

Strategies to Reduce the Risk of Diabetes Complications



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The following program is a taped presentation by Carolyn Robertson.

Ms. Robertson is a certified diabetes educator (CDE) and board certified in Advanced Diabetes Management (BC-ADM). She has more than 30 years of experience in diabetes education in intensive/flexible diabetes management, with an active patient caseload for more than 25 years. Ms. Robertson was a pioneer in the intensive management of diabetic pregnancies with over 400 successful pregnancies, as well as an early pioneer in insulin pump therapy. She also has expertise in type 2 diabetes management and in the management of patients with kidney and pancreas transplantation.

At the present time, Ms. Robertson has a private practice (*Customized Diabetes Education*) located in New York, serves as the Associate Director of a nonprofit program, and has a contract with the Gonda Diabetes Center at UCLA in California as director of special projects. She is also on the editorial board of *Diabetes Self-Management*, a patient-oriented magazine. Ms. Robertson remains actively involved in clinical research, consultation, and mentoring. Ms. Robertson has been a local board member of both the Juvenile Diabetes Research Foundation International and the American Diabetes Association (ADA). She has published widely in peer-reviewed journals, trade journals, newsletters, as well as on the Internet. Ms. Robertson lectures frequently to local, national, and international audiences of health care professionals, patients, and the general public.

We'll now join Ms. Robertson.

Program Objectives

- Identify the chronic complications of diabetes and how they impact morbidity and mortality
- Explain how the results of various clinical trials reinforce the need for comprehensive risk management
- Review the current recommendations for the prevention and treatment of diabetes complications

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- Explain how the results of various clinical trials reinforce the need for comprehensive risk management.
- Review the current recommendations for the prevention and treatment of diabetes complications.

Diabetes Complications

Macrovascular

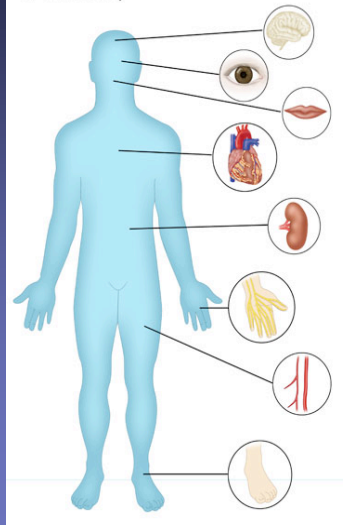
- Coronary artery disease (CAD)
 - Atherosclerosis
 - Myocardial infarction (MI)
- Cerebrovascular disease (CVD) (stroke)
- Peripheral vascular disease (PVD)

Microvascular

- Nephropathy
- Retinopathy
- Neuropathy

Other

- Bone density changes (osteoporosis, fractures)
- Collagen disorders (scleroderma)
- Frozen shoulder
- Impaired wound healing
- Altered clotting factors
- Periodontal disease
- Erectile dysfunction



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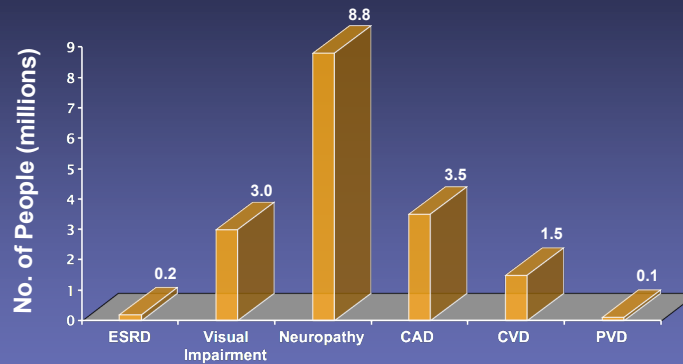
Diabetes is unfortunately associated with complications. These complications traditionally have been divided into 2 major categories: macrovascular and microvascular.

Macrovascular complications primarily affect large blood vessels and can lead to heart disease, cerebrovascular disease (CVD), and peripheral vascular disease (PVD).

Microvascular complications affect smaller blood vessels and can lead to damage to the kidneys, eyes, or nerves.

Other less well-known complications include bone conditions (such as osteoporosis in type 1 diabetes and fractures in type 2 diabetes), collagen disorders such as scleroderma, frozen shoulder, impaired wound healing, altered clotting factors, periodontal disease, and erectile dysfunction. Many of these complications share cellular, metabolic, and pathophysiologic mechanisms with macro- and microvascular complications.

Prevalence of Diabetes Complications (2005)



ESRD = end-stage renal disease; CAD = coronary artery disease; CVD = cerebrovascular disease (stroke); PVD = peripheral vascular disease.

NIDDK. US Renal Data System 2007 Annual Report. Available at: <http://www.usrds.org>.

CDC. Data and trends: National diabetes surveillance system. Available at:

<http://www.cdc.gov/diabetes/statistics/index.htm#lea>. 2006.

CDC. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf.

According to data from the Centers for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a large number of people with diabetes suffer from micro- and macrovascular complications. In 2005:

- About 1/4 million people with diabetes had end-stage renal disease (ESRD).
- Approximately 3 million were visually impaired as a result of diabetes.
- Almost 9 million were hospitalized for diabetic neuropathy.
- Another 3.5 million people with diabetes had coronary artery disease (CAD); while 1-1/2 million people had a CVD (stroke).
- Finally, 100,000 people were hospitalized for diabetes-associated PVD.

Impact of Diabetes-Related Macrovascular Complications

- **CAD and CVD in patients with diabetes**
 - Account for ~65% of deaths
 - Death rate from CAD ~2–4X higher
 - Risk for stroke ~2–4X higher
 - ~50% of patients with CAD have undiagnosed diabetes or impaired glucose tolerance
- **PVD in patients with diabetes**
 - Risk factor for lower-limb amputation
 - More than 60% of nontraumatic lower-limb amputations occur in patients with diabetes

CDC. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf.
Bartnik M et al. *Eur Heart J*. 2004;25:1880–1890.
Taubert G et al. *Am Heart J*. 2003;145:285–291.

In terms of macrovascular complications:

- ~65% of deaths among people with diabetes are caused by myocardial infarction (MI) or stroke.
- The death rate from CAD is about 2 to 4 times higher among people with diabetes than those without diabetes.
- The risk for stroke is also approximately 2–4 times higher in people with diabetes as compared with those without diabetes.
- By the time diabetes or prediabetes (impaired glucose tolerance) is diagnosed, half of the people already have CVD.
- If a patient has both diabetes and PVD, he is at risk for lower-limb amputation.
- More than 60% of all nontraumatic lower-limb amputations occur in patients with diabetes.

Impact of Diabetes-Related Microvascular Complications

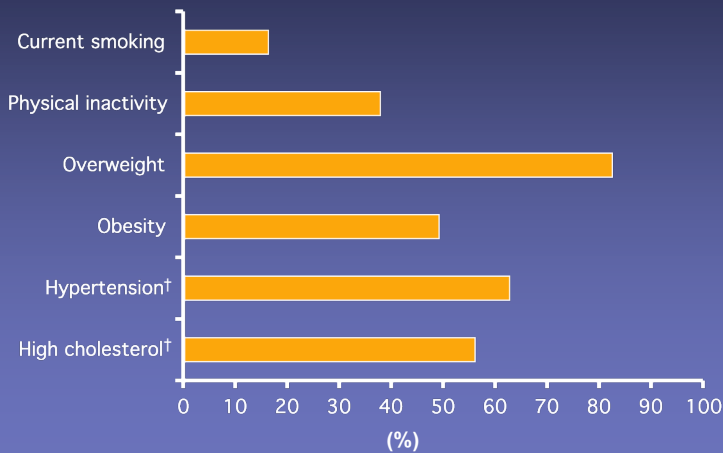
- **Diabetic nephropathy**
 - Leading cause of ESRD (~44% of new cases in 2003)
- **Retinopathy**
 - Leading cause of new cases of blindness in adults
- **Neuropathy**
 - Severe forms are major contributing cause of lower-extremity amputations

CDC. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf.

Epidemiological data from the CDC also demonstrate the tremendous impact of microvascular complications on morbidity and mortality:

- Diabetic nephropathy is the leading cause of ESRD accounting for ~44% of new cases in 2003.
- Diabetic retinopathy is the leading cause of new cases of blindness in adults.
- Severe forms of diabetic neuropathy are a major contributing cause of lower-extremity amputations.

Prevalence* of Risk Factors for Complications (2004)



CDC. Data and trends: National diabetes surveillance system.
Available at: <http://www.cdc.gov/diabetes/statistics/comp/fig10.htm>. 2008.

*In people with diabetes.
†2003 data.

Large-scale clinical trials (which will be outlined on the next few slides) have shown the direct link between hyperglycemia and diabetes complications. There are numerous other risk factors that contribute to the poor outcomes among people with diabetes. These risk factors, which include smoking, physical inactivity, overweight, obesity, hypertension, and high cholesterol, range in prevalence from ~20% to 80%. It is important to emphasize that each of these risk factors can be modified.

Rationale for Comprehensive Risk Management

- **Glycemic control**
 - Each 1% drop in A1C reduces risk of microvascular complications ~40%
- **Blood pressure control**
 - Reduces risk for CAD or CVD ~33% to 50%
 - Reduces risk of microvascular complications ~33%
- **Lipid control**
 - Reduces risk for CAD or CVD ~20% to 50%

CDC. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf.

So what is the rationale for risk management? Controlling glucose, blood pressure, and lipid levels can significantly reduce the risk for diabetes complications. Based on data from major clinical trials:

- Each 1% drop in A1C (eg, a drop from 8% to 7%) can reduce the risk of microvascular complications by ~40%.
- Blood pressure control can reduce the risk of coronary artery disease and cerebral vascular disease by ~33% to 50% and the risk for microvascular complications by ~33%.
- Reducing cholesterol levels can reduce the risk for coronary artery disease and cerebral vascular disease by ~20% to 50%.

Rationale for Comprehensive Risk Management (Cont.)

- **Nephropathy detection and treatment**
 - Reduces decline in kidney function ~30% to 70%
- **Retinopathy detection and treatment**
 - Reduces severe vision loss ~50% to 60%
- **Foot care**
 - Reduces amputation rates ~45% to 85%

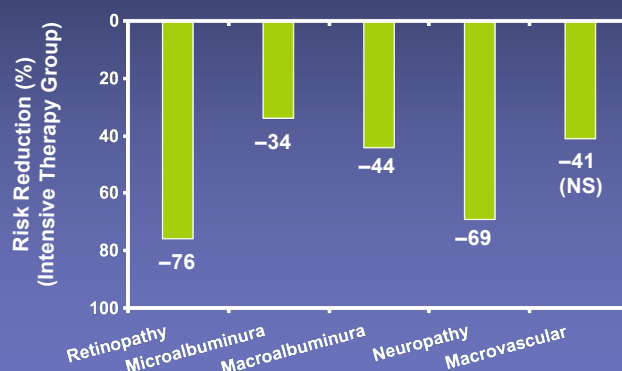
CDC. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf.

Additionally, there are other important prevention strategies that can significantly reduce the risk and severity of diabetes complications:

- Nephropathy screening, by measuring levels of microalbumin creatinine in the urine, and aggressive treatment of nephropathy has the potential to reduce the decline in kidney function by ~30% to 70%.
- Screening for retinopathy by examining a dilated eye and following with appropriate treatment can reduce severe vision loss by ~50% to 60%.
- Regular foot care, which includes foot inspections by both the patient and provider, can reduce amputation rates by ~45% to 85%.

Diabetes Control and Complications Trial (DCCT)

Mean plasma glucose*: 231 mg/dL (Conventional) 155 mg/dL (Intensive)
 Mean A1C*: 9.0% (Conventional) 7.2% (Intensive)



*End of study.
 NS = not significant.

DCCT Research Group. *N Engl J Med.* 1993;329:977-986.

The benefits of intensive diabetes control have been demonstrated in several large studies. This slide identifies the results of the Diabetes Control and Complications Trial (DCCT). The DCCT evaluated the effects of different treatment approaches on the long-term complications of type 1 diabetes. A total of 1441 participants were randomized to receive intensive therapy with an insulin pump or ≥ 3 daily insulin injections and frequent blood glucose monitoring, or to receive conventional therapy with 1 or 2 daily insulin injections.

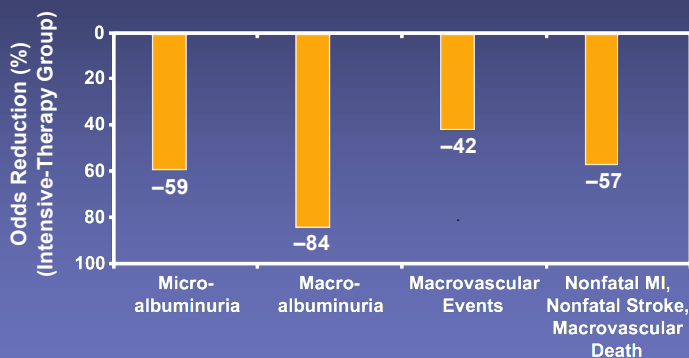
The study was ended early after ~6.5 years of follow-up. It was found that intensive efforts to achieve glucose control with either multiple daily injections of insulin or insulin pumps were associated with better glycemic control and lower risk of complications than twice-a-day insulin.

The mean plasma glucose and A1C among those who received conventional therapy were 231 mg/dL and 9.0%, respectively, as compared with 155 mg/dL and 7.2%, respectively, among patients who received intensive therapy. This difference was statistically significant.

The percent risk reduction in retinopathy, microalbuminuria, macroalbuminuria, and neuropathy among patients who received intensive therapy ranged from 34% for microalbuminuria to 76% for retinopathy. These reductions in risk for microvascular complications were also statistically significant.

A 41%, albeit nonsignificant, reduction in macrovascular risk was noted. However, the relative youth of the patient population made detection of treatment-related differences in rate of macrovascular disease unlikely.

Epidemiology of Diabetes Interventions and Complications (EDIC) Study



DCCT/EDIC Research Group. *JAMA*. 2003;290:2159–2167.
Nathan DM et al. *N Engl J Med*. 2005;353:2643–2653.

The Epidemiology of Diabetes Interventions and Complications (also known as EDIC) study followed patients after the DCCT study for an additional 8 years to determine whether the effects of intensive therapy could be sustained.

During the EDIC study, the difference in A1C levels between the intensive- and conventional-treatment groups of the DCCT diminished. Yet, the differences in the outcomes between the 2 groups, including the risk for developing micro- and macrovascular complications, persisted.

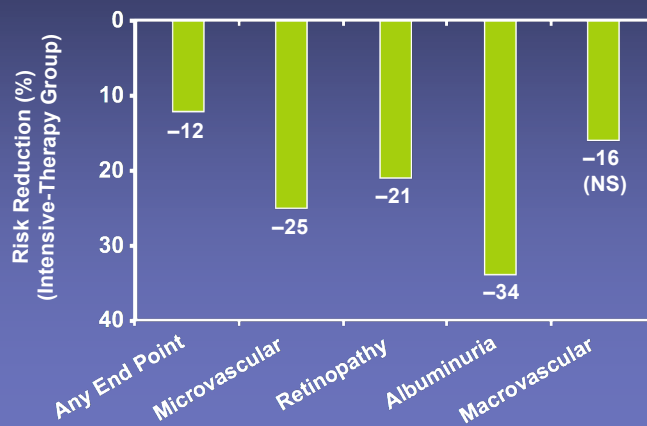
Specifically, the EDIC study demonstrated the following:

- 59% reduction in odds of new cases of microalbuminuria
- 84% reduction in odds of new cases of macroalbuminuria
- 42% reduced risk of any cardiovascular disease event
- 57% reduced risk of nonfatal MI, nonfatal stroke, and death from cardiovascular disease

The beneficial reduction in both micro- and macrovascular end points among those initially treated aggressively has been attributed to a metabolic memory of good and poor glucose control that persists over time. Thus, results of the EDIC study suggest that at any stage of diabetes, glycemic control can have long-term benefits.

United Kingdom Prospective Diabetes Study (UKPDS)

Mean A1C at end of study: 7.9% (Conventional) 7.0% (Intensive)



UKPDS Group. *Lancet*. 1998;352:837-853.

While the DCCT and EDIC studies evaluated the effects of intensive therapy in people with type 1 diabetes, they did not answer whether intensive therapy would have the same effect in patients with type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) evaluated the effects of intensive therapy in people with type 2 diabetes.

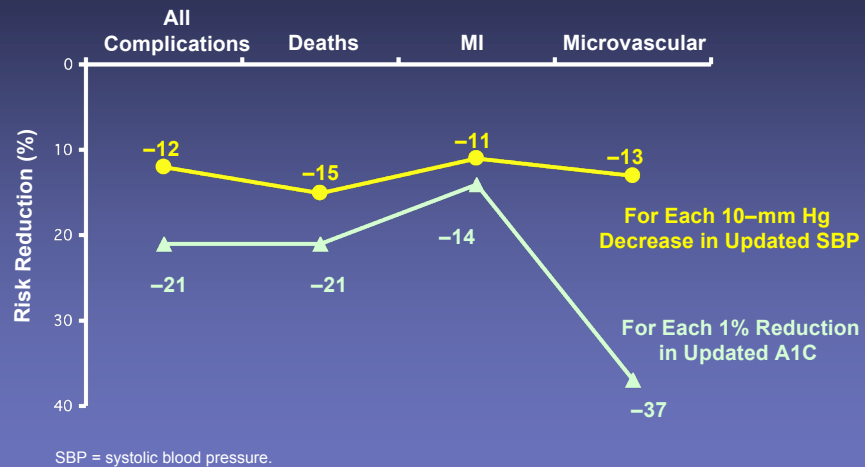
This was the largest and most comprehensive study of people with type 2 diabetes to date. The UKPDS randomized about 4000 patients with newly diagnosed type 2 diabetes to intensive therapy with a sulfonylurea or insulin, or to conventional therapy with diet.

Over 10 years, participants who received intensive therapy maintained an A1C level of 7.0% as compared with an A1C level of 7.9% among those who received conventional therapy.

Intensive therapy was associated with clinically and statistically significant reductions in the risk of developing:

- Any diabetes-related complication (12%)
- Microvascular complications (25%)
- Retinopathy (21%)
- Albuminuria (34%)

UKPDS: A1C and Blood Pressure



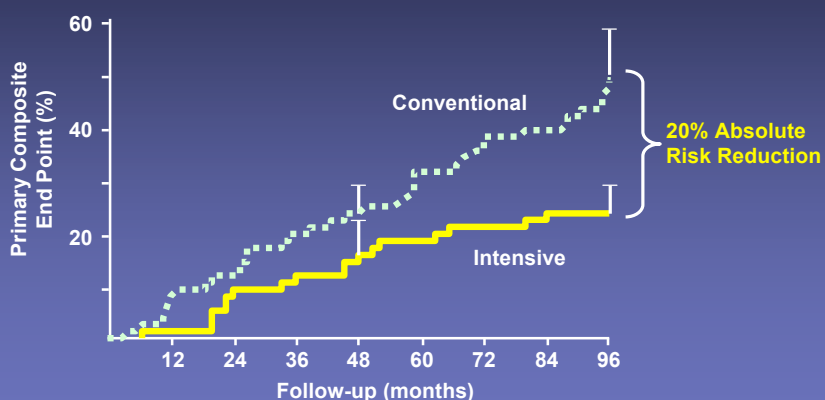
Adler I et al. *BMJ*. 2000;321:412–419.
Stratton IM et al. *BMJ*. 2000;321:405–412.

This slide demonstrates the impact of A1C and blood pressure reductions. The light blue line on the graph represents the risk reduction related to A1C. For each 1% reduction in A1C there was a 21% reduction in the incidence of all clinical complications, 21% reduction in deaths related to diabetes, 14% reduction in MI, and 37% reduction in microvascular complications, with no threshold for any end point.

The yellow line represents the effects of lowering systolic blood pressure. For each 10–mm Hg reduction in systolic blood pressure, a 12% reduction in the incidence of all clinical complications, a 15% reduction in deaths, an 11% reduction in MI, and a 13% reduction in microvascular complications was observed.

A decreased risk of macrovascular end points approached, but did not reach statistical significance in this study.

Multifactorial Intervention Study (Steno 2)



Gaede P et al. *N Engl J Med.* 2003;348:383–393.

The STENO 2 study was yet another study that evaluated the benefits of intensive therapy on the development of diabetes complications. This multifactorial intervention study compared the benefits of targeted, intensified intervention with that of conventional therapy on outcomes in patients with type 2 diabetes.

Eighty patients with type 2 diabetes and microalbuminuria were assigned to receive conventional therapy according to national guidelines, while another 80 patients received intensive treatment with a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria along with secondary prevention of cardiovascular disease with aspirin.

After ~8 years of follow-up, intensive multifactorial intervention reduced the risk of microvascular and cardiovascular events by ~50%.

This graph shows the Kaplan-Meier estimates of the composite end point (death from cardiovascular causes, nonfatal MI, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation, or surgery for PVD) between the 2 treatment groups. The study estimated a 20% absolute reduction in the risk of cardiovascular events with intensive multifactorial intervention.

Current Management Goals

Parameter	ADA	AACE
A1C	<7%	≤6.5%
Fasting/preprandial glucose (mg/dL)	70–130	<110
Postprandial glucose (mg/dL)	<180*	<140†
Blood pressure (mm Hg)	<130/80	
LDL cholesterol (mg/dL)	<100 (<70 for existing CVD)	
HDL cholesterol (mg/dL)	>40 for men or >50 for women	
Triglycerides (mg/dL)	<150	

ADA = American Diabetes Association; AACE = American Association of Clinical Endocrinologists;
LDL = low-density lipoprotein; HDL = high-density lipoprotein.

*Peak postprandial capillary plasma glucose.

†2-Hour postprandial glucose.

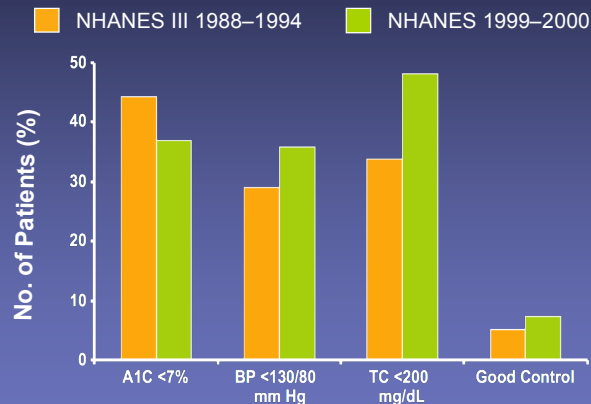
American Diabetes Association. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.

American Association of Clinical Endocrinologists. *Endocr Pract*. 2007;13(Suppl 1):4–68.

The management goals for diabetes aim to reduce the risk of complications by addressing multiple variables: improving glycemic control, reducing blood pressure, and treating dyslipidemia.

Because no studies have identified a threshold below which the risk of complications is zero, the targets for A1C and fasting glucose levels are intended to maintain glucose levels as near to normal as possible without an excessive risk of hypoglycemia.

No Improvements in Achieving Goals Over Time



NHANES = National Health and Nutrition Examination Survey; BP = blood pressure; TC = total cholesterol.

Resnick HE et al. *Diabetes Care*. 2006;29:531–537.
Saydah SH et al. *JAMA*. 2004;291:335–342.

Despite the evidence that achieving control makes a difference, the National Health and Nutrition Examination Survey (NHANES), conducted 1999–2000, identified that only 7.3% of adults with diabetes attain the combined targets of an A1C <7.0%, blood pressure <130/80 mm Hg, and total cholesterol <200 mg/dL. Good control refers to meeting the target goals for ABC's of diabetes management—A1C, blood pressure, and total cholesterol.

Compared with the NHANES data from 1988–1994, it becomes obvious that control has not improved in the last 10 years. These findings signify tremendous deficiencies in the management of diabetes and diabetes complications. Although the cause of these deficiencies may be multifactorial, improving adherence to guidelines for glycemic, blood pressure, and lipid control can have a big impact.

Question

The primary cause of death in patients with diabetes is:

- A. Renal disease
- B. Impaired wound healing
- C. Cardiovascular disease
- D. Neuropathy complications

Now it is time for a question.

The primary cause of death in patients with diabetes is:

- A. Renal disease
- B. Impaired wound healing
- C. Cardiovascular disease
- D. Neuropathy complications

Answer

C. Cardiovascular disease accounts for 65% of all deaths in diabetes.

The correct answer is C.

Cardiovascular disease accounts for 65% of all deaths in diabetes.

Cardiovascular Risk Factors

- Hypertension
- Obesity (BMI ≥ 30 kg/m²)
- Dyslipidemia
- Cigarette smoking
- Physical inactivity
- Microalbuminuria
- Diabetes mellitus
- GFR < 60 mL/min
- Age (older than 55 for men, 65 for women)
- Family history of premature cardiovascular disease (men under 55, women under 65)

BMI = body mass index; GFR = glomerular filtration rate.

Chobanian AV et al. *JAMA*. 2003;289:2560–2572.

Numerous cardiovascular risk factors, in addition to diabetes, contribute to the development of macrovascular complications. These include risk factors that can be modified, such as hypertension, obesity, dyslipidemia, smoking, physical inactivity, and microalbuminuria. Risk factors that cannot be modified include diabetes, a glomerular filtration rate of < 60 mL/min, age, and family history.

It is interesting to note that hypertension, obesity, and dyslipidemia commonly coexist with diabetes and together comprise the metabolic syndrome. A condition that is also associated with a high risk of cardiovascular disease.

Macrovascular Complications

- CAD
 - Atherosclerosis
 - Angina
 - MI
- PVD
 - Ischemia and infarction
- CVD
 - Transient ischemic attacks
 - Ischemic stroke
 - Cerebral thrombosis
 - Cerebral occlusion
 - Hemorrhagic stroke
 - Aneurysm
 - Arteriovenous malformation

As previously mentioned, the macrovascular complications of diabetes include CAD, CVD, and PVD.

Blockage of the coronary arteries that occurs with CAD can lead to the development of acute coronary syndromes, a constellation of clinical symptoms caused by myocardial ischemia. It can include:

- Angina (chest pain that occurs with exertion)
- Unstable angina (chest pain that occurs at rest)
- Myocardial infarction resulting from coronary thrombosis or occlusion

When vessels supplying the brain become blocked, transient ischemic attacks or strokes can occur. Two types of strokes can develop:

- Ischemic stroke resulting from cerebral thrombosis or occlusion
- Hemorrhagic stroke resulting from rupture of an aneurysm or arteriovenous malformation

Blockage of vessels that supply the lower extremities can cause ischemia and infarction that result in leg pain and gangrene.

CAD in Women with Diabetes

- Relative risk for diabetes-related CAD death in women is **50% greater** than in men
- Reasons
 - Women with diabetes have worse adverse-risk profiles than men with diabetes and women without diabetes
 - Greater degrees of dyslipidemia, hypertension, BMI, lack of glycemic control
 - Loss of protective effect of estrogen
 - More aggressive treatment bias toward men?

Huxley R et al. *BMJ*. 2006;332:73–78.
Juutilainen A et al. *Diabetes Care*. 2004;27:2898–2904.
Gouni-Berthold I et al. *Diabetes Care*. 2008;31:1389–1391.

Several studies have demonstrated that women with diabetes and CAD fare worse than men with diabetes and CAD. A meta-analysis of 37 studies looking at type 2 diabetes and fatal CAD found that the relative risk for CAD death was 50% greater among diabetic women than diabetic men. This increased risk is attributed at least in part to a heavier risk factor burden among diabetic women relative to nondiabetic women or diabetic men.

Some investigators have suggested that inflammatory factors may interact with female sex hormones, decreasing their protective effect on body fat distribution and insulin action. This could also be the case among postmenopausal diabetic women. In addition, women with CAD and diabetes are less likely to have their modifiable risk factors controlled and less likely to receive lipid-lowering treatments, suggesting a treatment bias toward men.

Another explanation (but true for men as well) is the sometimes atypical nature of the presentation. Patients may not present complaining of chest pain. Rather, the symptoms may be a sore shoulder, toothache, etc.

Screening for Macrovascular Disease

Assess for cardiovascular risk factors **at least annually**

- Dyslipidemia
- Hypertension
- Smoking
- Family history of premature coronary disease
- Presence of albuminuria (micro or macro)

Stratify patients by 10-year risk and treat risk factors accordingly

- Online risk calculators available

Screen for PVD using ankle-brachial index

ADA. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.
Buse JB et al. *Circulation*. 2007;115:114–126.

All patients with diabetes should be evaluated and have an assessment of cardiovascular risk performed at least annually. Clinicians should be alert for symptoms of atherosclerosis. In asymptomatic patients, risk factors should be evaluated to stratify patients by 10-year risk; risk factors should be treated accordingly. There are several risk calculators available, including:

1. Framingham risk calculator
2. UKPDS risk engine
3. American Diabetes Association (ADA)'s Diabetes Personal Health Decisions

The ankle-brachial index (ABI) is used to screen for PVD. The ABI is a ratio of systolic blood pressure at the ankle and the brachial artery.

An important component of screening is patient education. At a minimum, patients should be given information regarding the signs and symptoms of a heart attack or stroke. Patients should be told to report any pain above the waist, as it may indicate a heart attack, and to seek immediate attention if a stroke is suspected.

Primary Prevention of Cardiovascular Disease

- Glycemic control
- Blood pressure control (at each visit)
- Lipid control (annually and as needed)
- Lifestyle modification
 - Medical nutrition therapy (MNT)
 - Physical activity
 - Weight management
 - Tobacco cessation
- Antiplatelet agents

ADA. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.
Buse JB et al. *Circulation*. 2007;115:114–126.

Since cardiovascular disease is the major cause of morbidity and mortality among people with diabetes, prevention of macrovascular complications that contribute to cardiovascular disease is a primary goal of diabetes management. Diabetes itself, hypertension, and dyslipidemia are all contributing factors and each should be managed appropriately according to established guidelines and recommendations to reduce the morbidity and mortality associated with the disease.

As previously noted, glycemic control (A1C <7%), treatment of blood pressure (goal <130/80 mm Hg), and lipid control according to established guidelines are essential to the primary prevention of cardiovascular disease. Lifestyle management considerations, such as medical nutrition therapy (MNT), physical activity, weight management, and tobacco (smoking) cessation, are also important. Lastly, antiplatelet therapy is recommended as a primary prevention strategy in patients at increased cardiovascular risk.

Lifestyle Changes and Blood Pressure

<u>Modification</u>	<u>Approximate Systolic Blood Pressure Reduction</u>
Weight reduction	5–20 mm Hg for each 10-kg weight loss
Adopt DASH diet	8–14 mm Hg
Dietary sodium reduction	2–8 mm Hg
Physical activity	4–9 mm Hg
Moderation of alcohol consumption	2–4 mm Hg

DASH = Dietary Approaches to Stop Hypertension

Chobanian AV et al. *JAMA*. 2003;289:2560–2572.

The impact of lifestyle changes can be impressive. This slide includes a number of lifestyle changes and the impact they can have on the reduction of systolic blood pressure.

Every 10 kg of weight loss can reduce blood pressure by 5 to 20 mm Hg.

Following the program called “The Dietary Approaches to Stop Hypertension” (DASH) can lower blood pressure by 8 to 14 mm Hg.

Reducing dietary sodium accounts for a drop of 2 to 8 mm Hg, increasing physical activity lowers blood pressure by 4 to 9 mm Hg, and moderation in alcohol intake for a reduction of 2 to 4 mm Hg.

Glycemic Control and Macrovascular Complications

Trial Acronym	Mean A1C (%)		Follow-up Period (y)	Main Results
	Intensive	Standard		
ACCORD	6.4	7.5	3.5	Intensive therapy increased mortality; no difference in major CV events between treatments
ADVANCE	6.5	7.3	5	No significant differences between groups in major macrovascular events
VADT	< 7	8-9	5-7	No significant differences between groups in reducing CV death, though a favorable trend (except CV deaths) in the intensive arm

CV = cardiovascular.

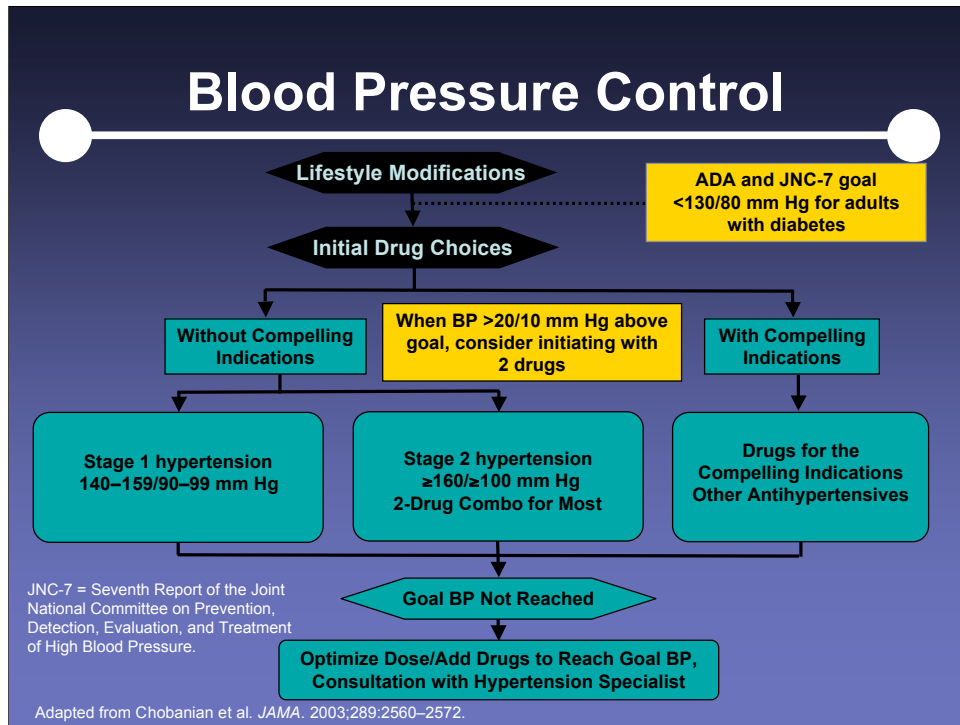
ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559.
 ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.
 Duckworth WC. ADA. June 8, 2008.

Three recent trials have demonstrated no benefit of long-term, intensive glycemic control in reducing macrovascular complications in type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized over 10,000 patients with type 2 diabetes and a mean A1C of 8.1% to receive intensive therapy with a target A1C of <6% or to standard therapy with a target A1C between 7% and 7.9%. After a mean follow-up of 3.5 years, significantly more patients receiving intensive diabetes therapy died (n = 257) than those receiving standard therapy (n = 203; $P = 0.04$). This led to a discontinuation of diabetes intensive therapy. At the same time, there was no significant difference between groups in the primary outcome of composite nonfatal MI, nonfatal stroke, or death from cardiovascular cause.

In the ADVANCE trial, over 11,000 patients with type 2 diabetes received a sulfonylurea and other drugs, as needed, to achieve A1C goals. The primary outcomes were a composite of major macrovascular events and major microvascular events, assessed together and separately. After a median follow-up of 5 years, there was a significant reduction in total events in favor of intensive control versus standard control (18.1% vs 20.0%, respectively; $P = 0.01$), primarily as a reduction in nephropathy with intensive control. Results presented at the 2008 European Association for the Study of Diabetes meeting suggest that there was a 24% risk of death from heart attacks and the risk of kidney complications was lowered by 33%.

Lastly, results of the Veterans Affairs Diabetes Trial (VADT) were recently reported. Rosiglitazone was used in a majority of patients in the study. After a 5- to 7-year follow-up, there was no significant reduction in major cardiovascular events with intensive therapy though there was a trend toward a reduction of all cardiovascular events, except cardiovascular death, in the intensive arm.

Together, these findings warrant a reconsideration of the notion that “lower is better” with respect to glycemic control and macrovascular outcomes. Rather, given the burden of macrovascular complications in diabetes, treatment of the patients should focus on reducing all modifiable risk factors associated with cardiovascular risk, such as smoking cessation, diet, exercise, blood pressure control, and aspirin and statin use.



The ADA and Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) both recommend a blood pressure of <130/80 mm Hg for people with diabetes. This is lower than that for people without diabetes (<140/90 mm Hg) since a more aggressive approach to reducing cardiovascular and renal morbidity and mortality is needed in the diabetes population, which is already at high risk for CVD.

The JNC-7 guidelines further recommend that treatment and prevention of high blood pressure begin with lifestyle modifications, such as weight reduction in obese persons, adoption of the DASH diet, and adequate physical activity.

Combination treatment with ≥ 2 antihypertensive drugs from different classes is often needed to achieve blood pressure goals. Specific drugs are recommended for compelling indications.

Consultation with a specialist is recommended for patients who do not attain their blood pressure goals after optimal dosages and a trial of additional drugs.

Compelling Indications

Compelling Indication	Recommended Drugs					
	Diuretic	β -Blocker	ACE Inhibitor	ARB	CCB	Aldo ant
Heart failure	✓	✓	✓	✓		✓
Post-MI		✓	✓			✓
High CAD risk	✓	✓	✓		✓	
Diabetes	✓	✓	✓	✓	✓	
Chronic kidney disease			✓	✓		
Recurrent stroke prevention	✓		✓			

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; Aldo ant = aldosterone antagonist.

Adapted from Chobanian et al. *JAMA*. 2003;289:2560–2572.

The JNC-7 recommendations for selecting a specific drug according to comorbidity are based on data from benefits observed in outcome studies. This slide identifies recommended classes for specific indications. All drug classes except aldosterone antagonists are recommended for the management of hypertension when it coexists with diabetes.

The ADA recommends that first-line pharmacologic therapy for patients with diabetes and hypertension should include either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).

Lipid Control

ADA Goals

LDL <100 mg/dL* HDL, Male >40 mg/dL
TG <150 mg/dL HDL, Female >50 mg/dL

*In patients with overt CVD, LDL goal <70 mg/dL with high-dose statin is an option.

Test at least annually for lipid disorders in adults,
more often if needed to achieve goals.

NCEP ATP III

LDL <70 mg/dL in patients considered very high risk (ie, multiple major risk factors [especially diabetes], severe and poorly controlled risk factors [continued smoking], multiple risk factors of the metabolic syndrome, and patients with acute coronary syndrome).

TG = triglyceride; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

ADA. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.

NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Circulation*. 2002;106:3143–3421.

Both the ADA and the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) recommend maintaining the low-density lipoprotein (LDL) level <100 mg/dL. Both guidelines also suggest an optional LDL goal of <70 mg/dL in people with diabetes who are considered high-risk individuals and receiving statin therapy.

In addition to the primary LDL goals, the ADA recommends that men maintain a high-density lipoprotein (HDL) >40 mg/dL, women an HDL >50 mg/dL, and all persons with diabetes a triglyceride level <150 mg/dL.

Nutrition Recommendations

- Individualized MNT
- Weight loss, if overweight (7% of body weight)
- Physical activity (150 minutes/week)
- Carbohydrate monitoring
 - Fruits, vegetables, whole grains, low-fat milk
- Fat and cholesterol
 - Saturated fat <7% total calories
 - Dietary cholesterol <200 mg/day
 - Limit *trans* fat
 - ≥2 Servings of fish per week

ADA. *Diabetes Care*. 2008;31(Suppl 1):S61–S78.

Medical nutrition therapy is an integral part of diabetes prevention and management. Patients should receive MNT provided, when possible, by a registered dietitian. MNT should be planned to achieve the glycemic goals first since weight loss is often a more challenging problem. A weight loss equal to 7% of body weight is recommended for overweight and obese individuals at risk or with diabetes because it can improve insulin resistance. Medications and bariatric surgery can be considered in certain individuals. Regular physical activity (150 minutes per week) is an important component of weight loss and in maintaining healthy weight.

Carbohydrate monitoring and counting is an integral part of secondary prevention of complications in diabetes. A dietary pattern that is high in carbohydrates from vegetables, whole grains, legumes, fruits, and low-fat milk is encouraged for good health.

Fat and cholesterol intake must also be managed in diabetes. Saturated fat should not exceed 7% of total calorie intake. Trans fat intake should be minimized, and dietary cholesterol intake should not exceed 200 mg/day. To provide n-3 polyunsaturated fatty acids, ≥2 servings per week of non-fried fish are recommended.

Nutrition Recommendations

- Moderate alcohol consumption (≤ 1 drink daily for women and ≤ 2 for men)
- Controlling complications
 - Reduce protein intake to 0.8 to 1.0 g/kg body weight per day in chronic kidney disease
 - Dietary sodium ~ 1500 mg/day in patients with hypertension
 - DASH diet
 - Modest weight loss improves hypertension

ADA. *Diabetes Care*. 2008;31(Suppl 1):S61–S78.

http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf

If patients choose to drink alcohol, it should be limited to ≤ 1 drink per day for women and ≤ 2 drinks per day for men.

Additional recommendations have been made for controlling complications in diabetes. Protein intake should be reduced in patients who are in early stages of kidney disease. Patients with evidence of structural heart diseases or heart failure should reduce their sodium intake to < 2 grams daily.

As previously mentioned, the DASH diet, sodium restriction, and weight loss improve blood pressure levels.

Additional Pharmacotherapy Recommendations

	Patients with Known CAD	Patients at Risk for CAD
Antiplatelet	Yes	Yes
Statin	Yes	Yes
ACE inhibitor	Yes	Yes
β -Blocker	If previous MI	No recommendation
Metformin	Contraindicated in treated CHF	
Thiazolidinediones	Use with caution in treated CHF	

CHF = congestive heart failure.

ADA. *Diabetes Care*. 2008;31(Suppl 1):S12-S54.

As you will note on this slide, there are additional recommendations for the treatment of CAD in people with diabetes. The ADA suggests the following therapy in patients with CAD or at risk for CAD:

- Treatment with antiplatelet therapy (eg, aspirin).
- Statin therapy for all patients age 40 years and older and in those under 40 years who are at increased risk due to other cardiovascular risk factors and who are not achieving lipid goals. (Note: statins are contraindicated in pregnancy.)
- ACE inhibitors are indicated for patients with diabetes and an additional risk factor (eg, CAD, stroke, PVD, hypertension, dyslipidemia, microalbuminuria, smoking). The Heart Outcomes Prevention Evaluation (HOPE) study found that ACE-inhibitor use reduced the incidence of new-onset diabetes in patients >55 years of age and also significantly reduced the risk of cardiovascular events and complications related to diabetes. An ARB may be considered in patients intolerant of ACE inhibitors.
- Beta-blockers should be considered for patients who have had a previous MI or are undergoing major surgery to reduce mortality.
- In people who have treated congestive heart failure, avoid metformin and use thiazolidinediones with caution.

Antiplatelet Therapy

- Aspirin 75 to 162 mg daily
- Cardiovascular risk factors
 - >40 Years old
 - Family history of cardiovascular disease
 - Hypertension
 - Smoker
 - Dyslipidemia
 - Albuminuria
- Aspirin is contraindicated in aspirin allergy, bleeding tendency, active hepatic disease, other anticoagulant therapy (clopidogrel is an alternative)
- Not recommended for patients aged <30 years



Buse JB et al. *Circulation*. 2007;115:114–126.
ADA. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.

Antiplatelet therapy is recommended as a primary prevention strategy in patients with diabetes. Because of the risk for gastrointestinal bleeding, its use is only recommended in patients at risk for cardiovascular disease and at low doses (75 –162 mg/day). In addition to the already mentioned cardiovascular disease risk factors (and noted again here), this would include patients aged >40 years.

Aspirin is contraindicated in patients with a known aspirin allergy, have a bleeding tendency or had a recent gastrointestinal bleed, have clinically active hepatic disease, or are receiving anticoagulation therapy. Aspirin therapy is not recommended in patients with diabetes under 30 years of age. In patients who are intolerant of aspirin, the antiplatelet agent clopidogrel should be considered. Similarly, aspirin plus clopidogrel can be combined in patients with severe and progressive cardiovascular disease.

Question

What percentage of patients with diabetes achieve the combined goals of A1C <7%, BP <130/80 mm Hg, and TC <200 mg/dL?

- A. 45% to 55%
- B. 35% to 45%
- C. 25% to 35%
- D. 15% to 25%
- E. <10%

It is time for another review question.

What percentage of patients with diabetes achieve the combined goals of A1C <7%, BP <130/80 mm Hg, and TC <200 mg/dL?

- A. 45% to 55%
- B. 35% to 45%
- C. 25% to 35%
- D. 15% to 25%
- E. <10%

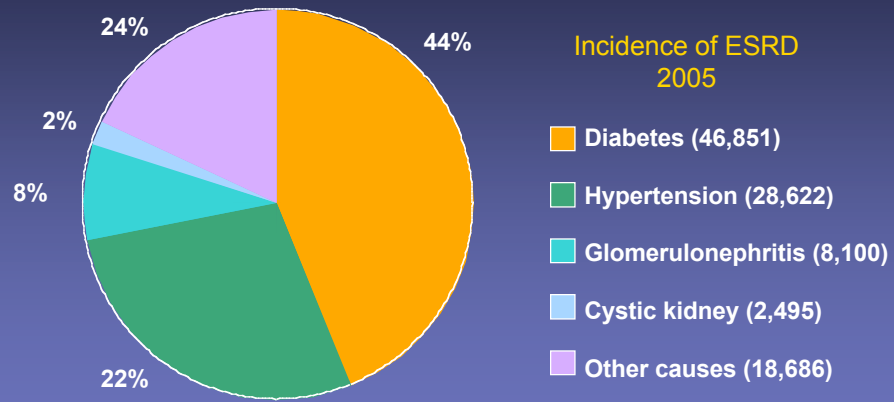
Answer

E. Less than 10% of patients with diabetes achieve the combined goals of A1C <7%, BP <130/80 mm Hg, and TC <200 mg/dL.

The correct answer is E.

Despite the proven benefits of aggressive comprehensive risk factor management on diabetes outcomes, <10% of patients with diabetes achieve the combined goals of A1C <7%, BP <130/80 mm Hg, and TC <200 mg/dL.

Diabetic Nephropathy



United States Renal Data System (USRDS) 2007 Annual report. Available at: www.usrds.org.

According to 2005 data, almost 1/2 million US residents were in treatment for end-stage renal disease. Over 106,000 people began treatment in 2005. While there are a number of causes of ESRD, diabetes is by far the most common cause, followed by hypertension. Almost one quarter of those cases are from other or unknown causes.

Stages of Nephropathy

Stage	Description	GFR (mL/min/1.73 m ² body surface area)	Action
1	Functional changes (hypertrophy, hyperfiltration)	≥90	Diagnose, treat comorbid conditions, reduce risk of cardiovascular disease
2	Structural changes (renal lesions, clinically silent)	60-89	Estimate progression
3	Incipient nephropathy (microalbuminuria, generally asymptomatic)	30-59	Treat complications (eg, anemia, malnutrition, metabolic bone disease)
4	Overt nephropathy (proteinuria, nephrotic syndrome, hypertension)	15-29	Prepare for kidney replacement therapy
5	Renal failure or ESRD (fluid retention, CHF, uremia)	<15 or dialysis	Replacement if uremia present

GFR = glomerular filtration rate

Levey AS et al. *Ann Intern Med.* 2003;139:137-147.
www.kdoqi.org

Diabetic nephropathy progresses through 5 different stages.

- The first stage *Stage 1* is characterized by hyperfiltration and renal hypertrophy. Changes are usually seen at the time of diagnosis of diabetes. Increased hyperfiltration is a consequence of hyperglycemia.
- During *Stage 2*, structural changes occur, such as glomerular basement membrane thickening, mesangial expansion, and diffuse intercapillary glomerulosclerosis. Hyperfiltration continues as the disease remains clinically silent.
- During *Stage 3*, also referred to as incipient diabetic nephropathy, microscopic amounts of albumin (microalbuminuria) inadvertently slip through sclerosed glomerular membranes, signifying a progressive deterioration in kidney filtration. Metabolic wastes begin to accumulate in the blood because unaffected nephrons can no longer compensate, and responsiveness to diuretic therapy decreases. Blood pressure may be normal or slightly elevated. This stage usually develops after 7 to 15 years of diabetes. The glomerular filtration rate (GFR) has decreased to between 30 to 59 mL/min.
- *Stage 4*, also referred to as overt or clinical diabetic nephropathy, is characterized by detection of significantly large amounts of protein in the urine (macroalbuminuria). Notable amounts of metabolic waste begin to accumulate, particularly urea and creatinine. Patients generally do not become symptomatic until this stage when oliguria, edema, and hypertension can develop.
- Without, and sometimes in spite of, aggressive treatment, deteriorating vasculature or ESRD results in *Stage 5*.

Screening

Test	When	Values
Blood pressure	Each office visit	Goal <130/80 mm Hg
Microalbuminuria (spot albumin-to-creatinine ratio)	Type 2: annually beginning at diagnosis Type 1: annually beginning 5 years after diagnosis During pregnancy	Normal <30 mg albumin/g creatinine Microalbuminuria 30–299 Macroalbuminuria ≥300
Serum creatinine	Annually for estimation of GFR in all adults with diabetes regardless of degree of urine albumin excretion	Normal 0.5 to 1.4 mg/dL

AACE. *Endocr Pract.* 2007;13(Suppl 1):1–68.

Risk factors for diabetic nephropathy include duration of diabetes and hypertension. Thus, screening for diabetic nephropathy should include:

- Evaluation of blood pressure at every office visit with a blood pressure goal of <130/80 mm Hg.
- Screening for microalbuminuria (usually with a spot albumin-to-creatinine ratio) annually beginning at diagnosis for people with type 2 diabetes and annually beginning at ≥5 years of diagnosis for people with type 1 diabetes, and during pregnancy for women.
- Serum creatinine can be affected by body shape, size, and dietary intake and thus should never be used alone as a measure of kidney function. Nonetheless, serum creatinine is useful as an estimation of glomerular filtration rate using validated calculation methods. Serum creatinine should be measured at least annually in all adults with diabetes to determine GFR regardless of the degree of urine excretion. The estimated GFR is used to estimate the stage of diabetic nephropathy.

Prevention and Management of Nephropathy

- **Glycemic control**
 - A1C \leq 6.5%
 - Preprandial plasma glucose $<$ 110 mg/dL
 - 2-Hour postprandial plasma glucose $<$ 140 mg/dL
- **Blood pressure control \leq 130/80 mm Hg and reduction of microalbuminuria**
 - ACE inhibitors*
 - ARBs*
- **Protein restriction**
 - 0.8–1.0 g/kg body weight per day, depending on degree of chronic kidney disease

*Nonpregnancy only.

AACE. *Endocr Pract.* 2007;13(Suppl 1):1–68.
ADA. *Diabetes Care.* 2008;31(Suppl 1):S12–S54.

Glycemic and blood pressure control, as recommended by national guidelines, form the basis for the prevention and management of diabetic nephropathy.

Antihypertensives recommended for nonpregnant patients with micro- or macroalbuminuria include:

- ACE inhibitors
- ARBs

These agents have been shown to delay the progression of diabetic nephropathy and should be prescribed even in patients without uncontrolled hypertension. If these agents cannot be used, non-dihydropyridine calcium channel blockers can be used to reduce albuminuria. Caution should be used in women during their childbearing years as ACE inhibitors and ARBs are not indicated in pregnancy and may cause birth defects.

Protein restriction should be initiated in the presence of nephropathy (0.8–1.0 g/kg body weight per day [\sim 10% of daily calories] in earlier stages of chronic kidney disease, and 0.8 g/kg body weight per day in later stages of chronic kidney disease). These restrictions may improve measures of renal function, such as urine albumin excretion rate or GFR.

Management of ESRD

- **Hemodialysis**
 - Fistula
 - Graft
- **Peritoneal dialysis**
 - Continuous ambulatory peritoneal dialysis (CAPD)
 - Continuous cycler-assisted peritoneal dialysis (CCPD)
 - Combined CAPD and CCPD
- **Kidney transplant**
 - Cadaveric kidney
 - Related or nonrelated living donor kidney
- **Annual mortality: 224.5 dialysis, 33.7 transplant per 1000 patient-years at risk**

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Available at: <http://niddk.gov/nih.gov/kidiseases/pubs>.

For patients who progress to ESRD, management may include hemodialysis, peritoneal dialysis, or kidney transplant.

- In hemodialysis, a fistula or graft is created for access to the bloodstream. Hemodialysis is generally performed 3 times a week and can be done at a medical facility or at home.
- In peritoneal dialysis, waste products and extra fluid pass from the blood into the dialysis solution via the peritoneum, which lines the walls of the abdominal cavity. A dialysis machine is not required for the most common form of peritoneal dialysis, known as continuous ambulatory peritoneal dialysis (CAPD). Patients are able to be mobile with the dialysis solution in their abdomen. Other forms of peritoneal dialysis require a machine called a cycler to fill and drain the abdomen. Peritoneal dialysis can also be done using a combination of both CAPD and continuous cycler-assisted peritoneal dialysis.
- Kidney transplantation can be performed with a kidney from a nonliving or living donor. Factors that must be taken into consideration to determine a kidney/recipient match include blood type, human leukocyte antigens, and cross-matching antigens.

Mortality rates are notable in patients with ESRD. In 2005, mortality rates were 224.5 per 1000 patient-years at risk among dialysis patients and 33.7 per 1000 patient-years at risk among transplant patients.

Question

At what stage of diabetic nephropathy do symptoms generally become clinically apparent?

- A. Stage 1
- B. Stage 2
- C. Stage 3
- D. Stage 4
- E. Stage 5

It's now time for another question.

At what stage of diabetic nephropathy do symptoms generally become clinically apparent?

- A. Stage 1
- B. Stage 2
- C. Stage 3
- D. Stage 4
- E. Stage 5

Answer

D. In diabetic nephropathy, symptoms generally become clinically apparent at Stage 4.

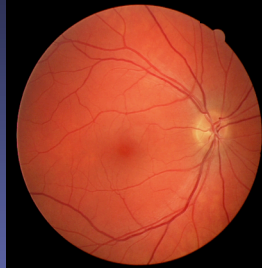
The correct answer is D.

Symptoms of diabetic nephropathy generally do not appear until late in the disease course at stage 4 when nephrotic syndrome and hypertension develop. Thus, routine screening and prevention measures are very important in the management of diabetic nephropathy.

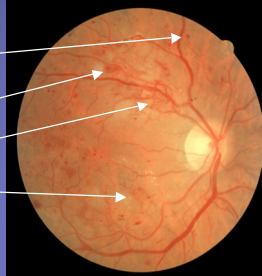
Diabetic Retinopathy

- During first 2 decades of disease, nearly all with type 1 diabetes and >60% with type 2 diabetes will develop retinopathy
- **Nonproliferative diabetic retinopathy (NPDR)**
 - Mild NPDR
 - Moderate NPDR
 - Severe NPDR
- **Proliferative diabetic retinopathy (PDR)**

Normal eye



- Dot hemorrhage
- Flame hemorrhage
- Neovascularization
- Hard exudates




Fong DS et al. *Diabetes Care*. 2004;27:S84–S87.

Diabetic retinopathy is a highly specific vascular complication of type 1 and type 2 diabetes. During the first 2 decades of disease, nearly all people with type 1 diabetes and >60% of people with type 2 diabetes will develop some form of retinopathy. As mentioned earlier, retinopathy is the leading cause of blindness among adults aged 20 to 74 years. Vision loss can be avoided or minimized with proper ophthalmologic assessments to identify retinopathy in its early stages.

Diabetic retinopathy is generally classified as nonproliferative (NPDR) or proliferative (PDR). These are essentially progressive stages of the condition. The photo in the lower right of the slide shows an example of proliferative retinopathy.

Clinical Features



Progression*	Clinical Features
Mild NPDR	Increased vascular permeability, microaneurysms, intraretinal hemorrhages
Moderate NPDR	Venous caliber changes, intraretinal microvascular abnormalities (IRMAs), intraretinal hemorrhages
Severe NPDR	Retinal ischemia, IRMAs, extensive hemorrhage and microaneurysms
PDR	Ischemia-induced neovascularization, vitreous hemorrhage, retinal traction, tears, and detachment

*Macular edema can develop at all stages of retinopathy.

ADA. Diabetic Retinopathy Slides. Available at: <http://www.diabetes.org/for-health-professionals-and-scientists/slide-sets-professional.jsp>.

The rate of progression of diabetic retinopathy varies among patients, but the stages generally follow a natural course if untreated. Macular edema, a contributor to blindness, can develop at any stage of retinopathy. Clinically significant macular edema (CSME) occurs when edema threatens the center of vision.

Mild NPDR is characterized by increased vascular permeability, microaneurysms, and intraretinal hemorrhages. Moderate NPDR is identified by venous caliber changes, intraretinal microvascular abnormalities (IRMAs), and intraretinal hemorrhages and possibly CSME. Severe NPDR is characterized by retinal ischemia, IRMAs, extensive hemorrhage, and microaneurysms.

PDR occurs when new blood vessels form as a result of retinal ischemia. This usually occurs at the optic disk. The new vessels are very weak and tend to break, causing vitreous hemorrhage. The new vessels can also cause retinal traction, tears, and detachment.

Other manifestations of diabetic eye disease include cataracts, glaucoma, dry eye, and iritis.

Screening

	Recommendation
Type 1 diabetes	Within 3–5 years after onset for adults and adolescents
Type 2 diabetes	At time of diagnosis
Pregnancy	Prior to conception and during 1 st trimester, with close follow-up throughout pregnancy and for 1 year postpartum (does not apply to GDM)
Examination	Dilated indirect ophthalmoscopy with biomicroscopy and 7-standard field stereoscopic 30° fundus photography

GDM = gestational diabetes mellitus.

ADA. *Diabetes Care*. 2008;21(Suppl 1):S12–S54.

Screening recommendations for diabetic retinopathy vary depending on type of diabetes. In adults and adolescents with type 1 diabetes, screening should be performed within 3 to 5 years after onset. In patients with type 2 diabetes, screening should be conducted at the time of diagnosis.

The difference in recommendations between type 1 and type 2 diabetes is because any retinopathy in patients with type 1 diabetes is usually diagnosed at its onset, whereas retinopathy in patients with type 2 diabetes often goes undiagnosed for years, and the complications have begun to develop.

Pregnancy can accelerate the development of retinopathy. For women with diabetes who become pregnant, screening should be conducted prior to conception, if possible, and once during the first trimester with close follow-up throughout pregnancy and at least 1 year postpartum. This screening is not recommended for women who develop gestational diabetes, because they are not at an increased risk for diabetic retinopathy.

Screening consists of a dilated and comprehensive eye examination by an ophthalmologist or optometrist and includes dilated indirect ophthalmoscopy with biomicroscopy and 7-standard field stereoscopic 30-degree fundus photography.

Prevention

Optimize glycemic and blood pressure control

– Glycemic control

- A1C \leq 6.5%
- Preprandial plasma glucose <110 mg/dL
- 2-Hour postprandial plasma glucose <140 mg/dL

– Blood pressure control

- 130/80 mm Hg

Annual dilated eye exams

- May consider reducing to every 2 to 3 years in some cases, or more frequently if retinopathy is progressing

AACE. *Endocr Pract.* 2007;13(Suppl 1):1–68.
ADA. *Diabetes Care.* 2008;31(Suppl 1):S12–S54.

The first step toward preventing or delaying the onset of diabetic retinopathy is to achieve and maintain tight glycemic control and blood pressure. As mentioned earlier, landmark studies have shown that maintenance of tight glycemic control reduces the risk of microvascular complications, such as diabetic retinopathy, and maintaining blood pressure control reduces the rate of progression of diabetic retinopathy. Both the ADA and American Association of Clinical Endocrinologists guidelines advocate the same recommendations in this regard.

All patients should be followed at least annually. This may identify treatable retinopathy before any vision loss is apparent to the patient. Patients should be promptly referred to a retinal specialist if there is evidence that early retinopathy is progressing or if advanced retinopathy exists. In some cases, patients, in consultation with their eye care professionals, may consider reducing the frequency of this examination to every 2 to 3 years, or increasing the frequency if retinopathy is progressing.

Management

Progression	Management*
Mild NPDR	Annual follow-up
Moderate NPDR	6–12 Month follow-up, color fundus photography
Severe NPDR	3–4 Month follow-up, color fundus photography; possible panretinal photocoagulation
PDR	2–4 Month follow-up, color fundus photography; panretinal photocoagulation (3–4 month follow-up)

*Macular edema: color fundus photography, fluorescein, angiography, photocoagulation, 3–4 month follow-up

ADA. Diabetic Retinopathy Slides. Available at: <http://www.diabetes.org/for-health-professionals-and-scientists/slide-sets-professional.jsp>.

The frequency of follow-up and management of retinopathy differ depending on the severity of the disease.

Mild retinopathy can be followed by a trained examiner on an annual basis unless it worsens. Patients with moderate retinopathy without clinically significant macular edema should have ophthalmic examinations every 6 to 12 months to monitor disease progression. Severe retinopathy should be followed more frequently (every 3–4 months), and proliferative diabetic retinopathy, even more frequently (every 2–4 months).

Color fundus photography should be used to follow disease progression in moderate NPR and more severe cases, and in patients with CSME at any stage. Color fundus photography is helpful in documenting the extent of retinopathy and comparing changes in disease progression between visits.

Treatment Interventions

Surgical

- Laser
 - Panretinal photocoagulation
 - Focal photocoagulation
- Vitrectomy

Pharmacologic

- Corticosteroids
- Antivascular endothelial growth factor agents
- Somatostatin
- Protein kinase C inhibitors

Fong DS et al. *Diabetes Care*. 2004;27(Suppl 1):S84–S87.
Lang GE. *Ophthalmologica*. 2007;221:112–117.

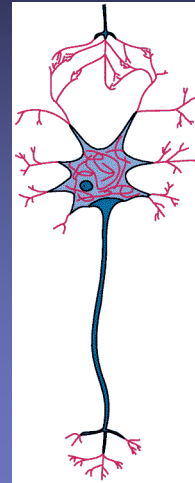
A main motivation for continued screening for diabetic retinopathy is that laser photocoagulation surgery has been shown to prevent visual loss and, therefore, is the standard of care for treatment. Laser photocoagulation can “shrink” abnormal retinal blood vessels and is recommended for the treatment of severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and any stage of clinically significant macular edema. If panretinal photocoagulation is to be carried out in patients who also have macular edema, then focal photocoagulation is generally conducted beforehand to avoid worsening of the macular edema.

Vitreous surgery may be performed for patients with PDR or refractory macular edema.

Several pharmacologic options also have been investigated in diabetic retinopathy. Most of these interventions involve inhibition of growth factors that have been shown to be upregulated in diabetic retinopathy. These include injected corticosteroids, antibodies or agents that inhibit vascular endothelial growth factor, somatostatin analogues, and protein kinase C inhibitors.

Diabetic Neuropathies

- Can be focal or diffuse, with diverse clinical manifestations
- Generalized symmetric polyneuropathies
 - Chronic sensorimotor (distal peripheral neuropathy [DPN])
 - Autonomic neuropathy
 - Acute sensory
- Focal and multifocal
 - Cranial
 - Truncal
 - Focal limb
 - Proximal motor (amyotrophy)
 - Coexisting chronic inflammatory demyelinating polyneuropathy (CIDP)



Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Many people think of diabetic neuropathy as altered sensation in the feet of a diabetic patient, which can lead to amputation. This is only one presentation of diabetic neuropathy. Diabetic neuropathies are heterogeneous, affecting different parts of the nervous system and presenting with diverse clinical manifestations. Most common are chronic sensorimotor distal peripheral neuropathy (DPN), such as the commonly known problems in the feet, and autonomic neuropathies, which can involve every system in the body.

About 1 in 5 patients with diabetes over age 40 years has a peripheral neuropathy. In a 30-year follow-up of the Pittsburgh Epidemiology of Diabetes Complications Study, the incidence of DPN was 1.48 per 100 person-years for type 1 diabetes, and the rate for symptomatic autonomic neuropathy was 0.78.

Although many classification systems have been proposed, the ADA's position statement on diabetic neuropathy classifies it into 2 major categories: generalized symmetric and focal multifocal.

Screening

	Chronic Sensorimotor DPN	Autonomic Neuropathy
Type 1 Diabetes	At diagnosis, then annually	5 years after diagnosis, then annually
Type 2 Diabetes	At diagnosis, then annually	At diagnosis, then annually

ADA. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.
Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Early recognition and appropriate management of neuropathies in diabetes is important for several reasons. First, they are a common problem in patients with diabetes. They may be treatable, and early recognition and treatment may reduce morbidity, such as foot ulceration and amputation, and mortality. For both chronic sensorimotor DPN and autonomic neuropathy, screening is recommended at 5 years after the diagnosis of type 1 diabetes and annually thereafter, and at diagnosis and annually thereafter for people with type 2 diabetes.

Examinations

- **Chronic sensorimotor DPN**

- Visual inspection
- Sensory function (pain, pressure, temperature, vibration)
- Ankle reflexes
- Check footwear for proper fit
- Foot exam and foot care education at every visit (every 3–6 months for established DPN)

- **Autonomic neuropathy**

- History and exam for signs of autonomic dysfunction
- Test for heart rate variability
 - Valsalva maneuver
 - Inspiration to expiration ratio

ADA. *Diabetes Care*. 2008;31(Suppl 1):S12–S54.
Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Screening for chronic sensorimotor DPN should include:

- Visual inspection of the feet and lower limbs, looking for ulcers, calluses, distended veins, and deformities
- Assessment of sensory function including pain sensation, temperature/vibration perception, and pressure sensation. Pain can be assessed via pinprick. Vibration can be assessed using a 128-Hz tuning fork. Pressure perception is measured at the distal halluces using a 10-g monofilament.
- Ankle reflexes should also be assessed
- Footwear should be examined for proper fit
- Foot examinations should occur at each visit, more frequently (every 3–6 months) for people with established DPN.

Screening for autonomic neuropathy should include:

- A history and exam for signs of autonomic dysfunction
- Testing for heart rate variability, including response to the Valsalva maneuver and inspiration to expiration ratio. If these tests are positive, additional diagnostic tests and treatment are warranted.
 - The Valsalva maneuver is performed by forcibly exhaling into the mouthpiece of a manometer to 40 mm Hg for 15 seconds during electrocardiogram (ECG) monitoring. Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The ratio of longest R-R interval to shortest R-R interval should be >1.2.
 - The lowest normal value for inspiration to expiration ratio is 1.17 for ages 20 to 24 years. It is determined with the patient at rest and supine and heart rate monitoring by ECG as the patient breathes in and out 6 breaths per minute. A heart rate difference of >15 bpm is normal; <10 bpm is abnormal.

Chronic Sensorimotor DPN

- Most common form of diabetic neuropathy
- Symptoms (only present in 50% of patients)
 - Burning pain
 - Electrical or stabbing sensations
 - Paresthesia/hyperparesthesia
 - Deep aching pain
 - Mostly in feet and lower limbs, though hands may be affected
- Diagnosis by exclusion: rule out nondiabetic causes
 - CIDP, B₁₂ deficiency, hypothyroidism, uremia
 - Distal sensory loss with absent reflexes (± typical symptoms) is highly suggestive

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Chronic sensorimotor DPN is the most common form of diabetic neuropathy. Symptoms include burning pain, electrical or stabbing sensations, paresthesia/hyperparesthesia, and deep aching pain. Chronic sensorimotor DPN mostly affects the feet and lower limbs but can also affect the hands. Up to 50% of patients may be asymptomatic, and chronic sensorimotor may only be diagnosed when the patient presents with a foot ulcer.

Given that other forms of neuropathy, such as coexisting chronic inflammatory demyelinating polyneuropathy (CIDP), and those caused by vitamin B₁₂ deficiency, hypothyroidism, and uremia occur more frequently in diabetics than chronic sensorimotor DPN, these other causes must be ruled out before a diagnosis can be made. The signs of absent reflexes and distal sensory loss with or without the presence of typical symptoms is highly suggestive of chronic sensorimotor DPN.

Management of DPN

- Address underlying pathology
 - Glycemic control
 - Foot care
- Symptom relief
 - Pharmacologic
 - Tricyclic agents
 - Selective serotonin/norepinephrine reuptake inhibitors
 - Anticonvulsants
 - Opioids
 - Nonpharmacologic

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

The first step in treating DPN is to address the underlying pathology by achieving stable and optimal glycemic control and proper regular foot care. Several observation studies have suggested that neuropathic symptoms improve with avoidance of extreme glucose fluctuations.

Treatment for painful symptoms include both pharmacologic and nonpharmacologic options. Pharmacologic agents include tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin uptake inhibitors, anticonvulsants, and opioids for pain management. The SNRI duloxetine (Cymbalta®) is specifically approved for diabetic neuropathic pain, as is the anticonvulsant agent pregabalin (Lyrica®). Nonpharmacologic options include physical therapy and the use of topical agents. Often combinations of agents with different sites and mechanisms of action are used to target the various pathways that lead to neuropathic pain, particularly in severe pain.

Acute Sensory Neuropathy

- Rare
- Tends to follow:
 - Periods of poor metabolic control
 - Sudden change in glycemic control
- Acute onset of severe sensory symptoms with marked nocturnal exacerbation
- Few neurologic signs on leg exam

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Acute sensory neuropathy is rare and tends to follow periods of poor metabolic control (eg, ketoacidosis) or sudden changes in glycemic control. It is sometimes referred to as “insulin neuritis”.

The condition is characterized by acute onset of severe sensory symptoms, worsening at night. However, on examination of the legs there are few neurologic signs.

Foot Care Education

- Proper foot care can reduce the risk of amputation by 45% to 85%
- Advise patients to:
 - Self-examine feet
 - Use lotion to prevent dryness and cracking
 - File calluses with a pumice stone
 - Cut toenails weekly or as needed
 - Always wear socks and well-fitting shoes
 - Notify their health care provider immediately if any foot problems occur
- Patients with neuropathy - visual inspection of feet at every visit with a health care professional



ADA. Diabetic Neuropathy Slides. Available at: <http://www.diabetes.org/for-health-professionals-and-scientists/slide-sets-professional.jsp>.

As previously mentioned, proper foot care can reduce the risk of amputation by 45% to 85%.

Patients should be advised regularly on how to properly care for feet. In addition to annual foot examinations, this consists of daily self-examinations of feet:

- Patients should check for dry, cracking skin, calluses, and signs of infection between the toes and around the toenail.
- Lotion should be used to prevent dryness and cracking.
- Calluses should be filed with a pumice stone.
- Toenails should be cut approximately weekly.
- Patients should always wear socks and well-fitting shoes.

If any problems occur, the patient should be advised to contact his/her health care provider immediately. Patients with neuropathy should have a visual inspection of their feet at every health care visit.

Be sure that the patient has the skills and the ability to examine his feet. Telling him to examine his feet when he cannot see or cannot bend over is not sufficient. It may be necessary to teach him how to use adjunctives such as a long-handled mirror, or the task may need to be delegated to another person.

Cardiovascular Autonomic Neuropathy

Clinical Features

- Most clinically important form of distal autonomic neuropathy
- Potentially life threatening
- Resting tachycardia (>100 bpm)
- Exercise intolerance
- Orthostasis
- Thermoregulation, autonomic disturbances

Management

- Exercise intolerance – Graded supervised exercise, ACE inhibitor, β -blocker
- Hypotension - Slow posture changes, elevate bed, increase plasma volume, clonidine, midodrine, octreotide

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

ADA. Diabetic Neuropathy Slides. Available at: <http://www.diabetes.org/for-health-professionals-and-scientists/slide-sets-professional.jsp>.

Cardiovascular autonomic dysfunction is the most studied and clinically important form of distal autonomic neuropathy because of its potentially life-threatening consequences. Clinical features include a resting tachycardia (>100 bpm), exercise intolerance, postural hypotension (a fall of >20 mm Hg in systolic blood pressure 2 minutes after standing) without an appropriate heart rate response, thermoregulation difficulties, and other autonomic disturbances involving the skin, pupils, gastrointestinal or genitourinary systems.

Graded supervised exercise and/or treatment with an ACE inhibitor or beta-blocker is suggested for the management of exercise intolerance. Because patients have difficulties with thermoregulation, they should be advised to avoid exercise in hot or cold extremes and to be vigilant about adequate hydration. For symptomatic hypotension, slow posture changes; mechanical measures such as elevating the bed; increasing plasma volume; and pharmacologic agents such as clonidine, midodrine, and octreotide may help in the management of hypotension.

Gastrointestinal Autonomic Neuropathy

Clinical Features

- Esophageal dysfunction - Difficulty swallowing, heart burn
- Gastroparesis - Anorexia, nausea, vomiting, early satiety
- Diabetic enteropathy - Diarrhea, constipation, incontinence

Management

- Esophageal dysfunction - Metoclopramide
- Gastroparesis - Small frequent meals, prokinetic agents
- Enteropathy - Antibiotics, antiemetics, stool softeners, or dietary supplement

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

ADA. Diabetic Neuropathy Slides. Available at: <http://www.diabetes.org/for-health-professionals-and-scientists/slide-sets-professional.jsp>.

Vinik AI. *Therapy for Diabetes Mellitus and Related Disorders*. 1998:186–203.

Neuropathy of the gastrointestinal tract can affect the esophagus, stomach, and intestines causing a number of symptoms that vary depending on which area of the digestive tract is affected.

Esophageal autonomic complications include altered peristalsis and impaired sphincter control, which could cause difficulty swallowing and symptoms of heart burn. The dopamine antagonists metoclopramide and domperidone may provide some relief.

Gastroparesis can cause anorexia, nausea, vomiting, early satiety, and postprandial fullness. It is treated by encouraging the patient to eat smaller, more frequent meals to prevent nausea. A dietitian should be consulted when designing a meal plan for someone with gastroparesis. Dopamine antagonists can also be used before meals to improve gastric emptying. Patients with gastroparesis and impaired absorption should be monitored for hypoglycemia.

Widespread neuropathy of the intestines can cause enteropathy, which can lead to diarrhea, constipation, or incontinence. Diarrhea can be caused by a number of factors in patients with diabetes, including bacterial overgrowth, poor intestinal motility, celiac disease, and other disorders. The cause of the diarrhea should be determined before treatment is initiated. Loperamide may be administered to treat intestinal motility disorders. Antibiotics can be used for bacterial overgrowth. Stool softeners and increased dietary fiber can be used to treat constipation.

Genitourinary Autonomic Neuropathy

Clinical Features	Management
Bladder dysfunction	Bethanechol, intermittent catheterization
Erectile dysfunction	Sildenafil, verdenafil, tadalafil, prostaglandin
Dyspareunia	Lubricants

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Genitourinary autonomic neuropathy can lead to bladder dysfunction, erectile dysfunction or retrograde ejaculation, and dyspareunia. This form of neuropathy should be suspect in patients with recurrent urinary tract infections, pyelonephritis, incontinence, a palpable bladder, or men with impotence.

In addition to general preventive measures (ie, glycemic and blood pressure control), bethanechol and intermittent catheterization may be used in the treatment of bladder dysfunction; traditional pharmacologic and nonpharmacologic (ie, devices) therapies can be used to treat erectile dysfunction; and lubricants may help to reduce dyspareunia.

Other Autonomic Neuropathies

Clinical Features	Management
Sudomotor (sweating) dysfunction (Anhidrosis, heat intolerance, dry skin, hyperhidrosis)	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators
Pupillomotor (Visual blurring, impaired adaptation to ambient light, impaired visceral sensation)	Care driving at night, recognition of unusual presentations of myocardial infarction

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Diabetic autonomic neuropathies also may manifest as sudomotor and pupillomotor dysfunction. Patients with sudomotor dysfunction exhibit sweat-related abnormalities ranging from anhidrosis (no sweating) to hyperhidrosis (excessive sweating). Tests to confirm sudomotor dysfunction include quantitative sudomotor axon reflex, a sweat test, and skin blood flow tests. Agents used to combat the various symptoms include emollients and dry skin lubricants to improve dry skin; scopolamine, glycopyrrolate, and botulinum toxin to reduce sweating; and vasodilators to improve heat tolerance.

Pupillomotor symptoms include visual blurring, impaired adaptation to ambient light, and impaired visceral sensation. Pupillometry and heart rate variability are used to diagnose this neuropathy. Treatments include using extra care when driving at night as well as recognition of unusual presentations of MI.

Focal and Multifocal Neuropathies

- **Focal limb or truncal**
 - Sudden onset
 - Involve ulnar, median, peroneal, and medial plantar nerve entrapment (most common) or demyelination/axonal degeneration
- **Cranial neuropathies**
 - Extremely rare
 - Often resolve spontaneously within months
- **Proximal motor (amyotrophy)**
 - Usually in older type 2 diabetics
 - Severe neuropathic pain, uni- or bilateral muscle weakness, and atrophy in proximal thigh muscles
 - Must rule out spinal stenosis
- **Coexisting chronic inflammatory demyelinating polyneuropathy (CIDP)**
 - Severe motor deficits, progressive polyneuropathy in spite of optimal glycemic control

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Focal limb or truncal neuropathies often have a sudden onset and occur as a result of pathology of the median, ulnar, radial, and peroneal nerves. Most of these are nerve entrapments, but the neuropathy can also be a result of demyelination or axonal degeneration. Cranial neuropathies are extremely rare (only 0.05% of cases) and involve cranial nerves III, IV, VI, and VII. These are believed to be infarct related and usually spontaneously resolve in a few months.

Patients who develop severe neuropathic pain with uni- or bilateral muscle weakness and atrophy in proximal thigh muscles should be evaluated for proximal motor (amyotrophy) neuropathy. Spinal stenosis and chronic inflammatory demyelinating polyneuropathy must also be considered. CIDP is suggested by progressive symmetric or asymmetric motor deficits, progressive sensory neuropathy in spite of optimal glycemic control (with typical electrophysiologic findings), and an unusually high cerebrospinal fluid protein level.

Management of Focal and Multifocal Neuropathies

- Decompression of nerve entrapments
- Treatment for neuropathic pain
- CIDP
 - Refer to neurologist
 - Immunomodulatory therapy
 - Corticosteroids
 - Plasmapheresis
 - Immune globulin

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

Pain management should be prescribed as necessary for focal and multifocal neuropathies. Nerve entrapments may require decompression. If a diagnosis of chronic inflammatory demyelinating polyneuropathy is suspected, patients should be referred to a neurologist. Combinations of corticosteroids, plasmapheresis, and intravenous immune globulin have been shown to improve neurologic deficits in some cases.

Diagnosis and Prevention of Diabetic Neuropathy

- **Diagnosis**

- Assess symptoms
- Sensory testing
- Autonomic function testing
- Electrophysiology

- **Prevention**

- Glycemic control
- Manage other risk factors (no definitive prevention studies)
 - Blood pressure control
 - Lipid control
 - Avoid smoking and excess alcohol

Boulton AJ et al. *Diabetes Care*. 2005;28:956–962.

The diagnosis of diabetic neuropathy is made based on assessment of symptoms (muscle weakness, muscle cramps, prickling, numbness or pain, vomiting, diarrhea, poor bladder control, sexual dysfunction, etc), sensory testing, autonomic function testing, and electrophysiology.

Once again glycemic control represents the primary prevention and management measure for diabetic neuropathy. Blood pressure control, lipid control, and avoiding both smoking and excess alcohol are also suggested, although no definitive prevention studies have been performed on the benefit of managing these other risk factors.

Question

What percentage of DPN cases may be asymptomatic in patients with diabetes?

- A. 20%
- B. 30%
- C. 40%
- D. 50%

This is our final question.

What percentage of DPN cases may be asymptomatic in patients with diabetes?

- A. 20%
- B. 30%
- C. 40%
- D. 50%

Answer

D. Up to 50% of cases of DPN may be asymptomatic. These patients are at risk for insensate foot injuries.

The correct answer is D.

Up to 50% of cases of DPN may be asymptomatic. These patients are at risk for insensate foot injuries.

Conclusion

- Diabetes is a highly prevalent disease that is associated with numerous complications
- Comprehensive risk factor management can significantly reduce diabetes complications and improve patient outcomes
- **Treat underlying pathologies!**
- Glycemic, blood pressure, and lipid control are essential to the prevention and management of diabetes complications

In conclusion:

- Diabetes is a highly prevalent disease that is associated with numerous micro- and macrovascular complications.
- Comprehensive risk factor management can significantly reduce diabetes complications and improve patient outcomes.
- Treatment of the underlying pathogenic mechanisms in diabetes is critical in preventing and managing complications, as most complications can be tied back to these mechanisms. In this regard, glycemic, blood pressure, and lipid control are essential.