SYMPTOM TO DIAGNOSIS
An Evidence-Based Guide

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I have a patient who is concerned that she has diabetes. How do I confirm or exclude the diagnosis?

CHIEF COMPLAINT

Mrs. D is a 50-year-old African American woman who is worried she has diabetes.

What is the differential diagnosis of diabetes? How would you frame the differential?

CONSTRUCTING A DIFFERENTIAL DIAGNOSIS

The differential diagnosis of diabetes mellitus is actually a classification of the different causes of diabetes:

A. Type 1 diabetes mellitus (DM)
   1. Five to 10% of diabetics in Canada, the United States, and Europe
   2. Usually caused by immune-mediated destruction of the pancreatic beta cells in genetically susceptible individuals, triggered by an environmental agent
      a. Antibodies found include islet cell antibodies (ICAs) and antibodies to glutamic acid dehydrogenase
      b. Risk is 0.4% in patients without family history, 5–6% in siblings and children, and 30% in monozygotic twins
   3. Occasionally idiopathic or resulting from surgery or chronic pancreatitis
   4. Insulin therapy always necessary
   5. At high risk for diabetic ketoacidosis (DKA)

B. Type 2 DM
   1. More than 80% of cases
   2. Caused by a combination of impaired insulin secretion and insulin resistance
   3. Strong genetic component
      a. Two to 6 times more prevalent in African Americans, Native Americans, Pima Indians, and Hispanic Americans in the United States than in whites
      b. Among patients, 39% have at least 1 parent with diabetes
      c. Sixty to 90% concordance in monozygotic twins
      d. Lifetime risk of a first-degree relative of a patient with type 2 DM is 5–10 times higher than that of age- and weight-matched individuals without a family history
   4. Most important environmental contributor is obesity, which induces insulin resistance

C. Other causes of diabetes
   1. Genetic defects of beta cell function or insulin action
   2. Exocrine pancreatic diseases
   3. Endocrinopathies
   4. Medications (especially corticosteroids)
   5. Infections

D. Gestational diabetes

Type 1 diabetes generally occurs in children; approximately 7.5–10% of adults assumed to have type 2 DM actually have type 1, as defined by the presence of circulating antibodies.

Type 2 DM is becoming more prevalent in teenagers and young adults, presumably related to the increased prevalence of obesity in the young.

Type 2 diabetics can develop ketoacidosis; do not assume all patients with ketoacidosis have type 1 diabetes.
In most patients, the distinction between type 1 and type 2 diabetes is clear. Thus, the primary tasks of the internist are to determine who should be tested for diabetes, who has diabetes, which complications to monitor, and how to treat the patient. Because of its relative predominance in adults, this chapter focuses on type 2 diabetes. Additionally, selected data on outcomes in type 1 diabetes are included.

Mrs. D’s father died from complications of diabetes, and so she has always been worried about developing it herself. Over the last couple of weeks, she has been urinating more than usual. She is aware that excess urination can be a symptom of diabetes and so scheduled an appointment.

At this point, what is the leading hypothesis, and what are the active alternatives? What other tests should be ordered?

**ORGANIZING THE DIFFERENTIAL DIAGNOSIS**

Mrs. D’s pretest probability of diabetes is high because of her family history and urinary symptoms. The rest of the differential diagnosis consists of other entities that can cause urinary frequency, such as urinary tract infection, excess fluid intake, and bladder dysfunction. One should also consider diseases that cause true polyuria, defined as urine output of > 3 L/day (Table 25–1).

**Table 25–1. Diagnostic Hypotheses for Mrs. D**

<table>
<thead>
<tr>
<th>Diagnostic Hypotheses</th>
<th>Clinical Clues</th>
<th>Important Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leading hypothesis</td>
<td>Family history, obesity, hypertension, ethnic group, polyuria, polydipsia</td>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active alternatives: most common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>Urgency, frequency, hematuria</td>
<td>Urinalysis, culture History</td>
</tr>
<tr>
<td>Excess fluid intake</td>
<td>Polyuria, frequency</td>
<td>Postvoid residual, urodynamic testing</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
<td>Urgency, frequency, incontinence</td>
<td></td>
</tr>
<tr>
<td>Other hypotheses</td>
<td>Polyuria &gt; 3 L/day</td>
<td>Water restriction test</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Polyuria &gt; 3 L/day</td>
<td></td>
</tr>
<tr>
<td>Primary polydipsia</td>
<td>Polyuria &gt; 3 L/day, excess water intake</td>
<td>Water restriction test</td>
</tr>
</tbody>
</table>

Mrs. D has no dysuria or hematuria. She takes no medications, drinks 1 cup of coffee per day, and uses alcohol rarely. She has been trying to lose weight and has been drinking more water in an attempt to reduce her appetite.

On physical exam, she looks a bit tired. Vital signs are as follows: BP, 138/82; pulse, 96; RR, 16. The remainder of the physical exam is normal. A random plasma glucose is 152 mg/dL.

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

**Leading Hypothesis: Type 2 DM**

**Textbook Presentation**

Patients with type 2 DM can present with the classic symptoms of polyuria, polydipsia, and weight loss. The presentation can also be more subtle, with patients complaining that they feel tired or “just not right.” Many patients are asymptomatic and are diagnosed
through plasma glucose testing. Patients can also present with complications of diabetes.

**Disease Highlights**

**A.** Prevalence in the United States is about 13–14%; up to half of patients are unaware of the diagnosis.

**B.** The lifetime risk of developing diabetes for individuals born in 2000 is estimated to be 32.8% for males and 38.5% for females; rates are as high as 50% for African American and Hispanic women.

**C.** Risk factors include
1. Age ≥ 45
2. Body mass index (BMI) ≥ 25 kg/m²
3. A first-degree relative with diabetes
4. Physical inactivity
5. Being a member of a high-risk ethnic group (African American, Hispanic American, Native American, Asian American, Pacific Islander)
6. Having delivered a baby weighing > 9 pounds or having had gestational DM
7. Hypertension
8. Metabolic syndrome (high-density lipoprotein [HDL] cholesterol < 35 mg/dL and/or triglycerides > 250 mg/dL)
9. Polycystic ovary syndrome
10. History of impaired glucose tolerance or impaired fasting glucose (see Table 25–2 for definitions)

**D.** Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)
1. Metabolic stage between normal glucose homeostasis and diabetes, sometimes called “prediabetes”
2. Patients with IFG or IGT have normal or near normal HbA1c levels
3. Both are risk factors for the development of diabetes and cardiovascular disease
4. Both are associated with the metabolic syndrome (insulin resistance, compensatory hyperinsulinemia, obesity, hypertension, and dyslipidemia consisting of high triglycerides and low HDL)

**Evidence-Based Diagnosis**

**A.** See Table 25–2 for ADA diagnostic criteria; additionally, a random plasma glucose > 200 in a symptomatic patient is diagnostic.

**B.** The ADA recommends that all abnormal results be confirmed with a second test.

**C.** The criteria for diagnosing diabetes were chosen based on the observation that the risk for retinopathy increases substantially at a fasting plasma glucose (FPG) of 126.

**D.** FPG measurements are more reproducible than oral glucose tolerance test (OGTT) measurements.

**E.** The ADA does not recommend using the HbA1c to diagnose diabetes because of a lack of standardization of the assay and the variable correlation with FPG.

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**Table 25–2. American Diabetes Association Diagnostic Criteria for Diabetes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fasting plasma glucose</th>
<th>2-h plasma glucose (post 75 g oral glucose load)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 100 mg/dL</td>
<td>≤ 140 mg/dL</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>100–125 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>140–199 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥ 126 mg/dL</td>
<td>≥ 200 mg/dL</td>
</tr>
</tbody>
</table>

*aSame as oral glucose tolerance test.*
1. See Table 25–3 for test characteristics compared with a gold standard of FPG > 126 mg/dL.

2. Other experts recommend using the HbA1c in the diagnosis of diabetes, making the following points:
   a. Improved standardization since 1999 and good correlation with FPG
   b. HbA1c > 6.0% does predict development of diabetic complications
   c. Decisions about whether to start medication generally based on HbA1c result

3. One study found that the combination of FPG ≥ 126 and HbA1c ≥ 5.9 has better test characteristics than either test alone for diagnosing diabetes compared with a gold standard of the OGTT.
   a. Sensitivity of combination, 71.7%; specificity, 95%
   b. LR+, 14.3, LR−, 0.3

F. Although the ADA does not recommend using the OGTT to diagnose diabetes, studies suggest that some patients with a normal FPG have abnormal OGTT results, and that such patients are at increased cardiovascular risk.

Diabetes is diagnosed when a patient has a fasting plasma glucose ≥ 126 mg/dL.

### Making a Diagnosis

Mrs. D’s random glucose is elevated but is not diagnostic of diabetes. She reports that even though she is urinating often, the urine volumes are small. You ask her to return for more testing:

- Fasting plasma glucose, 120 mg/dL
- HbA1c, 5.8%
- Urinalysis: negative for protein, glucose, and blood; no white blood cell count (WBC) or bacteria; specific gravity, 1.015.

Have you crossed a diagnostic threshold for the leading hypothesis, type 2 DM? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

### Case Resolution

Mrs. D does not have diabetes, but she does have impaired fasting glucose. This does not cause glycosuria of a degree sufficient to cause urinary frequency. A urinary tract infection is ruled out by the normal urinalysis. She has increased her water consumption, so excess fluid intake is a likely cause of her symptoms. Bladder dysfunction should be considered if her symptoms do not resolve with reduction in fluid intake. Diabetes insipidus and primary polydipsia are rare diseases that do not need to be considered unless she has a documented urine output of more than 3 L/day. The next diagnostic test should be reducing her fluid intake.

### Table 25–3. Test Characteristics for HbA1c in the Diagnosis of Diabetes

<table>
<thead>
<tr>
<th>HbA1c Cutoff (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>83.4</td>
<td>84.4</td>
<td>5.35</td>
<td>0.2</td>
</tr>
<tr>
<td>6.1</td>
<td>63.2</td>
<td>97.4</td>
<td>243</td>
<td>0.38</td>
</tr>
<tr>
<td>6.5</td>
<td>42.8</td>
<td>99.6</td>
<td>107</td>
<td>0.57</td>
</tr>
<tr>
<td>7.1</td>
<td>28.3</td>
<td>99.9</td>
<td>283</td>
<td>0.72</td>
</tr>
</tbody>
</table>

### Treatment of IFG/IGT

**A.** The goals are to prevent or delay the onset of diabetes and to optimize other cardiac risk factors.
B. Large randomized trials have shown that lifestyle modification or medication can prevent or delay diabetes.

1. Finnish patients with IGT randomized to brief diet/exercise counseling or intensive individualized instruction
   a. There was a 58% relative reduction in the development of diabetes in the intensive group.
   b. Number needed to treat (NNT) for 1 year to prevent 1 case of DM was 22, with an NNT of 5 over 5 years.

2. US patients (45% African American or Hispanic) randomized to intensive diet/exercise program, metformin, or placebo
   a. There was a 58% relative reduction in the development of DM in the intensive diet/exercise group and a 31% relative reduction in metformin group.
   b. NNT over 3 years to prevent 1 case of diabetes was 7 for the intensive diet/exercise group and 14 for the metformin group.

3. Patients with IGT randomized to acarbose or placebo had a 36% relative reduction in the development of diabetes in the acarbose group.

   Lifestyle modification is the best way to prevent or delay the onset of diabetes.

C. Recommended lifestyle modification goals are 30 min of modest physical activity daily and loss of 5–10% of body weight.

D. Hypertension should be treated to a goal of <140/90.

E. Lipids should be treated according to National Cholesterol Education Program (NCEP) guidelines for nondiabetic patients (see Chapter 28).

At this point, what is the leading hypothesis, and what are the active alternatives? What other tests should be ordered?

ORGANIZING THE DIFFERENTIAL DIAGNOSIS

It is clear that Mrs. D has developed type 2 DM. At this point, in addition to starting treatment, the clinician should focus on identifying and managing diabetic complications and associated cardiovascular risk factors rather than ruling out other diagnoses (Table 25–4).

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

Leading Hypothesis: Diabetic Complications

Retinopathy

Textbook Presentation

Most patients with retinopathy are asymptomatic. Others present with either gradual or sudden vision loss.

Disease Highlights

A. Most frequent cause of new cases of blindness in adults aged 20–74 years
Types of retinopathy

1. "Background" retinopathy
   a. Earliest stage
   b. Increased vascular permeability and microaneurysms
   c. Characterized by dot intraretinal hemorrhages and cotton wool spots
   d. Present in 80% of type 2 and 100% of type 1 diabetics who have had DM for 20 years

2. Nonproliferative diabetic retinopathy (NPDR)
   a. Second stage
   b. Regional failure of retinal microvascular circulation, leading to ischemia
   c. Characterized by increasing cotton wool spots
   d. Present in 10% of type 2 diabetics at 10 years and in 60% at 20 years

3. Proliferative diabetic retinopathy (PDR)
   a. Most advanced form
   b. Formation of new blood vessels on the retina and vitreous, as a result of ischemia; leads to visual loss because of hemorrhage or retinal detachment
   c. Present in 50% of type 1 and 15% of type 2 diabetics who have had DM for 15 years

4. Macular edema
   a. Can develop at any stage of retinopathy
   b. Plasma leaks from the macular vessels, causing swelling and formation of hard exudates
   c. Incidence over 10 years is 20% in type 1 DM, 25% in insulin requiring type 2 diabetics, and 14% in noninsulin-requiring type 2 diabetics

Risk factors

1. Duration of diabetes strongest risk factor
2. Progression can be accelerated by pregnancy, puberty, poor glycemic control, hypertension, and cataract surgery.

Evidence-Based Diagnosis

A. Evaluation should include dilated indirect ophthalmoscopy and/or fundus photography by an ophthalmologist or optometrist.

B. Patients with type 1 diabetes should have an exam within 3–5 years of disease onset, followed by at least annual exams.
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C. Patients with type 2 diabetes should have an exam at the time of diagnosis, followed by at least annual exams.

All type 2 diabetics need eye exams by an eye specialist at least annually.

Treatment
A. Glycemic control
1. In type 1 diabetics without retinopathy, the risk of developing it is reduced 76% by tight control.
2. In type 1 diabetics with retinopathy, the risk of progression is reduced by 54% with tight control.
3. In type 2 diabetics, better control reduces the risk of microvascular complications (retinopathy and nephropathy) by 25%.
4. In type 2 diabetics, for every percentage point decrease in HbA1c, there is a 35% reduction in the risk of microvascular complications.
B. Better BP control reduces the risk of progression of retinopathy.
C. Aspirin neither improves nor worsens retinopathy.
D. Photocoagulation reduces the rate of developing severe vision loss in patients with either proliferative retinopathy or macular edema.

Neuropathy

Textbook Presentation
Diabetic peripheral neuropathy classically presents as paresthesias or burning pain in a “glove-stocking” distribution. Diabetic autonomic neuropathy can manifest in a variety of ways, including orthostatic dizziness, diarrhea, urinary incontinence, and gastroparesis.

Disease Highlights
A. Diabetic peripheral neuropathy
1. Types
a. Symmetric distal polyneuropathy (DPN)
b. Focal neuropathies
   (1) Cranial
      (a) Usually cranial nerve III or VI
      (b) Usually acute and transient
      (c) Caused by ischemia
   (2) Thoracolumbar
   (3) Limb
(a) Median nerve most common site
(b) Ulnar, femoral, and peroneal also affected
c. Diabetic amyotrophy (pain, severe asymmetric muscle weakness, and wasting of the iliopsoas and quadriceps).

2. Epidemiology of DPN
a. Affects up to 50% of diabetics, with chronic neuropathic pain in 20% of patients with diabetes for over 10 years
b. Severity related to duration of disease, degree of glycemic control, presence of hypertension and hyperlipidemia
c. Independent risk factor for foot ulceration and amputation; patients with neuropathy have a 15% lifetime risk of amputation

3. Clinical manifestations of DPN
a. History
   (1) Burning, shooting, or lancinating pain
   (2) Paresthesias, hyperesthesias
   (3) Often worse at night
   (4) When symptoms ascend to the knees, upper extremity symptoms start
b. Physical exam
   (1) Decreased sensation (see Evidence-Based Diagnosis section)
   (2) Loss of DTRs
   (3) Distal muscle atrophy late in the course
c. Ten percent of patients develop Charcot joints, usually in the tarsometatarsal region.

4. Differential diagnosis
a. Consider other causes of neuropathy if
   (1) Neuropathy develops before or early in the course of the diabetes
   (2) Patient has a history of excellent glycemic control
   (3) Neuropathy is asymmetric
   (4) There is proximal or upper extremity involvement disproportionate to distal lower extremity involvement
b. Be sure to check for other treatable causes (hypothyroidism and vitamin B12 deficiency), even in patients with long-standing diabetes.

Think about other causes of neuropathy in diabetic patients with atypical presentations.
B. Diabetic autonomic neuropathy: can affect any organ innervated by the autonomic nervous system

1. Cardiovascular autonomic neuropathy: many possible manifestations
   a. Reduced heart rate variability, fixed heart rate, sinus tachycardia
   b. Inadequate increase in heart rate/BP with exercise
   c. Postural hypotension with systolic BP drop of > 29 mm Hg
   d. Intraoperative cardiac instability

2. Gustatory sweating
   a. Facial sweating, often accompanied by flushing, that occurs after eating
   b. Generally occurs in patients with nephropathy or peripheral neuropathy
   c. Cause unknown

3. GI dysfunction
   a. Reduced esophageal motility
   b. Gastroparesis
      (1) Abnormality of gastric motility leading to delayed gastric emptying
      (2) Symptoms include nausea, vomiting, anorexia, postprandial fullness, early satiety.
      (3) Poor correlation between demonstrated motility abnormalities and symptoms
   c. Diabetic diarrhea
      (1) Characterized by intermittent, brown watery, voluminous stools, occasionally accompanied by tenesmus
      (2) Can be episodic, separated by periods of normal bowel movements or constipation
      (3) Rare in the absence of other manifestations of neuropathy, either peripheral or autonomic
   d. Constipation
      (1) Constipation specifically resulting from autonomic neuropathy occurs in 20% of type 2 diabetics
      (2) Caused by abnormality in autonomic neural control of colonic motility
   e. Anorectal dysfunction
      (1) Results in fecal incontinence, even in the absence of diarrhea
      (2) Patients can generally sense the presence of stool, but cannot prevent passage

4. Genitourinary dysfunction
   a. Bladder dysfunction
      (1) Initially motor function normal, but sensation of bladder distention impaired
      (2) Then detrusor muscle hypocontractility occurs, leading to urinary retention and overflow incontinence
   b. Erectile dysfunction
      (1) Present in 28–45% of diabetic men
      (2) Most common organic cause of erectile dysfunction
      (3) Risk factors include duration of DM, glycemic control, smoking, other diabetic complications.

Evidence-Based Diagnosis
A. Diabetic peripheral neuropathy (DPN)
   1. Nerve conduction studies are the gold standard.
   2. Several physical exam maneuvers have been compared with nerve conduction studies.
   a. Semmes-Weinstein monofilament examination
      (1) Apply a 5.07/10-g monofilament to a noncallused site on the dorsum of the first toe just proximal to the nail bed.
      (2) Repeat 4 times on both feet in an arhythmic manner.
      (3) Add up the total number of times the monofilament is not perceived by the patient (score range = 0–8).
   b. On–off vibration testing
      (1) Apply a vibrating 128-Hz tuning fork to the bony prominence at the dorsum of the first toe just proximal to the nail bed.
      (2) Repeat twice on each foot.
      (3) Add up the total number of times the patient did not perceive the application of the vibrating tuning fork or the dampening of the vibration (score range = 0–8).
   c. Timed vibration testing
      (1) Apply a vibrating 128-Hz tuning fork to the same location used for the on–off vibration test.
      (2) Ask the patient to report the time at which vibration diminished beyond perception, and compare with the number of seconds perceived by the examiner when the tuning fork is applied to the examiner’s thumb.
(3) Record number of times patient’s perception time less than examiner’s (score range = 0–8).

d. Superficial pain sensation
   (1) Apply a sterile Neurotip to the same sites used for the monofilament.
   (2) Repeat 4 times on each foot.
   (3) Add up the total number of times the patient did not perceive the painful stimulus (score range = 0–8).

e. All tests have high LR+; monofilament and timed vibration have best LR− (Table 25–5).

f. Monofilament more reproducible than timed vibration.

The monofilament is the preferred physical exam method for detecting diabetic peripheral neuropathy.

B. Diabetic autonomic neuropathy

1. Cardiovascular autonomic neuropathy
   a. No easy way to analyze heart rate variability
   b. Postural change in systolic BP used to diagnose orthostatic hypotension caused by diabetic autonomic neuropathy.

2. Gustatory sweating is diagnosed by history.

3. GI dysfunction
   a. Esophageal dysmotility: EGD and manometry
   b. Gastroparesis: diagnosed by a “gastric emptying” study, consisting of double-isotope scintigraphy of either solids or liquids
   c. Diabetic diarrhea: rule out other causes of chronic diarrhea.
   d. Anorectal dysfunction: anorectal manometry and defecography can be done to document abnormalities.

4. Genitourinary dysfunction
   a. Urinary bladder dysfunction: ultrasound and urodynamic testing
   b. Erectile dysfunction: history

Treatment

A. Tight glycemic control definitely prevents and improves neuropathy in type 1 diabetics (relative risk reduction [RRR] of 60%, NNT of 15 to prevent 1 case of neuropathy in tightly controlled patients) and possibly does so in type 2 diabetics.

B. Otherwise, treatment is symptomatic.

1. Peripheral neuropathy
   a. Tricyclic antidepressants and gabapentin both shown to effectively reduce neuropathic pain
   b. Tramadol and opiates also effective
   c. Capsaicin possibly effective
   d. NSAIDs generally not effective

2. Autonomic neuropathy
   a. Cardiovascular
      (1) Orthostatic hypotension is usually the most disabling symptom.
      (a) Patients should raise head of bed, and rise slowly.
      (b) Patients can try an elasticized garment that extends from the feet to the costal margins.
      (c) Fludrocortisone is sometimes used, but must beware of supine hypertension, excessive salt, and water retention
      (2) Cardioselective beta blockers sometimes helpful

### Table 25–5. Physical Exam Findings in Diabetic Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Able to Perceive Stimulus ≤ 3 Times (Abnormal Test)</th>
<th>Able to Perceive Stimulus ≥ 7 Times (Normal Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR+</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>On–off vibration</td>
<td>26.6</td>
<td>99</td>
</tr>
<tr>
<td>Monofilament</td>
<td>10.2</td>
<td>96</td>
</tr>
<tr>
<td>Superficial pain</td>
<td>9.2</td>
<td>97</td>
</tr>
<tr>
<td>Timed vibration</td>
<td>18.5</td>
<td>98</td>
</tr>
</tbody>
</table>
b. Sweating: no specific treatment available; can try clonidine

c. Esophageal dysmotility: can try prokinetic agents such as metoclopramide

d. Gastroparesis
   (1) Severe gastroparesis is very difficult to manage.
   (2) Small meals sometimes help.
   (3) Can try metoclopramide or erythromycin
   (4) Gastric electrical stimulation being studied for refractory cases

e. Constipation
   (1) Increase fiber
   (2) Drug choices include lactulose, polyethylene glycol, stool softeners.
   (3) Avoid senna, cascara.

f. Urinary bladder dysfunction
   (1) Bethanechol
   (2) Intermittent self-catheterization

g. Erectile dysfunction: sildenafil and other similar agents

Nephropathy

Textbook Presentation

Diabetic nephropathy is asymptomatic until it is so advanced that the patient has symptoms of renal failure.

Disease Highlights

A. The most common cause of end-stage renal disease (ESRD) in the United States and Europe, accounting for about 40% of new cases of ESRD.

B. Definitions (Table 25–6)

Evidence-Based Diagnosis

A. ADA recommends annual screening for microalbuminuria beginning at the time of diagnosis for type 2 diabetics and at year 5 for type 1 diabetics.

Diabetic patients who are not already receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs) should be screened annually for microalbuminuria.

B. ADA recommended screening tests include 24-h urine collections, 4-h urine collection, or spot albumin/creatinine ratio.

1. 24-h urine collection is the gold standard but is inconvenient to obtain.

2. 4-h collections also inconvenient
3. Albumin–creatinine ratio in a random spot collection easiest to obtain
   a. There is diurnal variation, so first-void or early-morning specimens best; otherwise, try to obtain confirmatory specimen at same time of day as initial specimen.
   b. Short-term hyperglycemia, exercise, urinary tract infection, marked hypertension, heart failure, and acute febrile illness can cause transient elevations in albumin excretion.
   c. All abnormal tests should be confirmed by a second test.
   d. Sensitivity ranges from 70–100%, specificity from 91–98% for morning specimens (sensitivity 56–97%, specificity 81–92% for random specimens).
   e. Specificity might decrease with age: 1 study found a stable sensitivity of about 95%, but different specificities depending on age and sex (men: 84% for ages < 65 years, 72% for > 65 years; women: 89% for ages < 65 years, 82% for > 65 years).

Treatment

A. Tight glycemic control reduces nephropathy.
   1. Type 1 DM
      a. Incidence of microalbuminuria reduced by 34% (NNT = 83) in patients without retinopathy and by 43% (NNT = 47) in patients with retinopathy
      b. Incidence of macroalbuminuria reduced by 56% (NNT = 125) in patients with retinopathy
   2. Type 2 DM
      a. Microvascular complications (retinopathy plus nephropathy) reduced by 25% (NNT = 56 over 10 years)
      b. The microvascular complication rate was 58% for patients with a HbA1c ≥ 10 and 6.1% for patients with an HbA1c < 6.0.

B. BP control and choice of agents
   1. BP should be less than 130/80.
   2. See Table 25–7 for agents shown to delay progression of nephropathy.

C. Protein restriction to about 10% of daily calories may reduce progression of overt nephropathy.

D. It is not clear whether or how often albuminuria should be monitored in patients on ACE inhibitors or ARBs.

E. Refer to a nephrologist if the creatinine clearance is < 60 mL/min or hypertension cannot be controlled.

Diabetic Foot Ulcers

Textbook Presentation

A patient with peripheral neuropathy is unaware of minor trauma and the beginning of plantar ulceration. By the time the ulcer is discovered incidentally, it is often advanced, sometimes with associated osteomyelitis.

Disease Highlights

A. Lifetime risk of developing an ulcer is about 15%.

B. Ninety percent of patients with ulcers have neuropathy, and 15–20% have peripheral vascular disease.

C. Tend to occur at pressure points, so plantar surface, sites of calluses are common locations

D. Risk factors
   1. Duration of diabetes > 10 years
   2. Male sex
   3. Poor glycemic control
   4. Coexisting cardiovascular, renal, or retinal complication
   5. Peripheral neuropathy
   6. Altered biomechanics

Table 25–7. BP Medications That Reduce Progression of Nephropathy in Patients With Hypertension Based on Randomized Trials to Date

<table>
<thead>
<tr>
<th>Type of DM</th>
<th>Degree of Nephropathy</th>
<th>Recommended Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Any degree of albuminuria</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>2</td>
<td>Microalbuminuria</td>
<td>ACE inhibitors or ARBs</td>
</tr>
<tr>
<td>2</td>
<td>Macroalbuminuria and creatinine &gt; 1.5 mg/dL</td>
<td>ARBs</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; ARB, angiotensin receptor blocker.
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E. Pathophysiology
1. Repetitive mechanical stress occurs as a result of altered biomechanics, foot deformities, ill-fitting shoes.
2. Peripheral neuropathy causes loss of protective sensation, so the patient is unaware of the incipient ulceration.
3. Ischemia, resulting from macrovascular disease (commonly in the tibioperoneal vessels) or microvascular dysfunction from autonomic neuropathy, inhibits healing and promotes progression.

F. Classification
1. Non-limb-threatening
   a. Superficial infection, purulent discharge, and minimal (< 2 cm extension from the ulcer) or absent cellulitis
   b. No systemic toxicity (fever, leukocytosis, severe hyperglycemia, or osteomyelitis)
2. Limb threatening
   a. Ulceration to deep tissues, extensive purulent drainage, cellulitis extending more than 2 cm from the ulcer, and lymphangitis
   b. Systemic toxicity and significant ischemia, with or without gangrene, present
3. Life threatening
   a. Ulceration to deep tissues, extensive purulent drainage, cellulitis, necrosis, gangrene, osteomyelitis
   b. Marked systemic toxicity, including septic shock

G. Microbiology
1. Non-limb-threatening infections average 2 species/ulcer, but are often monomicrobial
2. Limb-threatening and life-threatening infections generally polymicrobial
3. Staphylococcus aureus most common organism, present in 50% of infections
4. Streptococci present in one third of cases
5. Gram-negative organisms, especially Proteus, Klebsiella, Escherichia coli, and Pseudomonas, present in polymicrobial infections
6. Anaerobic gram-positive cocci and Bacteroides present in up to 80% of polymicrobial infections

Evidence-Based Diagnosis
A. ADA recommendations include at least annual foot examinations that should include screening for neuropathy and assessing foot structure, biomechanics, vascular status, and skin integrity.

You cannot examine the feet of your diabetic patients too often!

B. Culturing ulcers
1. Can be difficult to distinguish between colonizing organisms and true pathogens
2. Deep cultures of the ulcer or the bone thought to be more reliable
3. If the patient is responding to empiric therapy, it is not necessary to culture.

C. Diagnosing complications
1. Cellulitis: clinical diagnosis (see Chapter 12)
2. Osteomyelitis
   a. Open bone biopsy with culture is the gold standard.
   b. Needle bone biopsy subject to sampling error (sensitivity, 87%; specificity, 93%; LR+, 12.4; LR−, 0.14)
   c. Being able to probe the ulcer down to bone has a sensitivity of 66% and specificity of 89% for the presence of osteomyelitis (LR+, 6; LR−, 0.38).
   d. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complete blood cell count (CBC), blood cultures not sufficiently sensitive or specific to diagnose osteomyelitis.
   e. Magnetic resonance imaging (MRI) is the imaging procedure with the best test characteristics (Table 25–8).

MRI scan is the best imaging procedure to diagnose osteomyelitis in a patient with a diabetic foot ulcer.

A normal CBC, CRP, or ESR does not rule out osteomyelitis.

Treatment
A. Preventive foot care
1. Improve glycemic control to reduce risk of neuropathy.
2. Reduce vascular risk factors (smoking cessation, BP control, lipid management).

3. Examine the feet of high-risk patients at every visit (patients with peripheral neuropathy, evidence of increased pressure, limited joint mobility, bony deformity, severe nail pathology, peripheral vascular disease, or a history of ulcers or amputation).

4. Examine the feet of low-risk patients at least annually.

5. Ensure patients wear well-fitted shoes.

6. Educate patients regarding need for daily visual inspection of feet.

7. Refer to podiatrist for débridement of calluses, assessment of bony deformities.

B. Treatment of ulcers

1. Treat any infection.
   a. Patients with non-limb-threatening infections
      (1) Can generally be treated with oral antibiotics in the outpatient setting
      (2) Oral antibiotic choices include first-generation cephalosporins, dicloxacillin, clindamycin, amoxicillin–clavulanate, fluoroquinolones.
      (3) Patients should be reassessed after 24–48 h and switched to IV therapy if there is no response.
   b. All other patients should be hospitalized and given IV antibiotics.
      (1) IV antibiotic choices include ampicillin–sulbactam, ticarcillin–clavulanate, levofloxacin, cefotaxin, cefotetan, imipenem–cilastin.
      (2) 10–14 days of therapy generally adequate for patients without osteomyelitis; those with osteomyelitis need 3–10 weeks
      (3) Can often switch from IV to oral therapy if patients improving

2. Determine need for revascularization, and revascularize as early as possible in patients with treatable peripheral vascular disease.

3. Heal the ulcer.
   a. Off loading: use orthotics or fiberglass casts to remove pressure from the wound while allowing the patient to remain active.
   b. Débride ulcers (surgically or with débriding agents such as hydrogels).
   c. Control edema.
   d. Growth factors being studied

4. Institute preventive measures once the ulcer has healed.

MAKING A DIAGNOSIS

The ophthalmologist reports that Mrs. D has no retinopathy. Her neurologic exam, including monofilament testing, is normal. She does not complain of orthostatic dizziness or any GI or genitourinary symptoms. She has bilateral bunions but no calluses or ulcers. Her albumin–creatinine ratio is 50 µg/mg, confirmed on repeat testing. Her HbA1c is 9.1%.

Have you crossed a diagnostic threshold for the leading hypothesis, diabetic complications? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

The evaluation for diabetic complications is complete. Mrs. D has no evidence of retinopathy, neuropathy, or diabetic foot disease, but she does have microalbuminuria. However, before formulating a treatment plan for Mrs. D, it is necessary to assess for the presence or absence of other cardiovascular risk factors and cardiovascular disease:

1. Dyslipidemia
2. Hypertension
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3. Obesity
4. Smoking
5. Coronary artery disease
6. Cerebrovascular disease
7. Peripheral vascular disease

See Table 25–9 for a summary of testing that must be performed on all patients with diabetes.

CASE RESOLUTION

Mrs. D has no symptoms of vascular disease on careful questioning, and her exercise tolerance is more than 1 mile. Her fasting lipid panel shows a total cholesterol of 230, HDL of 45, triglycerides of 200, and LDL of 145. You refer Mrs. D to a diabetes educator for instruction in home glucose monitoring and to a nutritionist for instruction about diet and exercise. You also prescribe metformin for the diabetes and atorvastatin for the hyperlipidemia. Because she has hypertension and microalbuminuria, you elect to start an ACE inhibitor, lisinopril, to treat her hypertension. You also recommend that she start taking aspirin, 81 mg daily. Over the next 12–18 months, Mrs. D loses 5 pounds. You increase the dose of metformin and then add glipizide to achieve an HbA1c of 6.9%. You also increase the dose of lisinopril and add hydrochlorothiazide and atenolol to achieve a BP of 128/80. Her LDL is now 85 mg/dL.

Treatment of Type 2 Diabetes

The treatment of type 2 diabetes involves not only the treatment of the hyperglycemia but the management of...
associated complications and cardiovascular risk factors as well. According to survey data, only 37% of participants reached HbA1c goals, 35.8% reached BP goals, and 48% reached cholesterol goals; only 7.3% reached all 3 goals.

It is common for patients to require 6–7 medications to reach the treatment goals outlined next.

Treatment of Hyperglycemia

A. Treatment goals
   1. ADA: HbA1c < 7.0%
   2. American College of Endocrinology: HbA1c ≤ 6.5%
   3. Goals should be modified for frail elderly, in whom avoidance of hypoglycemia and optimization of functional status may be more important than tight glycemic control.

B. Monitoring
   1. HbA1c levels every 3–6 months (see Table 25–10 for correlation between plasma glucose and HbA1c)
   2. Home glucose monitoring
      a. Patients on insulin should test several times/day if not well controlled and perhaps less often if well controlled.
      b. Optimal frequency for patients on oral agents unclear; patients in whom therapy is being changed should test more frequently.

C. Lifestyle modification
   1. Weight loss, diet modification, and exercise are the foundations of all treatment for diabetes.
   2. Best instituted in conjunction with a certified diabetes educator or nutritionist

D. Oral hypoglycemics
   1. Sulfonylureas (SU)
      a. Examples: glyburide, glipizide, glimepiride
      b. Increase insulin secretion.
      c. Average decrease in HbA1c about 1–2%
      d. Side effects include weight gain (2–5 kg) and hypoglycemia, especially in the elderly, patients with reduced renal function, and those with erratic eating habits.
      e. Shown to reduce diabetes-related end points and microvascular end points
      f. Can be used as monotherapy or in combination with insulin or other oral agents (except non-SU secretagogues)
   2. Biguanides
      a. Example: metformin
      b. Reduce hepatic glucose production.
      c. Average decrease in HbA1c about 1–2%
      d. Associated with weight loss (or at least no weight gain); hypoglycemia rare
      e. Most common side effects are GI (abdominal pain, nausea, diarrhea).
      f. Because of risk of lactic acidosis, should be avoided in patients with creatinine ≥ 1.5 mg/dL, congestive heart failure (CHF), hepatic dysfunction, metabolic acidosis, and alcoholism.
      g. Has been shown to decrease diabetes-related end points, macrovascular end point, and total mortality in obese type 2 diabetics
      h. Can be used as monotherapy or in combination with all other oral agents and insulin
   3. Alpha glucosidase inhibitors
      a. Example: acarbose
      b. Delay intestinal carbohydrate absorption, decreasing postprandial glucose swings
      c. About 50% less efficacious than sulfonylureas and metformin in reducing HbA1c

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Mean Plasma Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>135</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
</tr>
<tr>
<td>8</td>
<td>205</td>
</tr>
<tr>
<td>9</td>
<td>240</td>
</tr>
<tr>
<td>10</td>
<td>275</td>
</tr>
<tr>
<td>11</td>
<td>310</td>
</tr>
<tr>
<td>12</td>
<td>345</td>
</tr>
</tbody>
</table>

d. Side effects include flatulence, abdominal discomfort, and diarrhea.

e. No studies of effects on diabetes-related end points

f. Can be used as monotherapy, but this is rarely done because of relatively poor efficacy; can also be used in combination with sulfonylureas

4. Thiazolidinediones (TZDs)
   a. Examples: rosiglitazone, pioglitazone
   b. Increase insulin-stimulated glucose uptake by skeletal muscle cells.
   c. Average decrease in HbA1c about 1–2%
   d. Tend to increase HDL and decrease triglycerides
   e. Can take weeks or months to obtain maximum effect
   f. Side effects include weight gain (as great as or more so than that seen with sulfonylureas) and edema.
   g. Have not been associated with liver injury (unlike troglitazone, which is no longer available)
   h. Should be avoided in patients with CHF and hepatic impairment
   i. No long-term studies of effects on diabetes-related end points
   j. Can be used as monotherapy or in combination with sulfonylureas, metformin, and insulin

5. Non-SU secretagogues
   a. Examples: repaglinide, nateglinide
   b. Because of short half-life, causes brief, episodic increases in insulin secretion
   c. Primarily reduces postprandial glucose, with less risk of hypoglycemia than with SUs
   d. Efficacy of repaglinide similar to that of SUs and metformin; nateglinide less efficacious
   e. No long-term studies of effects on diabetes-related end points
   f. Must be dosed with every meal
   g. Should be used cautiously in patients with hepatic or renal dysfunction
   h. Can be used as monotherapy or in combination with metformin

E. Choosing an initial monotherapy

1. Must take into account cost and dosing schedule
   a. Medications taken once or twice daily are generally preferable to those taken more often.

2. Must consider presence of other diseases, especially advanced liver disease, renal insufficiency, and CHF

3. Sulfonylureas, metformin, repaglinide, and TZDs all have similar efficacy with regard to lowering HbA1c; outcome data are better for SUs and metformin.

4. Metformin generally the best choice for obese patients because of the lack of weight gain and data regarding reduction in mortality

F. Combination oral therapy

1. Seventy-five percent of patients require more than 1 drug by 9 years.

2. Combinations shown to reduce HbA1c beyond the reduction seen with single agents include metformin and SUs, metformin and TZDs, and SUs and TZDs.

3. No evidence that any specific combination is better than another

4. Triple therapy with an SU, metformin, and a TZD has been studied in 1 trial but is not currently approved by Food and Drug Administration.

G. Insulin

1. Types of insulin (see Table 25–11)

2. Adverse effects of insulin
   a. Hypoglycemia
   b. Weight gain (1.4–2.3 kg more than with sulfonylureas or metformin)

3. Using insulin in type 2 diabetics
   a. Beta cell function declines over time in type 2 DM, so many patients will eventually need insulin.

   b. Consider starting insulin if the HbA1c is > 8.0% despite optimal oral therapy.

      (i) Initially, will often combine oral agents and insulin to minimize insulin dose; combinations that have been studied include

      (a) Bedtime NPH plus metformin
      (b) Morning or bedtime glargine plus metformin
      (c) Sulfonylureas plus once- or twice-daily NPH
      (d) Pioglitazone plus insulin

    (e) There is less weight gain with metformin and insulin than with SUs or TZDs and insulin.
There are fewer nocturnal hypoglycemic episodes with bedtime glargine than with bedtime NPH.

As beta cell function continues to decline, "physiologic" insulin regimens that provide both basal and prandial insulin become more important.

Generally use premixed insulins twice daily (see Table 25–11).

Patients may need more than 100 U/day to achieve glycemic control.

### Treatment of Hypertension

**A.** BP goal is < 130/80.

1. See Nephropathy section and Hypertension chapter for details.

### Treatment of Hypercholesterolemia

**A.** For type 2 diabetic patients without coronary disease, the RRR of cardiovascular events with lipid-lowering therapy is 22%, with an NNT over 4 years of 35.

**B.** For type 2 diabetic patients with coronary disease, the RRR is 24%, with an NNT of 14 over 5 years.

### ADA guidelines

1. The LDL goal is < 100 mg/dL; very high risk patients should have an LDL < 70 mg/dL.

   a. Patients with an LDL > 130 should start pharmacologic therapy with a hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor ("statin").

   b. Patients with and LDL between 100 and 129 can be given a trial of diet modification.

   (1) Maximal expected decrease in LDL is 15–25 mg/dL.

   (2) Start medication if goal not reached in 3–6 months.

2. The HDL goal is > 40 mg/dL.

   a. Exercise is the best way to raise HDL.

   b. Fibrates (fenofibrate preferred to gemfibrozil) or niacin are modestly effective.

3. The triglyceride goal is < 150 mg/dL.

   a. Triglycerides often improve with improved glycemic control.

   b. Consider using fenofibrate if fasting triglycerides are consistently > 400 mg/dL.

### Data suggest that diabetic patients older than 40 benefit from statin therapy regardless of baseline LDL (Table 25–12).
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**Antiplatelet Therapy**

A. Low-dose aspirin (75–162 mg/day) prevents vascular events in diabetics with or without preexisting vascular disease.

B. ADA guidelines recommend low-dose aspirin for the following groups:

1. All patients with preexisting vascular disease
2. All type 2 diabetics older than 40

Table 25–12. Heart Protection Study Results: Rates of First Major Vascular Events (Coronary Event, Stroke, Revascularization) in Patients With Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>Relative Risk Reduction</th>
<th>Absolute Risk Reduction</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>19.8%</td>
<td>25.2%</td>
<td>22%</td>
<td>5.4%</td>
<td>19</td>
</tr>
<tr>
<td>Pts without CAD</td>
<td>9.3</td>
<td>13.5</td>
<td>32</td>
<td>4.2</td>
<td>24</td>
</tr>
<tr>
<td>DM &lt; 6 years</td>
<td>18.9</td>
<td>23</td>
<td>18</td>
<td>4.1</td>
<td>24</td>
</tr>
<tr>
<td>Hba1c &lt; 7.0</td>
<td>18.3</td>
<td>22.6</td>
<td>20</td>
<td>4.3</td>
<td>23</td>
</tr>
<tr>
<td>Total cholesterol &lt; 195</td>
<td>16.3</td>
<td>22.2</td>
<td>27</td>
<td>5.9</td>
<td>17</td>
</tr>
<tr>
<td>LDL &lt; 116</td>
<td>15.7</td>
<td>20.9</td>
<td>25</td>
<td>5.2</td>
<td>19</td>
</tr>
<tr>
<td>HDL &gt; 35</td>
<td>25.9</td>
<td>31.1</td>
<td>17</td>
<td>5.2</td>
<td>19</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; DM, diabetes mellitus; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NNT, number needed to treat.

**CHIEF COMPLAINT**

**PATIENT 2**

Mr. G is a 56-year-old African American man with diabetes, chronic hepatitis B, coronary artery disease status post myocardial infarction (MI) 2 months ago, hypertension, and a history of stroke 1 year ago. He is on many medications, including Humulin 70/30 20 U twice daily, metoprolol, aspirin, Lipitor, lisinopril, furosemide, and ribavirin. Despite all of these problems, he has been slowly improving and reported at his last visit 3 weeks ago that he had recently given up his walker for a cane. Today you are paged by his sister, who reports that Mr. G is very weak and cannot get up; his home glucose monitor reading is “critical high.” Mr. G’s voice is barely recognizable over the phone, and he is unable to respond to your questions. You advise his sister to call 911.

At this point, what is the leading hypothesis, and what are the active alternatives? What other tests should be ordered?

**ORGANIZING THE DIFFERENTIAL DIAGNOSIS**

The differential diagnosis at this point is very broad and difficult to organize. It is helpful to recognize that Mr. G is presenting with the syndrome of delirium and to
use the framework for delirium to organize your thinking (see Delirium chapter). It is also reasonable to consider Mr. G's underlying chronic medical problems and initially focus on the serious complications of these conditions; in other words, initially focus on diseases for which he has a high pretest probability:

1. Diabetes: DKA, hyperosmolar hyperglycemic state (HHS), infection with or without sepsis.
2. Coronary artery disease (CAD): recurrent MI, possibly with CHF or cardiogenic shock
3. Cerebrovascular disease: recurrent stroke
4. Chronic hepatitis B: hepatic encephalopathy

Mr. G could have any of these conditions or more than 1 of them. His critical high blood sugar makes a complication of diabetes the leading hypothesis; all of the other diagnoses are “can’t miss” hypotheses (Table 25–13).

When Mr. G arrives in the emergency room, he is barely responsive but able to move all 4 extremities. His BP is 85/50; pulse, 120; RR, 24; temperature, 99°F. His lungs are clear, and cardiac exam shows an S4 with no S3 or murmurs. His abdomen is nontender, and there is no peripheral edema. Initial lab tests include the following:

Sodium, 138; K, 4.9; Cl, 88; HCO3, 37; blood urea nitrogen, 99; creatinine, 4.3; glucose, 1246

Arterial blood gases: pH 7.40; PO2, 88; PCO2, 35

WBC is 8400, with 75 polymorphonuclear neutrophils, 3 bands, 18 lymphocytes, and 4 monocytes.

Albumin, 4.4; total bilirubin, 0.3; alkaline phosphatase, 175; AST (SGOT), 40; ALT (SGPT), 56; international normalized ratio (INR), 1.1.

Serum ketones, negative

Corrected Na (sodium) = measured Na + 1.6 × glucose – 100

= 138 + 1.6(11)
= 155

Urinalysis: 2+ protein, 4+ glucose, no ketones, 3–5 WBC/high-power field, occasional bacteria

Is the clinical information sufficient to make a diagnosis? If not, what other information do you need?

**Leading Hypothesis: Hyperosmolar Hyperglycemic State**

**Textbook Presentation**

Patients with HHS are usually older type 2 diabetics who present with the gradual onset of polydipsia, polyuria, and lethargy. They are extremely dehydrated and have very high serum glucose levels.

**Disease Highlights**

A. Epidemiology

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**Table 25–13. Diagnostic Hypotheses for Mr. G**

<table>
<thead>
<tr>
<th>Diagnostic Hypotheses</th>
<th>Clinical Clues</th>
<th>Important Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leading hypothesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperosmolar hyperglycemic</td>
<td>Delirium/coma, polyuria, polydipsia,</td>
<td>Plasma glucose, serum/urine ketones</td>
</tr>
<tr>
<td>state (HHS)</td>
<td>dehydration</td>
<td></td>
</tr>
<tr>
<td>Active alternatives: can’t miss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Delirium/coma, polyuria, polydipsia,</td>
<td>Blood glucose/ bicarbonate, serum/urine ketones, pH</td>
</tr>
<tr>
<td></td>
<td>dehydration</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Hypotension, fever</td>
<td>Blood cultures, u/a, CXR</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Chest pain, dyspnea</td>
<td>ECG, cardiac enzymes</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>Hemiparesis, aphasia</td>
<td>Physical exam, head CT</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>Delirium, liver disease</td>
<td>Clinical diagnosis</td>
</tr>
</tbody>
</table>
1. Incidence is 1/1000 person-years (DKA incidence is 4.6–8.0/1000 person years).
2. Mortality rate about 15%
3. Risk factors include older age, nursing home residence, inability to recognize thirst, and lack of access to fluids.

B. Pathogenesis
1. A reduction in the effective action of circulating insulin and a concomitant increase in counterregulatory hormones leads to increased hepatic and renal glucose production and impaired glucose utilization in peripheral tissues.
2. Glycosuria leads to an osmotic diuresis with loss of free water in excess of electrolytes, leading to hyperosmolarity.
3. As volume depletion occurs, urine output drops, and hyperglycemia worsens.
4. The absence of ketoacidosis in HHS is not completely understood; possible explanations are as follows:
   a. There are higher intraportal insulin levels than seen in DKA, sufficient to prevent lipolysis.
   b. The levels of counterregulatory hormones are lower than in DKA.
   c. The hyperosmolar state inhibits lipolysis.

C. Precipitating factors
1. The 3 most common precipitants are infection, lack of compliance with insulin, and first presentation of diabetes.
2. Other precipitants include postoperative state, cerebrovascular accident (CVA), MI, pancreatitis, alcohol abuse, trauma, thyrotoxicosis, and medications (eg, corticosteroids, total parenteral nutrition).

D. Clinical manifestations
1. History
   a. Symptoms and signs usually evolve over several days or even weeks.
   b. Common findings include polyuria, polydipsia, fatigue, and weight loss.
   c. Abdominal pain generally does not occur in HHS, as it does in DKA, but there are reports of a hypertonicity-induced gastroparesis leading to abdominal pain, distention, nausea, and vomiting.
   d. Neurologic manifestations
      (1) Lethargy and disorientation common
      (2) Focal neurologic findings, including seizures, can occur with hyperglycemia and resolve with normalization of serum glucose.

(3) Changes in mental status correlate with the degree of hyperosmolality.
   a. Twenty to 25% present with coma.
   b. Coma present in half of patients with effective serum osmolality of > 350 mOsm/L
   c. Must search for another cause of coma if osmolality < 345–350 mOsm/L

2. Physical exam
   a. Hypothermia often seen resulting from peripheral vasodilation
   b. Signs of dehydration (see Chapter 20) often seen
   c. Tachycardia and hypotension suggest severe dehydration or underlying sepsis.

Evidence-Based Diagnosis
A. Typical total body water deficit is 20–25% (about 9 L).
B. See Table 25–14 for laboratory findings in HHS compared with DKA.

MAKING A DIAGNOSIS

Mr. G’s glucose is > 600 mg/dL, ketones are negative, and calculated serum osmolality is 345 mOsm/L (effective serum osmolality = 2 × measured Na + glucose/18). Mr. G’s osmolality = (2 × 138) + 1246/18 = 345.

Have you crossed a diagnostic threshold for the leading hypothesis, hyperglycemic hyperosmolar syndrome? Have you ruled out the active alternatives? Do other tests need to be done to exclude the alternative diagnoses?

Mr. G fulfills the diagnostic criteria for HHS. It is not necessary to consider other diagnoses, but it is essential to determine the precipitant for this event. Considering Mr. G’s complicated history, he is at risk for many of the precipitants of HHS, especially infection, MI, and CVA.

Always look for the precipitant when patients present with either HHS or DKA.
Mr. G’s chest x-ray film is clear, his urine and blood cultures are negative, his ECG shows no acute changes, and his cardiac enzymes are normal. He responds well to IV hydration and insulin therapy. When he becomes more alert, he reports that he had become depressed and had stopped taking his insulin.

Treatment of HHS
A. Patients with HHS generally need more fluid and less insulin than those with DKA
B. See Figure 25–1 for a treatment algorithm.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>HHS</th>
<th>DKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>&gt; 600</td>
<td>&gt; 300</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>&gt; 7.30</td>
<td>&lt; 7.3 (&lt; 7.0 in severe DKA)</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>&gt;15</td>
<td>&lt;15 (&lt;10 in severe DKA)</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Negative or small</td>
<td>&gt; 3+</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Negative or small</td>
<td>Positive</td>
</tr>
<tr>
<td>Anion gap</td>
<td>Variable</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>Effective serum osmolality (mOsm/L)(^a)</td>
<td>&gt; 320</td>
<td>Variable</td>
</tr>
</tbody>
</table>

\(^a\)Effective serum osmolality = \(2 \times \text{Na (mEq/L)} + \text{glucose (mg/dL)}\)/18

### Table 25–14. Laboratory Findings in Hyperosmolar Hyperglycemic State (HHS) and Diabetic Ketoacidosis (DKA)
**Figure 25–1.** Management of adult patients with hyperosmolar hyperglycemic state. (Reproduced, with permission, from American Diabetes Association, *Diabetes Care*. 2004;27:S94–S102.)