glucagon secretion contributes to the decline in hepatic glucose production; this effect is mediated by direct inhibition of glucagon secretion and of the glucagon gene in the pancreatic alpha cells

Precipitating factors —

Both DKA and HHS are usually precipitated by stresses that act in part by increasing the secretion of glucagon, catecholamines, and cortisol.

- **Infection, such as pneumonia, gastroenteritis, and urinary tract infection, can be found in 40 to 50 percent of patients with hyperglycemic crisis; other stresses include pancreatitis, myocardial infarction, stroke, trauma, and alcohol and drug abuse.**

Spectrum of hyperglycemic crises — The basic mechanism underlying both DKA and HHS is reduction in the net effective action of circulating insulin, with concomitant elevation of counterregulatory hormones, primarily glucagon, but also catecholamines, cortisol, and growth hormone .

- The deficiency in insulin (absolute deficiency, or relative to excess counterregulatory hormones) is more severe in DKA compared with HHS. The residual insulin secretion in HHS is sufficient to minimize ketosis but does not control hyperglycemia .
- DKA and HHS are two extremes in the spectrum of hyperglycemic crisis and patients can fall anywhere along the disease continuum of diabetic metabolic derangement .
- The serum glucose concentration in HHS frequently exceeds 1000 mg/dL (56 mmol/L), but in DKA is generally below 800 mg/dL (44 mmol/L) .

At least two factors contribute to the lesser degree of hyperglycemia in DKA:

1) Patients with DKA often present early with symptoms of ketoacidosis (such as shortness of breath and abdominal pain), rather than late with symptoms due to hyperosmolality.
2) Patients with DKA tend to be young and to have a glomerular filtration rate that, at least in the first five years of diabetes, may be as much as 50 percent above normal. As a result, they have a much greater capacity to excrete glucose than the usually older patients with HHS, thereby limiting the degree of hyperglycemia.

Hyperglycemia — Hormonal alterations in DKA and HHS result in hyperglycemia by their impact on three fundamental processes in glucose metabolism :

1) Impaired glucose utilization in peripheral tissues
2) Increased gluconeogenesis (a both hepatic and renal)
3) Increased glycogenolysis

- The glucosuria associated with DKA and HHS initially minimizes the rise in serum glucose. However, the osmotic diuresis caused by glucosuria leads to volume depletion and a reduction in glomerular filtration rate that limits further glucose excretion .
- This effect is more pronounced in HHS which, as noted above, is usually associated with a higher serum glucose than seen in DKA .

Ketoacidosis

- Acetoacetic acid is the initial ketone formed; it may then be reduced to beta-hydroxybutyric acid, which is also an organic acid, or nonenzymatically decarboxylated to acetone, which is chemically neutral . Ketones provide an alternate source of energy when glucose utilization is impaired.
- Insulin deficiency and increased catecholamine lead to enhanced lipolysis, thereby increasing free fatty acid delivery to the liver . Normal subjects will convert these free fatty acids primarily into triglycerides. The development of ketoacidosis requires a specific alteration in hepatic metabolism so that free fatty acyl CoA can enter the mitochondria, where conversion to ketones occurs.

- In states of insulin deficiency, the combination of increased free fatty acid delivery and glucagon excess promotes ketogenesis.
- The factors responsible for the general absence of ketoacidosis in HHS are incompletely understood. One important factor may be the differential sensitivity of fat and glucose to the effects of insulin. Studies in humans have demonstrated that the concentration of insulin required to suppress lipolysis is only one-tenth that required to promote glucose utilization . Thus, moderate insulin deficiency, as seen in HHS, might be associated with sufficient insulin to block lipolysis (and therefore ketoacid formation) but not enough to promote glucose utilization and prevent the development of hyperglycemia

PRECIPITATING FACTORS

- The most common events are infection (often pneumonia or urinary tract infection) and discontinuation of or inadequate insulin therapy. Compromised water intake due to underlying medical conditions, particularly in elderly patients, can promote the development of severe dehydration and HHS.
- Other conditions and factors associated with DKA and HHS include:

  -Acute major illnesses such as myocardial infarction, cerebrovascular accident, or pancreatitis.

  -New onset type 1 diabetes, in which DKA is a common presentation.

  -Drugs that affect carbohydrate metabolism, including glucocorticoids, higher dose thiazide diuretics, sympathomimetic agents (eg, dobutamine and terbutaline) , and second-generation antipsychotic agents .

-Cocaine use, which has been associated with recurrent DKA .

-Psychological problems associated with eating disorders and purposeful insulin omission, particularly in young patients with type 1 diabetes . Factors that may lead to insulin omission in younger patients include fear of weight gain, fear of hypoglycemia, rebellion from authority, and the stress of chronic disease.

-Poor compliance with the insulin regimen. Compliance issues, with substance abuse as a contributory factor, is the main cause of decompensated diabetes in urban African Americans .

-Malfunction of continuous subcutaneous insulin infusion devices (CSII) was reported in the early 1980s . However, the lack of more recent reports suggests that this risk may no longer be of concern .

CLINICAL PRESENTATION —

- DKA usually evolves rapidly, over a 24-hour period. In contrast, symptoms of HHS develop more insidiously with polyuria, polydipsia, and weight loss, often persisting for several days before hospital admission.
- The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss. As the degree or duration of hyperglycemia progresses, neurologic symptoms, including lethargy, focal signs, and obtundation, which can progress to coma in later stages, can be seen. Neurological symptoms are most common in HHS, while hyperventilation and abdominal pain are primarily limited to patients with DKA.

Initial evaluation —

Both DKA and HHS are medical emergencies that require prompt recognition and management. An initial history and rapid but careful physical examination should focus on:

- Airway, breathing, and circulation (ABC) status
- Mental status
- Possible precipitating events (eg, source of infection, myocardial infarction)
- Volume status

Neurologic symptoms and plasma osmolality —

Neurologic deterioration primarily occurs in patients with an effective plasma osmolality above 320 to 330 mosmol/kg . Mental obtundation and coma are more frequent in HHS than DKA because of the usually greater degree of hyperosmolality in HHS . In addition, some patients with HHS have focal neurologic signs (hemiparesis or hemianopsia) and/or seizures . Mental obtundation may occur in patients with DKA, who have lesser degrees of hyperosmolality, when severe acidosis is also present .

- In the calculation of effective plasma osmolality, the urea concentration is not taken into account because urea is freely permeable and its accumulation does not induce major changes in intracellular (including brain) volume or the osmotic gradient across the cell membrane .

- The effective plasma osmolality (Posm, in mosmol/kg) can be estimated from either of the following equations:

  Effective Posm = [2 x Na (meq/L)] + [glucose (mg/dL) ÷ 18]

  Effective Posm = Measured Posm - [BUN (mg/dL) ÷ 28]

- Where Na is the serum sodium concentration, the multiple 2 accounts for the osmotic contribution of the anions accompanying sodium (primarily chloride and bicarbonate), and 18 and 28 are conversion factors from units of mg/dL into mmol/L. Where standard units are used, the following equations apply:
- Effective Posm = [2 x Na (mmol/L)] + glucose (mmol/L)
- Effective Posm = Measured Posm - BUN or blood urea (mmol/L)

Importance of osmotic diuresis — The rise in plasma osmolality in DKA and HHS is only in part due to the rise in serum glucose. The increase in plasma osmolality pulls water out of the cells, which reduces the plasma osmolality toward normal and lowers the serum sodium. The marked hyperosmolality seen in HHS is primarily due to the glucose osmotic diuresis that causes water loss in excess of sodium and potassium .

- These principles and the importance of effective plasma osmolality in the development of neurologic symptoms are illustrated by observations in diabetic patients with end-stage renal disease. These patients can develop severe hyperglycemia, with serum glucose concentrations that can exceed 1000 to 1500 mg/dL (56 to 83 mmol/L). However, because there is little or no osmotic diuresis, the rise in plasma osmolality is limited, hyponatremia is present, and there are few or no neurologic symptoms .
- The presence of stupor or coma in diabetic patients with an effective plasma osmolality lower than 320 mosmol/kg demands immediate consideration of other causes of the mental status change.

Abdominal pain in DKA — Patients with DKA may present with nausea, vomiting, and abdominal pain; although more common in children, these symptoms can be seen in adults .The presence of abdominal pain was associated with the severity of the metabolic acidosis (occurring in 86 and 13 percent of those with a serum bicarbonate ≤5 and ≥15 meq/L, respectively) but did not correlate with the severity of hyperglycemia or dehydration.

- Possible causes of abdominal pain include delayed gastric emptying and ileus induced by the metabolic acidosis and associated electrolyte abnormalities . Other causes for abdominal pain should be sought when it occurs in the absence of severe metabolic acidosis and when it persists after the resolution of ketoacidosis.

Physical examination —

- Signs of volume depletion are common in both DKA and HHS, including decreased skin turgor, dry axillae and oral mucosa, low jugular venous pressure and, if severe, hypotension.
- Patients with DKA may have a fruity odor (due to exhaled acetone and similar to the odor of nail polish remover).
- Deep respirations reflecting the compensatory hyperventilation (called Kussmaul respirations).
- Fever is rare even in the presence of infection, because of peripheral vasoconstriction due to hypovolemia.

LABORATORY FINDINGS —

- Hyperglycemia and hyperosmolality are the two primary laboratory findings in patients with DKA or HHS; patients with DKA also have a high anion gap metabolic acidosis. Most patients also have acute elevations in the blood urea nitrogen (BUN) and serum creatinine concentration, which reflect the reduction in glomerular filtration rate induced by hypovolemia.

The initial laboratory evaluation of a patient with suspected DKA or HHS should include determination of:

- Serum glucose
- Serum electrolytes (with calculation of the anion gap), BUN, and serum creatinine
- Complete blood count with differential
- Urinalysis, and urine ketones by dipstick

- Plasma osmolality
- Serum ketones (if urine ketones are present)
- Arterial blood gas (if urine ketones or anion gap are present)
- Electrocardiogram
- Additional testing, such as cultures of urine, sputum, and blood, serum lipase and amylase, and chest x-ray, should be performed on a case-by-case basis.
- Measurement of A1C may be useful in determining whether the acute episode is the culmination of an evolutionary process in previously undiagnosed or poorly controlled diabetes or a truly acute episode in an otherwise well-controlled patient.

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10	>18
Urine ketones	positive	positive	positive	small
Serum ketones	Positive	positive	positive	small
Effective serum osmolality (mOsm/kg)•	Variable	Variable	Variable	>320
Anion gapΔ	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

TREATMENT

- Treatment overview and protocols — The treatment of DKA and HHS is similar, including the administration of insulin and correction of the fluid and electrolyte abnormalities that are typically present, including hyperglycemia and hyperosmolality, hypovolemia, metabolic acidosis (in DKA), and potassium depletion.
- Stabilize the patient's airway, breathing, and circulation.
- Obtain large bore IV (≥16 gauge) access; monitor using a cardiac monitor, capnography, and pulse oximetry.
- Monitor serum glucose hourly, and basic electrolytes, plasma osmolality, and venous pH every two to four hours until the patient is stable.

- Determine and treat any underlying cause of DKA (eg, pneumonia or urinary infection, myocardial ischemia).
- Replete fluid deficits:
- Give several liters of isotonic (0.9 percent) saline as rapidly as possible to patients with signs of shock.
- • Give isotonic saline at 15 to 20 mL/kg per hour, in the absence of cardiac compromise, for the first few hours to hypovolemic patients without shock.
- • After intravascular volume is restored, give one-half isotonic (0.45 percent) saline at 4 to 14 mL/kg per hour if the corrected serum sodium is normal or elevated; isotonic saline is continued if the corrected serum sodium is reduced.
- • Add dextrose to the saline solution when the serum glucose reaches 200 mg/dL (11.1 mmol/L).

- **Replete potassium (K+) deficits:**
- **• Regardless of the initial measured serum potassium, patients with DKA have a large total body potassium deficit.**
- **• If initial serum K+ is below 3.3 mEq/L, hold insulin and give K+ 20 to 30 mEq/hour IV until K+ concentration is above 3.3 mEq/L.**
- **• If initial serum K+ is between 3.3 and 5.3 mEq/L, give K+ 20 to 30 mEq per liter IV fluid; maintain K+ between 4 to 5 mEq/L.**
- **• If initial serum K+ is above 5.3 mEq/L do not give K+; check K+ every 2 hours. Give insulin:**
- **• Do not give insulin if initial serum K+ is below 3.3 mEq/L; replete K+ first.**

- • Give all patients without a serum K+ below 3.3 mEq/L regular insulin. Either of two regimens can be used: 0.1 units/kg IV bolus, then start a continuous IV infusion 0.1 units/kg per hour; OR do not give bolus and start a continuous IV infusion at a rate of 0.14 units/kg per hour.
- • Continue insulin infusion until ketoacidosis is resolved, serum glucose is below 200 mg/dL (11.1 mmol/L), and subcutaneous insulin is begun.
- Give sodium bicarbonate to patients with pH below 7.00:
- • If the arterial pH is between 6.90 and 7.00, give 50 meq of sodium bicarbonate plus 10 meq of potassium chloride in 200 mL of sterile water over two hours.
- • If the arterial pH is below 6.90, give 100 meq of sodium bicarbonate plus 20 meq of potassium chloride in 400 mL sterile water over two hours.

- **The average fluid loss is 3 to 6 liters in DKA and up to 8 to 10 liters in HHS, due largely to the glucose osmotic diuresis.**
- **In addition to inducing water loss, glucosuria results in the loss of approximately 70 meq of sodium and potassium for each liter of fluid lost. The aim of therapy is to replete the extracellular fluid volume without inducing cerebral edema due to too rapid reduction in the plasma osmolality.**
- **Hyperglycemia in uncontrolled diabetes mellitus has a variable effect on the serum sodium concentration, as factors are present that can both lower and raise the measured value :**

  -By raising the serum osmolality, hyperglycemia results in osmotic water movement out of the cells, thereby lowering the serum sodium concentration by dilution.

  -The direct effect of hyperglycemia is counteracted by the glucosuria-induced osmotic diuresis. The diuresis results in water loss in excess of sodium and potassium, which will tend to raise the serum sodium concentration and plasma osmolality unless there is a comparable increase in water intake.

- The serum sodium concentration at presentation varies with the balance of these mechanisms.
- Reversing the hyperglycemia with insulin will lower the plasma osmolality, which will cause water to move from the extracellular fluid into the cells, thereby raising the serum sodium concentration . Thus, a patient with a normal initial serum sodium concentration will usually become hypernatremic during therapy with insulin and isotonic saline. The degree to which this is likely to occur can be estimated at presentation by calculation of the "corrected" serum sodium concentration, that is, the serum sodium concentration that should be present if the serum glucose concentration were lowered to normal with insulin alone :

- **Corrected serum Na = Measured serum Na + [ΔSG ÷ 42]**
- **Where ΔSG is the increment above normal in the serum glucose concentration (in mg/dL). The ΔSG should be divided by 2.3 if measured in mmol/L.**