BACKGROUND INFORMATION

This module reviews the complications that can arise in people with diabetes mellitus. However, in addition to evaluating and treating these complications, physicians need to know how to diagnose diabetes mellitus and monitor control of the disease.

Diagnosing Diabetes Mellitus

Per the American Diabetes Association, the diagnosis of diabetes mellitus can be made by one of three criteria: A fasting plasma glucose >126 mg/dl; a 2-hr plasma glucose >200 mg/dl during an observed glucose tolerance test (in which the patient drinks a 75g of a glucose solution and then has serial testing of plasma glucose at 1, 2, and 3 hours); or a random plasma glucose level of >200 mg/dl and symptoms of diabetes mellitus.

Notably, those individuals with a fasting glucose of 100-125 mg/dl or a 2-hr plasma glucose of 140-199 mg/dl have “impaired fasting glucose” or “impaired glucose tolerance”, respectively. These individuals are deemed to have "pre-diabetes" and are at risk of developing type 2 diabetes in the future if significant lifestyle changes are not made.

Type 1 diabetes often presents in childhood with patients complaining of polyuria and polydipsia. Thus, testing for diabetes typically occurs when the patient presents with these symptoms. In contrast, patients with type 2 diabetes may present with any number of symptoms ranging from blurry vision from hyperglycemia to kidney disease or myocardial infarction from microvascular and macrovascular complications, or be asymptomatic in which hyperglycemia is discovered by blood testing. The American Diabetes Association recommends screening for Type 2 diabetes in all adults > 45, or earlier if they have diabetic risk factors (such as obesity, family history, delivery of a large for gestational age infant, polycystic ovary syndrome, or are members of high risk ethnic/racial groups) or concomitant risk factors for atherosclerosis (such as hypertension, hyperlipidemia, or presence of vascular disease). The United States Preventive Services Task Force (USPSTF) recommends screening for Type 2 diabetes in adults with hypertension or hyperlipidemia.

Measuring Diabetes Control

All patients with diabetes mellitus who use insulin and most patients who use other hypoglycemic medications should measure their blood glucose concentrations. The usefulness of self-monitoring in patients with type 2 diabetes who do not use hypoglycemic medications is less clear. Overall glucose control is best measured by a Hemoglobin A1c value. The Hemoglobin (Hgb) A1c value indicates the amount of glycosylation of hemoglobin on erythrocytes; it reflects the degree of blood glucose control in the previous 2-4 months. The Hgb A1c in people who do not have diabetes is typically around 6, but in people with diabetes, a target goal of < 7.0 can reduce microvascular complications. Patients who are significantly above this value may require more aggressive treatment of their diabetes.

Fasting Blood Glucose Goals

The method of self-testing is known as a finger stick blood glucose (FSBG) test. The target fasting FSBG for people with diabetes is typically 80-120 mg/dl.

Helpful Tips for the Patient

In addition to providing specific recommendations for preventing and treating diabetic complications, another way that physicians can greatly benefit their patients is by providing them with materials to learn more about achieving a healthy lifestyle. Below are some patient-oriented reference materials to help patients learn more about sustaining a healthy lifestyle and joining their physician in the fight against diabetes.
Graham A Colditz. Patient Information: Diet and Health. UpToDate.
David K McCulloch, MD. Patient Information: Preventing complications of diabetes mellitus. UpToDate.
CARDIOVASCULAR COMPLICATIONS

Cardiovascular disease (CVD) is the leading cause of death among people with diabetes mellitus. Compared to people without diabetes, those with diabetes have a higher prevalence of CVD and are more likely to have myocardial infarctions or silent myocardial ischemia. Diabetes is an independent risk factor for CVD, but also acts synergistically with other cardiovascular risk factors (hypertension, smoking, hyperlipidemia, age, and family history) to further increase cardiovascular morbidity and mortality. Although it is not yet clear why diabetes increases one’s risk of CVD, it is believed that hyperglycemia, hyperinsulinism (in those with type 2 diabetes), and/or dyslipidemia may play a role. In fact, dyslipidemia is a major contributor to atherosclerosis: not only do people with diabetes have less HDL (“good”) cholesterol to help protect against oxidative damage, but their LDL particles are also smaller and more dense than in people without diabetes, making these particles more vulnerable to oxidation and thus more capable of contributing to atherosclerosis. Compare a normal coronary artery in Figure 1 to that in Figure 2, which has extensive blockage from atherosclerosis. Such advanced atherosclerosis in the vasculature of the heart leads to coronary artery disease (CAD), a major complication of diabetes.

More information about the cardiovascular complications of diabetes is discussed in the following articles:


History:
A patient with CAD will most commonly present with angina. Because CAD may lead to congestive heart failure (CHF), patients with this advanced condition may complain of fatigue and breathlessness.

Physical Exam:
Myocardial ischemia may produce an S4 from left ventricular wall stiffness. If CHF with reduced cardiac output is present, there may be an increased jugular venous pressure, as well as edema in the lower extremities. Pulmonary edema may also be present and will result in crackles that are heard upon lung auscultation. Also in CHF, elevated left ventricular filling pressures will result in an S3 that is heard upon cardiac auscultation.

Tests:
To evaluate the presence of current ischemia or past myocardial infarctions, an ECG should be ordered. It is important to note that a baseline ECG should be considered in older patients whether angina is present or not because patients with diabetes have a higher prevalence of “silent ischemia”. Patients with “silent ischemia” may even have myocardial infarctions without accompanying chest pain (this is thought to occur because of denervation of the heart, similar to the nerve damage that is seen in diabetic peripheral neuropathy); thus, ECG is critical to detect such events. To test for inducible ischemia, a stress test may be performed.

If suspicion of CHF exists, the patient will likely get an echocardiogram to evaluate left ventricular function.

Treatment:
First and foremost, the doctor and patient must work together to gain control of the diabetes and any concomitant modifiable cardiovascular risk factors (hypertension, hyperlipidemia, and smoking). Pharmacologic management may be started, with use of one or more of the following medications: aspirin and beta blockers if CAD is present; lipid-lowering agents such as “statins” to decrease the LDL cholesterol to less than 100 mg/dL; ACE inhibitors as a first line agent for hypertension; and if symptomatic CHF exists, diuretics and possibly digoxin. Finally, if the CAD continues to cause ischemia despite medical therapy, revascularization may be necessary, with either angioplasty or CABG.

Self Assessments:
A 55 year-old woman with type 2 diabetes presents to your clinic. Which of the following parts of the clinical encounter would be MOST suggestive of congestive heart failure (CHF) in this patient?
A. History reveals angina on exertion, but is otherwise unremarkable
B. Cardiac auscultation reveals physiological splitting of S2
C. Examination of the neck reveals no distention of the jugular veins at 30 degrees
D. Lung auscultation reveals inspiratory crackles

Explanations:
A. Incorrect. Angina on exertion is indicative of CAD, but not CHF. Fatigue and breathlessness would be common complaints of CHF.
B. Incorrect. Physiological splitting of S2 is a completely normal phenomenon that occurs during inspiration as the venous return to the right side of the heart increases. In CHF, due to elevated left ventricular filling pressures, an S3 may be heard.
C. Incorrect. Patients with CHF typically have elevated JVP reflecting increased preload; the findings of flat jugular veins at 30 degrees suggest that preload is decreased.
D. Correct! Inspiratory crackles are a sign of pulmonary edema, a common feature of CHF.

Which of the following is MOST CORRECT regarding diabetes mellitus and cardiovascular disease (CVD)?

A. Characteristic large LDL particles in a person with diabetes will clump together to contribute to atherosclerosis
B. Diabetes acts synergistically with other risk factors to further increase one’s risk of CVD
C. Diabetes will ultimately lead to CHF, regardless of how well one’s blood sugar is controlled
D. In and of itself, diabetes is not a risk factor for cardiovascular events

Explanations:
A. Incorrect. The LDL particles in diabetes are small and dense, thus making them more vulnerable to oxidation and thus more capable of contributing to atherosclerosis.
B. Correct!
C. Incorrect. One who maintains good control of their diabetes will not only decrease their risk of progressing to CHF, but may never develop symptomatic cardiovascular issues at all.
D. Incorrect.

A 67 year-old woman presents to her physician for a routine check-up. She has had type 2 diabetes for over 20 years. An ECG is obtained and shows evidence of myocardial infarct in the inferior leads. These findings are new since an ECG one year ago. She denies any symptoms. You suggest:

A. No further work-up. The ECG must be wrong.
B. No further work-up as she doesn’t have any symptoms of CAD
C. A stress test

Explanations:
A. Incorrect. The ECG might be wrong, mislabeling of records can happen. But this shouldn’t be presumed!
B. Incorrect. Patients with diabetes are at risk for “silent ischemia” and may not have classic symptoms of chest pain with angina or myocardial infarctions.
C. Correct! Patients with diabetes are at risk for “silent ischemia” and may not have classic symptoms of chest pain with angina or myocardial infarctions. She may have additional myocardium at risk for injury, so some additional investigation is warranted.
DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is a state of uncontrolled diabetes and it is characterized by hyperglycemia, a high anion gap acidosis, and the presence of ketonemia and ketonuria (ketone bodies in the blood and urine). Although it can occur in patients with type 2 diabetes (during periods of severe stress), DKA primarily occurs in patients with type 1. Type 1 diabetes is caused by the (usually autoimmune) destruction of the pancreatic beta cells, which leads to an absolute insulin deficiency. Thus, patients with type 1 have an absolute requirement for insulin and will develop DKA if they do not receive it.

The lack of insulin, the increase in glucagon (normally suppressed by insulin), and the high levels of the stress hormones epinephrine and cortisol all contribute to hyperglycemia in DKA. But despite such a large amount of sugar in the blood, the body’s organs are essentially starved for fuel because there is not enough insulin to stimulate their uptake of glucose. In an attempt to create an alternate source of energy, these organs begin diverting their metabolic resources to produce ketone bodies. Although ketone bodies allow cells to maintain a very minimal level of function, they are acids, and so can cause a dangerous anion gap acidosis.

The most common underlying causes of DKA are infection (which produces an increased need for insulin) and noncompliance with one’s insulin regimen. Because patients with type 1 diabetes have an absolute insulin deficiency, either of these scenarios can turn an already tenuously balanced metabolic state into a severely ketoacidotic one.

More information about diabetic ketoacidosis is discussed in the following articles:


History:

Normally, all glucose filtered by the kidney is reabsorbed. With hyperglycemia, this mechanism is overwhelmed and glucose “spills” into the filtrate, and pulls water with it. For these reasons, polyuria is a common feature of DKA. Because the hyperglycemia causes a rise in serum osmolarity, extreme thirst with polydipsia is also common. As the acidosis causes a very strong drive to breathe, patients may feel short of breath. Nausea and vomiting are also common in DKA (cause unknown), as well as a feeling of general malaise. These latter symptoms are often the reason for seeking medical attention.

Another fairly common patient report is blurred vision. While the vision problems in diabetic retinopathy result from years of hyperglycemia, blurry vision in DKA results from the rapid movement of water in and out of the orbit, a consequence of the osmotic shifts that occur with fluctuating serum glucose levels.

Physical Exam:

Inspection is quite valuable in DKA. Immediately upon talking with the patient, one may detect a pungent fruity smell on the patient’s breath, a result of the acetone (a ketone) that the body’s organs are producing. In addition, people with DKA have Kussmaul breathing (deep and rapid breaths), reflecting the body’s attempt to blow off carbon dioxide to compensate for the metabolic (keto)acidosis. Finally, because polyuria may cause severe dehydration (especially if the patient does not drink enough replacement fluids), the patient may be tachycardic and even hypotensive, and may show reduced skin turgor. Patients with severe hyperglycemia may exhibit signs of delirium as the associated shifts in fluid affect the brain.

Tests:

A finger prick to measure one’s plasma glucose level will reveal the presence of extreme hyperglycemia. (This should be confirmed with a serum glucose.) An electrolyte panel will reveal an
elevated anion gap metabolic acidosis, and the actual blood pH can be determined by an arterial blood gas.

Infection is a common precipitant of DKA; its presence is usually investigated with a complete blood count (to look for elevated white blood cells), urinalysis, and chest radiograph. In older patients, an ECG should be obtained since the medical stress from a myocardial infarction can precipitate DKA.

Treatment:
Because of the severe volume depletion that occurs as a result of hyperglycemia, isotonic fluids are given intravenously. As DKA reflects a state of insulin deficiency, IV insulin therapy is also administered. Finally, careful attention must be paid to electrolyte levels, with cautious addition of those ions whose levels have been depleted. For example, potassium re-enters cells as the acidosis resolves and will also be driven into cells by insulin. This exit of potassium from the blood will unveil a previously masked potassium depletion (from urine losses). Life-threatening hypokalemia can occur, so there should be close monitoring and replacement.

If infection is the precipitating cause of DKA, broad spectrum antibiotics should be administered.

More information about the treatment of diabetic ketoacidosis is discussed in the following article:

Self Assessments:
Which of the following would NOT be associated with diabetic ketoacidosis?

A. A fruity smell on the patient’s breath
B. Kussmaul breathing
C. A large anion gap
D. Hypertension

Explanations:
A. Incorrect. The fruity smell on the patient’s breath is from the production of acetone, an alternate source of fuel made by organs that are starved of glucose.
B. Incorrect. Kussmaul breathing is the body’s attempt to blow off as much carbon dioxide as possible in order to compensate for the metabolic acidosis from DKA.
C. Incorrect. A large anion gap indicates the presence of a metabolic acidosis, a key feature of DKA.
D. Correct! Due to the considerable amount of fluid lost in the urine (polyuria), the patient in DKA will be dehydrated. She may be normotensive, but tachycardic (reflecting her volume depletion), or she may even be hypotensive.

True of false: Blurry vision in DKA results from years of poor glycemic control.

A. True
B. False

Explanations:
A. Incorrect. Years of poor glycemic control leads to diabetic retinopathy, not the acutely fluctuating vision changes that occur because of the rapidly rising (or falling - if treatment has started) glucose levels in DKA.
B. Correct! The blurry vision in DKA results from rapidly fluctuating glucose levels, which cause fluid quantities in the eye to constantly change.
GASTROINTESTINAL COMPLICATIONS

Although difficulty with swallowing, constipation, and diarrhea all may occur as downstream effects of diabetes on the autonomic nervous system, the primary gastrointestinal complication of the disease is gastroparesis, or partial paralysis of the stomach. Because the vagus nerve controls the motility of the stomach, damage to the vagus – which occurs in diabetic autonomic neuropathy – can lead to impaired motility. This partial paralysis of the stomach results in impaired gastric emptying.

More information about gastroparesis and other gastrointestinal complications of diabetes is discussed in the following articles:


History:
Because the stomach can only contain a finite amount of food at any point in time, the more slowly food empties out of the stomach, the less food that can enter during a meal. Thus, people with gastroparesis will often experience bloating, abdominal discomfort, and early satiety when eating. In more advanced gastroparesis, they may even have nausea and vomiting. Patients may also report difficulty avoiding hyperglycemia, since gastroparesis may cause an unpredictable and delayed rise in post-meal serum glucose.

Physical Exam:
Physical exam will be normal in most patients, but in those with severe disease, a succusion splash may be heard by holding either side of the patient’s pelvis and gently shaking the abdomen. A succusion splash can indicate gastric dilation, a consequence of gastroparesis that results from the stomach’s retaining too much liquid. If the gastroparesis is profound, the patient may even have a distended abdomen.

Tests:
While history tends to strongly support the diagnosis of gastroparesis, radiographic studies can show delayed gastric emptying. Such studies may also be used to rule out structural lesions as the cause of the patient’s symptoms. (See figure.)

Treatment:
Although it has not been proven, it has been suggested that better glycemic control can improve one’s gastric motility and emptying. In addition, smaller, more frequent meals can decrease symptoms. In patients suffering from nausea and vomiting in association with their gastroparesis, metoclopramide – which has both antiemetic and prokinetic activity – may be prescribed.

More information about the treatment of gastroparesis is discussed in the following article:

- Camilleri, Michael. “Treatment of delayed gastric emptying.” UpToDate.com

Self Assessments:
All of the following are true regarding the features of gastroparesis in people with diabetes, EXCEPT:

A. Autoimmune inflammation of the stomach muscle leads to impaired motility
B. Early satiety may occur because of impaired gastric emptying
C. A succusion splash indicates dilation of the stomach
D. In order to rule out structural lesions as the cause, barium-swallow radiographs may be obtained

Explanations:
A. Correct! Damage to the vagus nerve (as a result of autonomic neuropathy) leads to impaired stomach motility, not damage to the stomach muscle itself.
B. Incorrect. This is a true statement.
C. Incorrect. Gastric dilation is a consequence of gastroparesis and succussion splash reveals its presence.
D. Incorrect. Barium aids in the visual analysis of radiographs involving the gastrointestinal tract and can be quite useful to rule out structural causes of delayed stomach emptying.
GENITOURINARY COMPLICATIONS

Two of the very important genitourinary complications of diabetes are urinary tract infections and erectile dysfunction.

Urinary Tract Infections:
Diabetes is a risk factor for urinary tract infections (UTIs). UTIs are much more common in women than men, whether they have diabetes or not. Although the reason for the association between diabetes and UTIs is not completely understood, it may be mediated by a combination of factors, including neurogenic bladder and impaired immune system function. Neurogenic bladder is linked to autonomic neuropathy, as impaired innervation of the bladder leads to incomplete emptying (and thus a nidus for infection). Impaired immune system function results from decreased blood flow, in which an insufficient amount of leukocytes is transported to the area of infection, allowing it to persist longer than normal. Regardless of the cause, if left untreated, UTIs can spread up the ureter and into the kidney to cause acute pyelonephritis, a serious infection of the kidney.

Erectile Dysfunction:
Erectile dysfunction in diabetes can be caused by nerve damage or impaired blood flow. With nerve damage, the parasympathetic activation of the penis is interrupted and is thus incapable of producing erection. Since increased blood flow to the penis is responsible for the mechanics of erection, impairment of blood flow will make it difficult to both initiate and sustain an erection.

More information about the genitourinary complications of diabetes is discussed in the following articles:

History:
The patient with a UTI will typically complain of pain with urination, voiding small volumes, and urinary urgency and frequency. However, some UTIs may be asymptomatic and discovered by findings of white blood cells or bacteria on a urinalysis.

The chief complaint of a patient with erectile dysfunction will be an inability to initiate or sustain an erection.

Physical Exam:
Although physical exam is not useful to detect UTIs, one should look for fever and costovertebral angle tenderness, which would suggest pyelonephritis.

For erectile dysfunction, in addition to a routine physical exam, femoral and peripheral pulses should be noted as an indication of peripheral vascular disease (PVD). PVD is common in people with diabetes and may contribute to erectile dysfunction.

Tests:
For UTIs, urinalysis will show pyuria (white blood cells in the urine) and sometimes bacteruria. As UTIs are easily treated in most cases with inexpensive antibiotics, urine culture is not necessary routinely and should be reserved for patients with recurrent UTIs or for those who do not respond to antibiotics.

For erectile dysfunction, the value of hormone testing for testosterone (unrelated to diabetes) is debated. Nocturnal penile tumescence (NPT) testing is a method that can determine the number and tumescence of erectile episodes during sleep. Men with impaired NPT often have peripheral vascular disease or autonomic neuropathy (for which diabetes is a risk factor).

Treatment:
If history and urinalysis imply the presence of a UTI, antibiotics are initiated.
For erectile dysfunction, the leading pharmacologic treatments are the **phosphodiesterase inhibitors**: sildenafil, vardenafil, and tadalafil. These medications prolong nitric oxide’s vasodilating effects, thus helping to both initiate and maintain erection.

**Self Assessments:**
Phosphodiesterase inhibitors like sildenafil are helpful in treating erectile dysfunction because they:

- A. Improve blood glucose levels
- B. Improve nerve conduction
- C. Help control hypertension
- D. Prolong nitric oxide’s vasodilating effects

**Explanations:**
- A. Incorrect.
- B. Incorrect.
- C. Incorrect. Although sildenafil can lower blood pressure, because of its intermittent use (and other effects), it is not a good choice for hypertension. Of note, the combination of sildenafil and nitrates (e.g., nitroglycerin) can lead to profound hypotension.
- D. Correct! By prolonging nitric oxide’s vasodilating effects, phosphodiesterase inhibitors partially combat the impaired blood flow that results from peripheral vascular disease in people with diabetes. Thus, erectile tissue is able to swell with more blood, improving one’s ability to initiate and maintain erection.

Urinary tract infections (UTIs):

- A. Are more common in men with diabetes than women with diabetes
- B. May be partially caused by a neurogenic bladder
- C. Always involve pain with urination
- D. Are treated using corticosteroids

**Explanations:**
- A. Incorrect. UTIs are more common in women than men, with or without diabetes.
- B. Correct! Impaired innervation of the bladder (associated with autonomic neuropathy) leads to incomplete emptying, which produces a nidus for infection.
- C. Incorrect. UTIs may be completely asymptomatic and are discovered by findings of white blood cells or bacteria on a urinalysis.
- D. Incorrect. Since a decreased blood flow from peripheral vascular disease has also compromised the immune response, further dampening this response with corticosteroids would not be prudent. Instead, it would be much more beneficial to help the immune system fight the infecting bacteria by using antibiotics.
RENAL COMPLICATIONS

Not only do the kidneys participate in signaling the onset of type 1 diabetes mellitus, but they also are vulnerable to severe damage over the long-term course of the disease.

One of the most common presenting symptoms of type 1 diabetes is polyuria, which occurs when hyperglycemia is so great that the amount of glucose entering the nephron exceeds the amount that can be reabsorbed in the proximal tubule. What follows is osmotic diuresis, in which the solute (glucose) is trapped in the tubule lumen and causes water to remain in the lumen and thus be excreted rather than reabsorbed. The ensuing dehydration that occurs is compensated by the patient’s intense thirst, or polydipsia.

Approximately 30-40% of patients with type 1 diabetes and 20-30% of patients with type 2 diabetes will develop diabetic nephropathy. Although the reasons for developing this disorder have not been completely elucidated, evidence indicates that both genetic and environmental factors may play a role. Poor control of one’s diabetes appears to be a particularly significant risk factor for diabetic nephropathy, with hyperglycemia being the proposed culprit. Consistently high blood sugar favors glycosylation, resulting in the formation of structures called advanced glycosylation endproducts (AGEs). Because these are highly reactive species, they contribute to cross-linking of proteins in the mesangial matrix, as well as to thickening of the glomerular basement membrane – two of the principal features of diabetic nephropathy. Without the proper management, diabetic nephropathy can progress to end-stage renal disease, a major source of diabetes-related morbidity and mortality.

More information about the renal complications of diabetes is discussed in the following articles:

History:
Patients with new-onset diabetes (especially type 1, in which blood glucose levels can be very high) often note polyuria (as a downstream result of hyperglycemia) and polydipsia. Patients with long-standing diabetes may present with advanced renal disease and have symptoms of uremia: nausea and vomiting. They may also complain of decreased urine output. If renal function falls to less than 10% of normal, neurological changes of poor cognitive function, uremic encephalopathy, and involuntary jerking movements in the hands (asterixis) may occur.

Physical Exam:
In patients with advanced kidney disease who have decreased urine output, there may be edema and hypertension from the buildup of fluid. Because of the disturbances to one’s blood chemistry from severe renal failure, patients may have asterixis and/or decreased cognitive abilities. Uremic encephalopathy may even cause coma.

Tests:
In a patient with suspected diabetic nephropathy, the first line of tests will be blood and urine tests. While urinalysis may show glycosuria if the serum glucose is high enough, the first sign of diabetic nephropathy is persistent microalbuminuria, which is discovered by collection of a 24-hour urine sample. Blood tests will also be performed: the serum creatinine level is a standard barometer of kidney function; the blood urea nitrogen (BUN) level indicates the presence of azotemia/uremia.

The three major histologic changes in the glomeruli in diabetic nephropathy include: mesangial expansion; glomerular basement membrane thickening; and glomerular sclerosis. Glomerular sclerosis may have a nodular appearance, referred to as a Kimmelstiel-Wilson lesion (or Kimmelstiel-Wilson bodies). Observe these nodular deposits in the figure below.

Treatment:
Whether early in the onset of diabetes, or after the presence of diabetic nephropathy, it is always critical to emphasize to patients the importance of controlling their blood sugar. Even in patients with established diabetic nephropathy, glycemic control and lipid control can partially reverse glomerular hypertrophy and decrease the amount of protein excreted in the urine. Thus, although for many patients controlling their diabetes is a very demanding task, the benefits of meeting this challenge are plentiful.

In terms of pharmacological therapy for the patient with diabetic nephropathy, ACE inhibitors or Angiotensin Receptor Blockers (ARBs) can not only treat the hypertension that results from the kidney damage, but they can also reduce the amount of proteinuria and actually slow the progression of nephropathy. For these reasons, patients with microalbuminuria are typically prescribed one of these medications.

Screening for microalbuminuria should be done at five years after the diagnosis of type 1 diabetes since the date of diabetes onset is usually clear (patients present to a physician with initial symptoms) and nephropathy is uncommon until at least five years post-onset. In contrast, because many individuals with type 2 diabetes will have had hyperglycemia for years before presenting to a physician, some experts recommend that screening in these individuals should begin immediately upon the diagnosis of type 2 diabetes.

Self Assessments:
A 19 year-old college student developed type 1 diabetes at age 14. You now see him in your primary care clinic. To decrease his future risk of developing kidney failure from diabetic nephropathy, you should:

A. Encourage strict glycemic control
B. Initiate annual urine screening for microalbuminuria
C. Both A and B

Explanations:
A. Incorrect
B. Incorrect
C. Correct! Strict glycemic control is extremely important to decrease one’s risk of diabetic nephropathy. In addition, five years after the diagnosis of type 1 diabetes, annual screening for microalbuminuria is recommended to catch early signs of diabetic nephropathy, so that medical and lifestyle interventions can keep the patient from developing kidney failure.

Ten years later, this same patient (he is now 29 years old) reestablishes care with you. His diabetes has been under variable control. A urinalysis reveals proteinuria and glycosuria. Which of the following is MOST LIKELY occurring in his kidneys?

A. Thinning of the glomerular basement membrane
B. The formation of advanced glycosylation endproducts (AGEs)
C. Retraction of the mesangial matrix
D. Absence of nodular deposits because he does not yet have end-stage renal disease

Explanations:
A. Incorrect. Diabetic nephropathy involves thickening of the glomerular basement membrane.
B. Correct! Consistently high blood sugar is believed to produce advanced glycosylation endproducts (AGEs), highly reactive species that damage the mesangial matrix and glomerular basement membrane.
C. Incorrect. Diabetic retinopathy involves mesangial expansion.
D. Incorrect. Kimmelstiel-Wilson bodies indicate glomerular sclerosis, one of the primary features of diabetic nephropathy.
NEUROLOGICAL COMPLICATIONS

People with diabetes mellitus have a significantly greater risk of atherosclerosis than the general population. Not only do people with diabetes tend to have less HDL cholesterol to protect against oxidative damage, but their LDL particles are also smaller and more dense than normal, making these particles more vulnerable to oxidation and thus more capable of contributing to atherosclerotic plaques. Atherosclerosis in cerebral arteries can lead to brain tissue infarction, or ischemic stroke, from the obstruction of blood flow and subsequent brain tissue death. Stroke is a major cause of morbidity and mortality among people with diabetes.

History:
Depending on the location of an ischemic stroke, any number of symptoms may be manifested in the patient history. Some of the more common presenting complaints (depending on the area of brain affected) include loss of speech capabilities, cognitive changes, unilateral weakness, or unilateral loss of vision.

Physical Exam:
Profound unilateral weakness is readily apparent on exam. Subtler weakness, changes in speech ability, milder cognitive deficits, etc. are found by a careful neurological exam.

Information about conducting a thorough neurologic examination can be found at the following website: http://www.neuroexam.com/

Tests:
A head CT scan is the preferred imaging study because stroke is an emergency and these scans can be done very quickly. Although a head CT may not reveal the area of ischemia in the first 24 hours, it helps to rule out a hemorrhagic stroke, which would be a contraindication to thrombolytic therapy. An MRI typically provides more information, but this test can be hard to arrange urgently and is thus reserved for patients for whom questions remain after the acute presentation.

The figure at right shows a head CT scan of a patient who has suffered an ischemic stroke.

Treatment:
In the acute management of stroke, intracranial hemorrhage is ruled out as soon as possible by obtaining a head CT scan. If no hemorrhage is present, some patients may benefit from thrombolytic therapy. In addition, there are several experimental agents that might provide some neuroprotection to ischemic (not yet totally infarcted) neurons; large clinical trials for such drugs are pending.

During recovery from stroke, treatment is highly multidisciplinary. Initial recovery in a stroke unit has been associated with better long-term outcomes, as have the rapid initiation of physical activity, and the close involvement of family members in the patient’s care. An enormous amount of the recovery from stroke takes place in the first three months, so prevention of secondary complications and encouragement in all aspects of functioning are especially critical at this stage.

In terms of prevention of further strokes, first and foremost, the doctor and patient must work together to gain control of the diabetes and any concomitant modifiable cardiovascular risk factors (hypertension, hyperlipidemia, smoking). For those patients with atherosclerotic plaques that occlude greater than 70% of the internal carotid artery, surgical removal of the plaque (carotid endarterectomy) may be indicated.

More information about the prevention of future strokes in diabetic patients is discussed in the following article:


Self Assessments:
Which of the following is MOST CORRECT about a head CT scan in the evaluation of stroke?

A. It helps to rule out an intracranial hemorrhage
B. It typically takes much longer to obtain than an MRI
C. It can immediately confirm the location of ischemic stroke
D. It is obtained only if the patient presents with profound unilateral weakness

Explanations:
A. Correct! This is the primary reason for using a head CT scan in management of stroke. Only after intracranial hemorrhage has been ruled out can a patient be considered for thrombolytic therapy to treat their ischemic stroke.
B. Incorrect. Head CT scan is extremely fast, with results in minutes. MRI takes much longer to perform and most hospitals do not staff MRI machines around the clock.
C. Incorrect. It takes several hours (typically 24 hours, though subtle changes may be seen as early as 6 hours) before the infarcted area in an ischemic stroke becomes visible in a head CT scan.
D. Incorrect. Unilateral weakness is only one symptom of stroke. Other symptoms (such as loss of speech capabilities, unilateral loss of vision, and sudden cognitive changes) are also concerning for stroke; anytime the doctor suspects a stroke, a head CT scan should be ordered as soon as possible.
PERIPHERAL NERVE COMPLICATIONS

Disorders of the peripheral and autonomic nervous systems are some of the most common complications of diabetes mellitus. (See specific organs like the stomach or the genitourinary tract for a discussion of autonomic neuropathy.) Although there are many different clinical manifestations of peripheral neuropathy, the most common in people with diabetes is distal symmetrical polyneuropathy (DSPN). This disorder is characterized by a progressive loss of distal sensation in a classic "stocking-glove" distribution (due to the loss of sensory axons). In severe cases, sensory loss can be followed by damage to the motor axons and the patient may develop weakness. Because a major characteristic of this disorder is loss of sensation in one’s feet, it is critical for patients to visually inspect their feet everyday. Since patients cannot otherwise sense minor cuts or areas of excess pressure from poorly fitting shoes, visual inspection is critical to detect early problems before they develop into pressure ulcers and infections (see an example of an ulcer in the figure below). It is estimated that 20% of hospitalizations for people with diabetes are related to foot problems, so the importance of detecting ulcers and/or infections early cannot be overstated.

The severity and duration of hyperglycemia appears to be the most important risk factor for peripheral neuropathy, as evidenced by the fact that tight glycemic control can both limit the progression of peripheral neuropathy, or prevent it altogether. Although there are several theories about the cause of peripheral neuropathy, hyperglycemia is implicated in two different ways: excess glucose damages the small blood vessels supplying the neuron, causing the neuron to become ischemic; in addition, hyperglycemia induces deleterious metabolic changes in the neuron itself.

More information about the peripheral nerve complications of diabetes is discussed in the following articles:


History:
Even if the patient has not suffered from foot ulcerations or infection, there are many other complaints that will cause him or her to present to a physician. The most typical presentation will be a patient who complains of numbness and tingling in the feet, which gradually progresses up the lower leg in a characteristic stocking distribution. The upper extremities will also be affected, in a glove distribution (see figure). Some patients may complain of a burning pain. At more advanced stages, DSPN can also involve damage to the motor nerves, so patients may complain of distal weakness and foot drop.

Physical Exam:
The hallmark of DSPN is loss of sensation in a “stocking-glove” distribution (pain and temperature sensation are the first to go, followed by vibration, proprioception, and two-point discrimination). The device used to measure pressure sensation is the microfilament, an example of which is shown in the figure. Vibration sensation is also tested on the dorsum of the foot, typically with the use of a 128-Hz tuning fork. Inspection in a patient with DSTP is also quite valuable, as it may reveal atrophy of the distal muscles (if motor neurons are damaged) in both the upper and lower extremities, as well as joint deformities (which can further predispose the patient to pressure ulcers). Inspection is also critical for detecting the presence of ulcers, clawed toes, Charcot’s arthropathy (characterized by collapse of the midfoot arch and replacement with bony prominences), or infection. If there is purulent discharge from an ulcer combined with erythema, warmth, swelling, and tenderness (all signs of cellulitis), infection should be suspected and further evaluation of the foot should be performed; this includes checking for fluctuance and expression of pus from sinus tracts (indicates deep tissue infection), as well as looking for purple/black discoloration (indicates a necrotizing infection).

Strength testing may reveal symmetrical distal weakness, which contributes to a “steppage gait” as a compensation for foot drop (so as not to drag one’s toes on the ground when walking). Both tone and deep tendon reflexes can be reduced.
More information about the physical examination of the diabetic foot is discussed in the following articles:

- Feldman EL; Stevens MJ; Thomas PK; Brown MB; Canal N; Greene DA. "A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy." Diabetes Care 1994; 11:1281-9.

### Tests:

Several scoring rubrics have been designed that appear to have good predictability for DSPN. These take into account the patient’s numbness, pain, and tingling, as well as measurements of the patient’s sensation (using a monofilament), ankle reflexes, and appearance of the feet. At the end of the first paragraph, added on the following sentences: One generally accepted quantitative scoring system (Michigan) is as follows: 2 points in each foot for an absent Achilles tendon reflex, 1 point in each foot for absent or reduced vibration sense, 1 point in each foot for absent or reduced pressure sensation, and 1 point for reduced temperature sensation. When combining all of these facets of the neurologic examination, a total score of 0-2 is considered normal, 3-5 is mild, 6-8 is moderate, and 9-10 is severe peripheral neuropathy.

Note, if soft tissue infection is present (as indicated erythema, warmth, swelling, tenderness, and potentially fluctuance and/or expression of pus from sinus tracts), a plain radiograph or MRI of the affected foot to rule out osteomyelitis may be indicated. It is also possible that curettage of the ulcer base or deep tissue culture may be indicated to guide the choice of antibiotics.

In the event that one’s diabetes status is not already known (peripheral neuropathy may be a presenting feature of type 2 diabetes), a **fasting blood glucose** test should be obtained.

### Treatment:

The doctor and patient must work together to **optimize glycemic control**. In addition, the patient should be counseled about the importance of visually inspecting his or her feet every day. Patients at high risk (loss of sensation by monofilament testing, foot deformities, or prior foot ulcer) should be referred to a podiatrist.

Diabetic foot infection is a serious condition that can ultimately lead to foot or even above-knee amputation if severe deep tissue infection or osteomyelitis should develop. In non-limb threatening situations, a course of antibiotics and close monitoring is usually sufficient. However, if a patient has a limb-threatening infection (as indicated by the presence of gangrene, severe ischemia, or tissue necrosis), hospitalization with surgical debridement and parenteral antibiotics may be required; this is especially true in the case of osteomyelitis.

More information about the treatment of diabetic foot infections is discussed in the following articles:


### Self Assessments:

**Which of the following is MOST CORRECT in a patient with diabetic peripheral neuropathy?**

- A. Numbness and tingling will be present in a truncal distribution
- B. Deep tendon reflexes will be increased
- C. Muscle tone may be reduced
- D. Weakness will primarily affect one side over the other

**Explanations:**

A. Incorrect. The hallmark of distal symmetrical polyneuropathy (DSPN) is the loss of sensation in a stocking-glove distribution.

B. Incorrect. As is common with lower motor neuron disease, deep tendon reflexes will be reduced.
C. Correct! If the neuropathy affects lower motor neurons, tone (as well as strength and reflexes) is reduced.
D. Incorrect. The weakness in distal symmetrical polyneuropathy (DSPN) is typically symmetrical.

Which of the following is critical to the management of diabetic peripheral neuropathy?

A. Strict glycemic control
B. Daily visual inspection of one's feet
C. Seeking immediate medical attention for foot ulcers
D. All of the above

Explanations:
A. Incorrect.
B. Incorrect.
C. Incorrect.
D. Correct! Each of these strategies is critical to the management of diabetic peripheral neuropathy.
PERIPHERAL VASCULAR COMPLICATIONS

Peripheral vascular disease (PVD) is the clinical term for atherosclerosis of the large arteries of the leg. Risk factors for PVD are the same as those for atherosclerosis of the coronary arteries, i.e. hypertension, diabetes, smoking, hyperlipidemia, older age, and family history. Due to atherosclerosis in the peripheral vasculature (specifically, the iliac, femoral, and popliteal arteries), PVD causes decreased blood flow to the lower extremities and can lead to intermittent claudication. Often referred to as “angina of the legs”, claudication involves lower extremity muscle pain during times of high metabolic demand (such as walking); the decreased blood flow is not able to provide the adequate oxygen and nutrients that the hard-working muscles require. Unless severe PVD exists, claudication is typically relieved by rest, which lowers the muscles’ metabolic requirements.

More information about the peripheral vascular complications of diabetes is discussed in the following articles:


History:
A patient with PVD will often present with exercise-induced pain or tightness in muscles of the lower limb, i.e., claudication. Often patients can quantify the amount of walking required to bring on pain by the number of blocks walked when the pain arises. Symptoms usually occur in the calf, but may be as high as the thigh or even buttock. For unclear reasons, the upper extremities are not usually affected by PVD. Patients with PVD may also complain of foot ulcers that do not heal. Because of atherosclerosis, the amount of blood flow to the ulcerated region is inadequate to heal the ulcer.

Physical Exam:
Inspection alone can be very telling in PVD: the decreased blood flow to the lower extremities may lead to selective loss of leg hair, causing the skin to appear shiny. In addition, there may be ulcers that do not heal over time.

Finally, another result of the decreased blood flow is that peripheral pulses will be diminished.

Tests:
A history indicating exercise-induced pain in the muscles of the leg, which is relieved by rest, is generally a reliable indicator of PVD. However, measurement of the ankle-brachial index, comparing resting and post-exercise systolic blood pressures in the ankle and arm, can confirm the diagnosis.

If revascularization is being considered to treat a patient’s PVD, an arteriogram of the arteries supplying the lower extremities may be ordered to guide the intervention. (Compare the narrowed iliac artery in Figure 1 to the same artery after stent placement in Figure 2.)

Treatment:
Because PVD is highly correlated with cardiovascular disease, the use of aspirin may be warranted to protect against cardiac events. Unfortunately, aspirin does not decrease the symptoms from claudication. A medication that has been shown to decrease claudication symptoms is cilostazol (a phosphodiesterase inhibitor).

Since atherosclerosis is the underlying cause of PVD, improving control of modifiable risk factors – hypertension, hyperlipidemia, smoking, and of course, diabetes – can be quite beneficial.

If none of the above treatments improves the patient’s claudication, or if there is pain at rest, gangrene, or persistent foot ulcers that fail to heal, revascularization may be indicated. This may be done by either angioplasty or surgery (with use of artificial bypass grafts).
Self Assessments:
Which of the following would be LEAST LIKELY to occur in a patient with peripheral vascular disease?

A. Exercise-induced pain in the calf
B. Exercise-induced pain in the buttock
C. Loss of leg hair
D. Loss of arm hair
E. Non-healing foot ulcers

Explanations:
A. Incorrect. This pain results from ischemia due to the compromised blood flow to the region.
B. Incorrect. This pain results from ischemia due to the compromised blood flow to the region.
C. Incorrect. With compromised blood flow, hair cells can no longer obtain adequate nutrients to stay alive.
D. Correct! Since peripheral vascular disease affects mainly the lower extremities, ischemia-induced hair loss in the upper extremities is not expected.
E. Incorrect. Because of atherosclerosis, the amount of blood flow to the ulcerated region is inadequate to heal the ulcer.

Revascularization:

A. Is a first-line treatment for peripheral vascular disease
B. May involve an arteriogram of the affected artery
C. Is indicated only if the patient complains of leg pain at rest

Explanations:
A. Incorrect. Unless there are serious warning signs, such as rest pain, gangrene, or non-healing foot ulcers, risk factor management and pharmacologic intervention should be tried prior to revascularization
B. Correct! An arteriogram indicates the area and severity of blockage, thus providing critical knowledge to the doctors performing an angioplasty.
C. Incorrect. Revascularization is indicated if there is: pain at rest, gangrene, or persistent foot ulcers that fail to heal.
VISUAL COMPLICATIONS

The leading cause of blindness in American adults is diabetic retinopathy, a common consequence of microvascular disease in people with diabetes. The small blood vessels supplying the retina are particularly vulnerable to hyperglycemia. Over time, chronic hyperglycemia leads to progressive occlusion of these vessels, as well as microaneurysms (which are outpouchings of weakened vessel walls). Both of these can be damaging to one’s sight. Microaneurysms can lead to leakage of lipid and protein material, so-called “hard exudate”. In addition, there can be macular edema and subsequent moderate vision loss. Vessel occlusion can cause retinal ischemia, which in turn promotes neovascularization, the body’s attempt to restore perfusion to the retina. Unfortunately, the newly generated vessels are prone to bleeding, which results in hemorrhages. All these processes – leakage of lipid and protein, macular edema, and hemorrhages – cause prolonged vision loss. In addition, the scarring that takes place after neovascularization may actually lead to retinal detachment and permanent loss of vision.

More information about the pathophysiology, evaluation, and management of diabetic retinopathy is discussed in the following articles:


History:
The history of patients with diabetic retinopathy may range widely, from being asymptomatic in individuals who present for routine checkups, to quite worrisome, with complaints of acute onset of blurry vision or even sudden blindness.

Physical Exam:
Certain features that are observed in the fundoscopic exam are used to divide diabetic retinopathy into two different stages: nonproliferative (or “background”) retinopathy and proliferative retinopathy. The key features of nonproliferative retinopathy include microaneurysms and hard exudates (see Figure 1). As its name implies, this stage of the disease does not involve neovascularization. Proliferative retinopathy, on the other hand, does involve neovascularization, as well as the presence of several hemorrhages because of the fragility of these new vessels (see Figure 2).

Tests:
Direct ophthalmoscopy by a well-trained person (typically an ophthalmologist or optometrist) is the best method for detecting diabetic retinopathy.

Treatment:
Strict glycemic control is very effective in not only preventing retinopathy, but also in slowing its rate of progression. Unfortunately, glycemic control shows little or no benefit in people with advanced retinopathy, demonstrating that it is critical for physicians to screen for the disorder early and emphasize the importance of glycemic control to their patients.

Pharmacological therapy may also be useful in treating diabetic retinopathy. Because both hypertension (which increases the risk of hemorrhage) and ischemia contribute to the progression of diabetic retinopathy, anti-hypertensive and anti-platelet drugs may be indicated.

In advanced retinopathy, photocoagulation (laser therapy to halt neovascularization) and vitrectomy (removal of the vitreous humor of the eye) may be indicated.

More information about current treatments for diabetic retinopathy is discussed in the following article:


Self Assessments:
All of the following components of diabetic retinopathy are correctly paired with their corresponding features, EXCEPT:

A. Neovascularization: hemorrhages
B. Hard exudates: lipids and proteins
C. Microaneurysm: thickened vessel walls

Explanations:
A. Incorrect. The new vessels resulting from neovascularization are very fragile and thus are prone to hemorrhage.
B. Incorrect. Together, the plasma lipids and proteins that escape through the vessel wall in microaneurysms compose hard exudate.
C. Correct! Microaneurysms are outpouchings of weakened vessel walls, not thickened vessel walls.

The most beneficial intervention for preventing diabetic retinopathy is:

A. Strict glycemic control
B. Vitrectomy
C. Photocoagulation

Explanations:
A. Correct! Strict glycemic control has been proven to not only slow the rate of progression of diabetic retinopathy, but also to prevent retinopathy altogether. Thus, the benefits of glycemic control must always be emphasized by the physician.
B. Incorrect. Although vitrectomy is helpful in the treatment of advanced retinopathy, it has no application in the prevention of the disease.
C. Incorrect. Although photocoagulation is helpful in the treatment of advanced retinopathy, it has no application in the prevention of the disease.