

# Chronic Complications of Diabetes

Supported by an educational grant from  
Novo Nordisk Inc. This program has been accredited  
by AADE for pharmacists, nurses, and dietitians.

This program is primarily designed for nurses, dietitians, and pharmacists working with persons with diabetes. Program content provides an overview of the types of chronic, long-term complications that are associated with diabetes. Chronic complications are categorized as either macrovascular or microvascular. Identified risk factors contributing to each complication are profiled along with diagnostic criteria, treatment strategies and preventive strategies.

# Program Objectives

1. Identify risk factors contributing to the development of chronic complications associated with diabetes
2. Describe three types of macrovascular complications that affect individuals with diabetes
3. Describe the diagnosis, treatment, and prevention of diabetic nephropathy
4. Describe the stages of diabetic retinopathy along with the strategies for both intervention and prevention
5. Describe the types of diabetic neuropathies, their effects and their intervention/prevention strategies
6. Identify the roles of the patient and all members of the diabetes-care team in both prevention and treatment of diabetes related complications

This program emphasizes importance of blood glucose control in the prevention of chronic complications associated with diabetes.

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# Defining Diabetes

**“A group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.”**

American Diabetes Association, *Diabetes Care*.  
2004;27 (Suppl 1):S5-S10.

Diabetes is a chronic, progressive, systemic disease for which there is no known cure at this time. Diabetes currently affects as estimated 18.2 million Americans or 6.3% of the U.S. population. It is a disease of altered glucose metabolism, and its hallmark is hyperglycemia. Diabetes is defined by the American Diabetes Association (ADA) as “a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both”. Irrespective of clinical diagnosis (type 1 or type 2 diabetes), the impact of this disease on the progression of microvascular and perhaps macrovascular complications is related to the magnitude of hyperglycemia.

#### Reference:

American Association of Diabetes Educators. *AADE core curriculum: Diabetes and Complications 5th ed.* Chicago, Illinois: American Association of Diabetes Educators; 2003.

American Diabetes Association. *Position statement: Diagnosis and classification of diabetes mellitus.* *Diabetes Care*. 2004; 27(suppl 1):S5-10.

National Institute of Diabetes and Digestive Kidney Diseases (NIDDK). NIH Publication No. 04-3873. Bethesda, MD: National Institutes of Health; November 2003. Available at: <http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm>. Accessed February 9, 2004.

# Good Management of Blood Glucose Counts!

**The risk of chronic complications associated with diabetes can be reduced.**

Strong evidence supports a direct link between hyperglycemia and the incidence of long-term diabetic complications. According to the ADA expert committee report on the diagnosis and classification of diabetes, it is the chronic hyperglycemia that is “associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.” Long-term diabetic complications are an unfortunate reality; the good news is that effective management of blood glucose levels can reduce risk, delay onset, and reduce the severity of these long-term complications.

Reference:

*American Diabetes Association. Position statement: Diagnosis and classification of diabetes mellitus. Diabetes Care. 2004; 27(suppl 1):S5-10.*

*Diabetes Control and Complications Trial Research Group. The effect of intensive treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine. 1993; 329:14:977-986.*

*United Kingdom Prospective on Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352:837-853.*

## Types of Chronic Complications

- Macrovascular complications
- Microvascular complications

Long-term complications of diabetes are divided into two categories: macrovascular and microvascular.

Macrovascular complications primarily affect large blood vessels and body organs.

Microvascular complications are those affecting smaller blood vessels, and are further differentiated by whether they primarily affect the kidneys (nephropathy), eyes (retinopathy), peripheral circulation (smaller blood vessels), or nerves (neuropathy).

## Diabetes Control and Complications Trial (DCCT) - (Type 1 diabetes)

	<u>Conventional Therapy</u>	<u>Intensive Therapy</u>
1. Mean blood glucose:	231 mg/dL	155 mg/dL
2. Mean A1C:	9.0%	7.1%
3. <u>Complications</u>	<u>Mean Risk Reduction</u> (Primary Prevention Cohort)	
Eye (Retinopathy)	76%	
Kidney (Nephropathy)		
Microalbuminuria	34%	
Albuminuria	44%	
Nerve (Neuropathy)	60%	

Current information regarding the importance of glycemic control has come from a few landmark multi-center clinical trials. The Diabetes Control and Complications Trial (1993) was the first major study to be published, followed by the Kumamoto study (1995) and the United Kingdom Prospective Diabetes Study (1998). Findings from the DCCT study were first published in the New England Journal of Medicine. The goal of this multi-center study was to test the proposition that the complications of diabetes were related to elevated plasma glucose concentration. Two groups of patients with type 1 diabetes were followed long term, one treated conventionally and another treated intensively. Conventional therapy in this study was defined as 1 to 2 injections of insulin each day. Intensive therapy was defined as 3 or more daily insulin injections or the use of an insulin pump. The primary objective was to evaluate if intensive therapy resulted in the prevention of retinopathy in patients with no overt symptoms, or in the progression of symptoms in patients with early disease. The effect of each type of therapy on the development of nephropathy and neuropathy was also evaluated. Retinopathy, nephropathy, and neuropathy were all evaluated because these are the major categories of chronic long-term complications involving microvascular (capillaries and small blood vessels) and biochemical changes at the cellular level. Findings revealed that the intensive therapy group (primary prevention cohort) had a 76% reduction in risk of retinopathy, a 60% reduction in risk of neuropathy, and a significantly reduced risk of nephropathy as measured by development of microalbuminuria (34%) or albuminuria (44%). The benefit of intensive treatment included a delay in the onset and a major slowing of the progression of these three complications. Analyses of macrovascular (large blood vessel and body organ) complications linked with diabetes showed an observed trend (although not statistically significant) indicating that macrovascular complications might also be reduced with intensive insulin therapy. Subsequent studies by the DCCT research group and other researchers have continued to support this observation.

### Reference:

- American Diabetes Association. Position statement: Implications of the diabetes control and complications trial. Diabetes Care. 2003; 26(suppl 1):S25-27.*
- Diabetes Control and Complications Trial Research Group. The effect of intensive treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine. 1993; 329:14:977-986.*
- Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. Journal of the American Medical Association. 1996; 276(17):1409-1415.*
- Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Research Clinical Practice. 1995; 28:103-117.*
- United Kingdom Prospective on Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352:837-853.*

## United Kingdom Prospective Diabetes Study (UKPDS) - (Type 2 diabetes)

- A1C levels of 7% (range 6.2% to 8.2%) in the intensive therapy group vs. 7.9% (range 6.9% to 8.8%) in the conventional group were maintained over 10 year period ( $p < 0.0001$ )
- Maintenance of lower A1C levels in the intensive therapy group reduced the risk of diabetes-related complications
- Maintaining tight blood pressure control with a BP level of 144/82 (anti-hypertensive therapy group) vs. 154/87mmHg (control group) also reduces the risk of complications

The largest and longest diabetes study focusing on type 2 diabetics was the UKPDS. Between 1977 and 1991, patients with newly diagnosed type 2 diabetes were randomly assigned to various treatment groups and followed for an average of 10 years. Primary objectives were to determine 1) whether intensive therapy for type 2 diabetes reduces the risk of complications; 2) whether a sulfonylurea, metformin, or insulin has specific advantages or disadvantages; 3) whether tight blood pressure control reduces the risk of complications; and 4) whether use of an angiotensin-converting enzyme (ACE) inhibitor or beta blocker offers particular therapeutic advantages or disadvantages. Participants randomized to an intensive blood glucose control group were treated with insulin, a sulfonylurea or metformin; participants randomized to a conventional treatment group were treated with diet modification.

Participants in the intensive therapy group maintained a fasting plasma glucose (FPG)  $< 108$  mg/dL (6 mmol/L), and the average A1C levels among these same participants was 7.0%, compared to 7.9% among those in the conventional therapy group. Within the intensive therapy group, there was a clinically and statistically significant reduced risk of developing any diabetes related complication (~12%,  $p=0.029$ ). Data showed that the risks of complications were significantly lowered for any participant when A1C was kept below 8 percent.

Microvascular complications, such as retinopathy, were reduced by 25% ( $p=0.0099$ ) in the intensive therapy group. Data indicated that for every decrease in percentage point of A1C (such as from 9 percent to 8 percent), the associated risk of complications was reduced by 35 percent. The UKPDS also assessed whether tight blood pressure control impacted the risk of diabetic complications. Mean blood pressure among participants treated for tight blood pressure control with an antihypertensive agent was 144/82 mmHg as compared to 154/87 mmHg in the control group. Maintaining tight blood pressure control reduced the overall risk of complications related to diabetes by ~24% ( $p=0.005$ ), microvascular endpoints by ~37% ( $p=0.009$ ), stroke by ~44% ( $p=0.013$ ), and death related to diabetes by ~32% ( $p=0.019$ ).

Reference:

*American Diabetes Association. Position statement: Implications of the united kingdom prospective diabetes study. Diabetes Care. 2003; 26(suppl 1):S28-32.*

*United Kingdom Prospective on Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352:837-853.*

## ADA & AACE Recommendations for Glycemic Control

### Plasma Glucose Values

### Goal

**Pre-prandial  
Plasma Glucose  
(mg/dL)**

**90 - 130**  
( $\leq$  110 AACE)

**Peak  
Post-prandial  
Glucose (mg/dL)**

**<180**  
( $\leq$  140 AACE)

**A1C**

**<7%**  
( $\leq$  6.5 % AACE)

**Positive Diagnosis  
of Diabetes**



**FPG  $\geq$ 126 mg/dL (on 2 separate days)**  
**Random PG  $\geq$  200 mg/dL (with signs and symptoms)**

Modified from American Diabetes Association. *Diabetes Care*. 2004;27(Suppl 1):S15-S35 and American College of Endocrinology. *Endocrine Practice*. 2002;v8(Suppl 1):5-11.

The American Diabetes Association and the American College of Endocrinology have both recommended guidelines for maintaining specific glucose levels in individuals with diabetes. Recommendations for glycemic control have been published because “abundant evidence is now available that long-term maintenance of near-normal blood glucose levels is protective of patients with diabetes and substantially reduces complications and mortality...” In adults with diabetes, the ADA guidelines recommend a pre-prandial plasma glucose of 90 to 130 mg/dL (5.0 to 7.2 mmol/L) and a peak post-prandial plasma glucose <180 mg/dL (<10.0 mmol/L). The AACE guidelines recommend a pre-prandial plasma glucose  $\leq$  110 mg/dL and a post-prandial plasma glucose of  $\leq$ 140 mg/dL.

The guideline for diagnosis of diabetes based on fasting plasma glucose (FPG) has been decreased from 140 mg/dL to 126 mg/dL. Currently, a fasting plasma glucose of  $\geq$ 126 mg/dL on two separate days is diagnostic of diabetes provided no concurrent illness is present that might result in temporary elevation of glucose levels, and no medication is in use that might lead to reversible elevations of blood glucose levels. Also a random or casual plasma glucose  $\geq$  200 mg/dL along with relevant signs/symptoms is diagnostic of diabetes. The diagnostic criteria for diabetes have been modified from those previously recommended by the National Diabetes Data Group (NDDG) and the World Health Organization (WHO), and it is believed that widespread adoption of the new criteria may have a large impact on the number of people actually diagnosed with diabetes. The upper threshold for normal FPG is <100 mg/dL, and FPG values  $\geq$ 100 mg/dl (5.6 mmol/l) and <126 mg/dl (7.0 mmol/l) reflect the existence of a metabolic stage intermediate between normal glucose homeostasis and diabetes, now referred to as pre-diabetes.

#### Reference:

*American College of Endocrinology. Consensus statement on guidelines for glycemic control. Endocrine Practice. 2002; 8(suppl 1):5-11.*

*American Diabetes Association. Position statement: Diagnosis and classification of diabetes mellitus. Diabetes Care. 2004; 27(suppl 1):S5-10.*

*American Diabetes Association. Position statement: Standards of medical care in diabetes. Diabetes Care. 2004; 27(suppl 1):S15-35.*

*American Association of Clinical Endocrinologists. Medical guidelines for the management of diabetes mellitus: The AACE system of intensive diabetes self-management – 2002 update. Endocrine Practice. 2002; 8(suppl 1):40-82.*

## Diabetes and Chronic Complications

- Risk for developing cardiovascular disease is 2 to 4 times greater in patients with diabetes
- Leading cause of renal failure
- Main cause blindness in the United States
- Increased frequency of infections
- Approximately 60% of non-traumatic amputations (~82,000/yr)

The majority of patients with diabetes will develop long-term vascular complications associated with organ and nerve damage. Patients with diabetes have a 2 to 4 fold greater risk for developing cardiovascular disease, diabetes is the leading cause of renal failure, and diabetes is the main cause of blindness in the United States. Individuals with diabetes have increased frequency of infections, and more than 60% of all non-traumatic amputations occur in patients with diabetes. From 2000-2001, approximately 82,000 non-traumatic lower limb amputations were performed each year in patients with diabetes. These complications contribute to serious health problems with significant morbidity and mortality.

### Reference:

*American Diabetes Association. National Diabetes Fact Sheet. Available at:*

*<http://www.diabetes.org/diabetes-statistics/national-diabetes-fact-sheet.jsp>. Accessed March 17, 2004.*

*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:176-182, 218-219.*

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:43-44, 68, 100, 115, 176, 196.*

## Macrovascular Complications

- Affects large blood vessels
- Role of atherosclerosis
- Types of macrovascular complications
  - » Cardiovascular disease
  - » Cerebrovascular disease
  - » Peripheral arterial disease

Atherosclerotic macrovascular disease significantly contributes to morbidity and mortality among those with diabetes.

Atherosclerotic vascular disease of the coronary vessels develops at an earlier age in patients with diabetes, and involves coronary vessels more extensively and diffusely. The increased incidence of atherosclerosis in patients with diabetes is due to an increase in risk factors such as dyslipidemia, hyperglycemia, hypertension, and obesity.

While the exact pathophysiology of atherosclerosis is not known, it is believed that lipid material accumulates beneath the endothelial lining of blood vessels, contributing to inflammation, focal narrowing, and the development of plaque deposits. Atherosclerotic plaques develop in the inner walls of blood vessels and increase in size over time. Eventually the plaque deposits may completely block the flow of blood or trigger the formation of a blood clot (thrombus) which can also lead to blockage. This blood clot may stay lodged to the vessel wall, or it may break apart into smaller fragments which enter the general circulation (emboli) and block additional blood vessels including those of the brain.

Macrovascular complications can be categorized based on the types of blood vessels affected. In cardiovascular disease, atherosclerotic plaque can impede blood flow or lead to a blockage of a blood vessel in the heart (myocardial infarction). 30% of patients with diabetes who experience an MI do not have characteristic symptoms in contrast to 5 to 10% of patients without diabetes. The increased incidence of cardiovascular disease in patients with diabetes contributes to 2 to 4 times higher rates of morbidity and mortality than in the general population. Individuals with diabetes are more likely to experience an acute MI at a younger age, and more likely to have complications from that MI than patients without diabetes.

In cerebrovascular disease, atherosclerotic plaque can impede blood flow or lead to blockage of a blood vessel in the brain (CVA – cerebrovascular accident).

In peripheral arterial disease, atherosclerotic plaques involve the blood vessels of the legs, particularly below the knee, and can lead to serious circulatory problems with legs and feet.

### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:100.*  
*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:176-189.*  
*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:100-126, 137-151.*

# Metabolic Syndrome

Dyslipidemia

Insulin resistance

Hypertension

Central Obesity

**Metabolic syndrome is diagnosed when any 3 of the following are present:**

- Abdominal obesity, waist >40 inches (men), > 35 inches, (women)
- Fasting triglycerides > 150 mg/dL
- HDL cholesterol < 40 mg/dL (men), <50mg/dL (women)
- Blood pressure  $\geq$ 130/85 mm Hg
- Fasting glucose  $\geq$ 110 mg/dL\*

\*Current ADA guidelines have lowered value to  $\geq$ 100 mg/dL

High rates of dyslipidemia, hypertension, and obesity are found in patients with type 2 diabetes. Collectively, these traits are known as the metabolic syndrome (syndrome X). Our understanding of the relationship between these traits is still in its infancy.

Diagnostic criteria for metabolic syndrome have been proposed by the National Cholesterol Education Program (NCEP). The presence of any 3 of the following traits (abdominal obesity, and elevations in triglycerides, blood pressure, and fasting plasma glucose as well as decreased HDL-cholesterol) confirms the diagnosis. Many patients with type 2 diabetes are obese. Increased visceral fat is associated with decreased insulin sensitivity in skeletal muscle and the liver along with impaired glucose uptake.

Reference:

*American Diabetes Association. Position statement: Standards of medical care in diabetes. Diabetes Care. 2004; 27(suppl 1):S15-35.*

*Wilson PWF, Grundy SM. The metabolic syndrome: practical guide to origins and treatment, part 1. Circulation. 2003; 108:1422-1425.*

## Risk Factors Contributing to Atherosclerotic Cardiovascular Disease

- Hyperglycemia
- Hypertension
- Dyslipidemia
- Smoking/Tobacco use
- Obesity and sedentary lifestyle

Risk factors for the development of atherosclerotic cardiovascular disease include the following.

**Hyperglycemia:** Strong evidence now exists to show that persistent hyperglycemia is one of several factors that can weaken and damage blood vessels. Specific damage occurs when permeability of the endothelial basement layer lining the endothelium is changed. In part, this change in permeability occurs as a result of the non-enzymatic glycosylation of many arterial proteins including basement membrane protein, resulting in increased permeability to many proteins and lipoproteins, particularly LDL-C. An accumulation of LDL-C occurs in the sub-endothelial intimal lining of the blood vessel, followed by uptake by macrophages and fibroblasts. These biochemical changes alter the vasculature, resulting in the inflammation and plaque formation that are so characteristic in atherosclerotic disease.

**Hypertension** is twice as common among patients with diabetes. The combination of hypertension and diabetes has an impact on the cardiovascular and renal body systems because they both accelerate the atherosclerotic changes that destroy blood vessels. There is a correlation between the duration of diabetes, the development of renal dysfunction, and the development of hypertension.

**Dyslipidemia** commonly exists at the time of diagnosis in patients with type 2 diabetes, and is a major risk factor for cardiovascular complications. Individuals with type 1 diabetes are more likely to develop dyslipidemia years after their initial diagnosis. Overall, the impact of cholesterol levels on cardiovascular disease is similar in individuals with or without diabetes, but individuals with diabetes have a clinically significant higher risk because of the presence of other risk factors.

**Smoking/tobacco use** appears to have an independent additive impact on the risk of cardiovascular disease development for patients with diabetes.

**Obesity and sedentary lifestyle** may increase the risk of cardiovascular disease.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:47.*

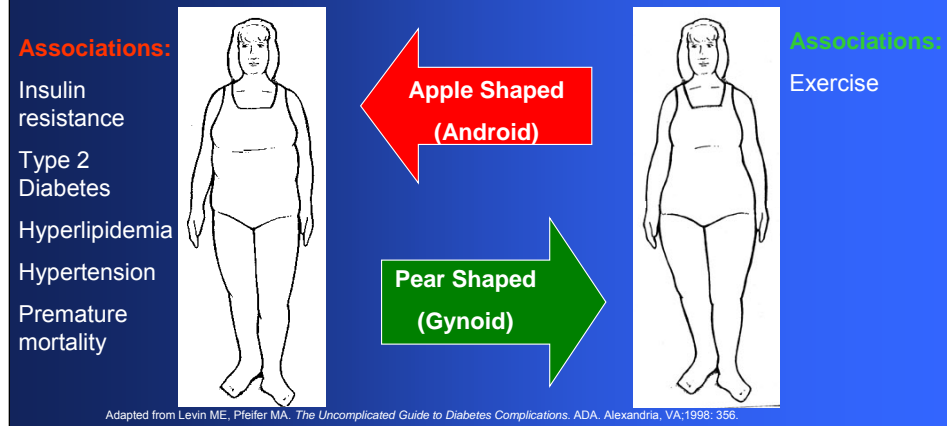
*American Diabetes Association. Position statement: Hypertension management in adults with diabetes. Diabetes Care. 2004; 27(suppl 1):S65-67.*

*American Diabetes Association. Position statement: Dyslipidemia management in adults with diabetes. Diabetes Care. 2004; 27(suppl 1):S68-71.*

*Beckman J, Creager M, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. Journal of the American Medical Association. 2002; 287(19):2570-2581.*

# Risk Factor Contributing to Atherosclerotic Cardiovascular Disease

## Body fat distribution



It is now recognized that the pattern of obesity is an important determinant for atherosclerotic disease progression. *Central body fat distribution* with a waist circumference exceeding 40 inches in men and 35 inches in women is associated with dyslipidemia, hypertension, and an increased prevalence of both cardiovascular disease and type 2 diabetes mellitus.

### Reference:

Levin ME, Pfeifer MA. *The Uncomplicated Guide to Diabetes Complications*. Alexandria, VA: American Diabetes Association; 1998:356.

Mokdad A, Ford E, Bowman B, Dietz W, Vinicor F, Bales V, Marks J. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *Journal of the American Medical Association*. 2003; 289(1):76-79.

## General Assessment of Atherosclerotic Cardiovascular Disease

- Complete medical history
  - » Symptoms
  - » Risk factor assessment
- Family history
- Physical examination
- Laboratory
- Lifestyle

When evaluating any individual with diabetes for the presence of macrovascular disease, the clinician should elicit a medical history to identify any current symptoms. Symptoms might include angina and dyspnea (associated with cardiovascular disease), dizziness and transient weakness (associated with cerebrovascular disease), or claudication and foot ulcers (associated with peripheral arterial disease).

Assessment of current risk factors is also important. The clinician should ask about smoking and family history, and evaluate the patient's cholesterol levels, hypertension, microalbuminuria and albuminuria.

A physical examination should include two measurements of blood pressure, lying or sitting. Additional evaluations should include an assessment for vascular bruits and heart murmur, status of feet (including presence and quality of peripheral pulses), and a calculation of the ankle/brachial index. Laboratory testing should include blood glucose, A1C, and a lipid profile (HDL, cholesterol, LDL, triglycerides).

Lifestyle modifications in terms of diet, exercise, and smoking cessation may be necessary. Clinicians should also make every effort to assess an individual's coping abilities, relevant knowledge, beliefs, attitudes, and skills so that targeted lifestyle modifications can be achieved whenever possible.

Reference:

*American Diabetes Association. Position statement: Standards of medical care in diabetes. Diabetes Care. 2004; 27(suppl 1):S15-35.*

*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:176-190.*

## Forms of Cardiovascular Disease Associated with Diabetes

- Coronary Artery Disease (CAD)
- Congestive Heart Failure (CHF)
- Hypertension (HTN)
- Peripheral Arterial Disease (PAD)

Cardiovascular disease is the leading cause of mortality among patients with diabetes. Blocked or narrowed coronary arteries (CAD) decrease the oxygen supply to the heart muscle (ischemia) and can result in myocardial infarction (MI). The most common symptom is pain (angina) or pressure in the chest, but pain is often blunted in those with diabetes. Angina (chest pain) generally occurs first with exercise or activity because heart rate is higher. Stable angina occurs with activity but stops with rest, and heart tests show no evidence of permanent damage. When the pain and symptoms occur at rest or abruptly worsen, this is known as unstable angina and can signify serious heart problems and lead to an MI.

Other symptoms of CAD may include shortness of breath (usually associated with chest pain, physical activity, or emotional stress), dizziness, diaphoresis, nausea and jaw pain. The presence of these symptoms requires an immediate examination by the physician. Cardiac testing is usually performed, and cardiac catheterization is indicated if the stress test is abnormal or severe chest pain is present. Conventional treatment includes nitrates, beta blockers, calcium channel blockers, angioplasty, and sometimes coronary artery bypass grafting (CABG).

Congestive Heart Failure (CHF) occurs when the heart muscle is weakened and is not able to pump blood to all parts of the body. Fluid accumulates in various parts of the body (such as the lungs) and also affects kidney function. Diabetic cardiomyopathy is a form of CHF and is caused by scarring and weakening of the heart muscle. Ischemic cardiomyopathy is caused by repeated episodes of decreased blood flow to the heart due to CAD. Signs and symptoms include shortness of breath, fatigue, swollen ankles (fluid retention), low cardiac output, and palpitations. Diagnosis is confirmed with chest X-ray and echocardiogram; treatment generally includes digoxin to strengthen the heart muscle and improve circulation, diuretics to help remove fluid from the body, and "afterload" reducers to decrease the work the heart has to perform (angiotensin converting enzyme inhibitors, nitrates).

Hypertension (HTN) occurs when pressure exerted by blood on the walls of the blood vessels stays consistently above 140/90 mm Hg. Hypertension is typically called "the silent killer" because patients are usually asymptomatic until some major organ is affected, often resulting in kidney disease or stroke. The strong association between hypertension and diabetes comes from atherosclerosis, because atherosclerotic changes decrease blood vessel size to directly influence the pressures needed to maintain adequate blood flow. According to ADA, blood pressure should be treated to <130/80 mm Hg.

### Reference:

American Diabetes Association. *Position statement: Standards of medical care in diabetes. Diabetes Care. 2004; 27(suppl 1):S15-35.*

American Diabetes Association. *Position statement: Hypertension management in adults with diabetes. Diabetes Care. 2004; 27(suppl 1):S65-67.*

DeFronzo RA. *Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:182-190.*

Levin ME, Pfeifer MA. *The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:100-122.*

## Cerebrovascular Disease

- Blockage or hemorrhage of blood vessels in the brain may lead to stroke
- Incidence of stroke: 2 to 4 times higher in patients with diabetes

The term cerebrovascular disease refers to acute stroke, and other health conditions that may lead to stroke, like carotid stenosis and aneurysms. Cerebrovascular disease and stroke result from the blockage or hemorrhage of a blood vessel in the brain. The incidence of cerebrovascular disease is approximately 2 times higher in patients with diabetes, whereas the risk of stroke is 2 to 4 times greater. Individuals with diabetes appear to develop cerebrovascular disease at an earlier age than those in the general population, and they tend to have more pronounced disease. People with diabetes have a higher mortality rate, worse neurological outcomes, and more severe disability after stroke than those without diabetes.

Strokes are categorized as either ischemic stroke or hemorrhagic stroke. Hemorrhagic stroke is less common, but more deadly, and occurs when there is bleeding into or around the brain itself. An acute cerebrovascular event is considered to be an ischemic stroke when blood flow to the brain is blocked. Ischemic strokes are the most common, and incidence increases when the carotid arteries, the vertebral arteries, or communicating arteries within the brain develop significant blockage due to atherosclerotic plaque build up. Early recognition and treatment of an ischemic stroke (within a few hours after onset) can dramatically improve outcome because of the potential to alleviate the blockage and restore tissue oxygenation. During a hemorrhagic stroke, an artery in or on the surface of the brain has ruptured or is leaking, causing bleeding and damage in or around the brain. Hemorrhagic stroke includes both intra-cerebral hemorrhage and subarachnoid hemorrhage.

Recognizing the “warning signs” of an impending stroke is important. One common warning sign is the occurrence of a transient ischemic attack (TIA). By definition, a TIA is a temporary cerebrovascular disruption (< 24 hours) that leaves no permanent damage. Typically, a TIA develops when an artery to the brain becomes temporarily blocked, either because of an acutely constricted vessel or the presence of a blood clot, and then opens before any permanent damage was sustained. TIA symptoms can include: numbness or weakness in the face, arm, or leg, especially on one side of the body; confusion or difficulty in talking or understanding speech; trouble seeing in one or both eyes; and difficulty with walking, dizziness, or loss of balance and coordination. Because TIA symptoms are temporary, their occurrence can become an opportunity for medical intervention to prevent a future, more devastating stroke.

Reference:

*American Association of Neurological Surgeons. Cerebrovascular disease 1998. Available at:*

[http://www.neurosurgery.org/pubpages/patres/features/jul99\\_cerebro.html](http://www.neurosurgery.org/pubpages/patres/features/jul99_cerebro.html) Accessed February 9, 2004.

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:196.*

## Peripheral Arterial Disease

- Affects small and large blood vessels
- Risk factors
- Signs and symptoms

In peripheral arterial disease (PAD), atherosclerotic plaques develop in both the large (macrovascular) and small (microvascular) blood vessels of the lower extremities, particularly below the knee. These plaques can lead to serious circulatory problems with legs and feet; diabetic complications related to peripheral circulation typically account for almost 50% of all non-traumatic amputations. The overall incidence of PAD is approximately 20 times higher in individuals with diabetes, and so preventive care is essential in reducing the risk of this complication.

Key risk factors for peripheral arterial disease are smoking, obesity, hypertension, and dyslipidemia.

Signs and symptoms of PAD focus on pain and discomfort. A classic symptom is intermittent claudication, which is pain or discomfort (usually localized in the calf) associated with walking. The affected individual needs to frequently stop and rest when walking or exercising; the pain generally goes away when the person stops walking, without the need to sit down. There may be an absent foot pulse, loss of hair on foot or toes, cold or discolored feet, toes or hands, and thickened nails. Loss of sensation in the legs and feet is due to neuropathy but may accompany PAD, and this loss of sensation is particularly troublesome because it can lead to injuries or wounds that go unnoticed. When this occurs, the wound can become severely infected and if left untreated can lead to complications such as gangrene.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:101.*  
*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:190-193.*  
*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:196.*

## Lifestyle Change May Decrease Macrovascular Complications

- Optimal control of hyperglycemia
- Smoking cessation
- Limited alcohol consumption
- Dietary modifications to reduce hyperlipidemia and dyslipidemia
- Regular exercise
- Regular foot examination; daily visual check by patient
- Regular visits to the healthcare provider

Diabetes is a disease that's managed for the most part by self care. Self blood glucose monitoring is an essential part of diabetes management. Because choices belong to the person with diabetes, every effort should be made to empower the patient using an overall supportive educational approach. Lifestyle changes may significantly decrease the onset and severity of long-term vascular complications. Compelling evidence suggests that individuals with diabetes can achieve substantial benefits when they maintain optimal control of hyperglycemia. Consistent and repeated efforts should be made to stress the importance of glycemic control through modifications in diet and exercise. Blood glucose monitoring should be routinely performed with each patient encounter, and A1C monitoring should be regularly scheduled.

Other recommended lifestyle changes include smoking cessation, limiting alcohol consumption, modifying diet to reduce hyperlipidemia and dyslipidemia, practicing regular foot examinations with a daily visual check, and regularly visiting the diabetes-care team.

### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:56-57.*

*American Diabetes Association. Position statement: Standards of medical care in diabetes. Diabetes Care. 2004; 27(suppl 1):S15-35.*

## Macrovascular Complications Treatment Goals in Diabetes

	<u>Treatment Goals</u> (mg/dL)
<b>Total Cholesterol</b>	<200
<b>LDL-C</b>	<100
<b>HDL-C</b>	> 40 (male) > 50 (female)
<b>Triglycerides</b>	<150

American Diabetes Association. Position statement: Dyslipidemia management in adults with diabetes. *Diabetes Care*. 2004; 27(suppl 1):S68-71.  
Lipsy, R.J. Effective management of patients with dyslipidemia. *The American Journal of Managed Care*. 2003; 2;9(suppl 1):S39-S58.

*Treating dyslipidemia* involves maintaining the ideal levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Reaching these treatment goals should result in fewer or less frequent long-term vascular complications.

Treatment strategies for dyslipidemia, according to the National Cholesterol Education Panel, should include aggressive cholesterol-lowering treatment goals. Patient counseling should focus on optimizing healthy eating, increasing physical activity, cessation of smoking, and encouraging weight loss when appropriate.

Careful evaluation of current medications may reveal drugs that may be causing or aggravating dyslipidemia. Those should be discontinued if possible. Other pharmacological treatment strategies involve prescribing agents for treatment of dyslipidemia such as nicotinic acid (niacin), HMG-CoA reductase inhibitors (statins), fibric acid derivatives, and bile acid resins.

### Reference:

American Diabetes Association. Position statement: Dyslipidemia management in adults with diabetes. *Diabetes Care*. 2004; 27(suppl 1):S68-71.  
DeFronzo RA. *Current Therapy of Diabetes Mellitus*. St. Louis, MO: Mosby Yearbook; 1998:123-133.  
Lipsy, R.J. Effective management of patients with dyslipidemia. *The American Journal of Managed Care*. 2003; 2;9(suppl 1):S39-S58.

## Microvascular Complications

- Affect small blood vessels and nerves
- Types of microvascular complications
  - » Nephropathy - kidneys
  - » Retinopathy - eyes
  - » Neuropathic complications - nerves

Microvascular complications, by definition, affect the small blood vessels of the body. They are caused by the same atherosclerotic changes that lead to long-term macrovascular complications. In addition to affecting the smaller peripheral blood vessels (PAD), microvascular changes most typically affect the kidneys (nephropathy), the eyes (retinopathy), and the nerves (neuropathy). Neuropathy is not strictly a microvascular complication, but the diabetes-related biochemical changes impacting the nerves are further affected by microvascular dysfunction.

Specific risk factors associated with microvascular complications include hyperglycemia, hypertension, duration of uncontrolled diabetes (over 5 years), and smoking.

Reference:

*American Diabetes Association. Position statement: Implications of the diabetes control and complications trial. Diabetes Care. 2003; 26(suppl 1):S25-27.*

## Diabetic Nephropathy

- Leading cause of renal failure in the United States
- Occurs in both type 1 and type 2 diabetes patients



Diabetic nephropathy is a significant complication in individuals with diabetes, increasing the risk of hypertension which in turn exacerbates the nephropathy and frequently develops into clinically significant renal disease. Diabetic nephropathy is the most common cause of renal failure (also known as end-stage renal disease or ESRD) in the United States and Europe; currently accounting for about 40% of new cases of ESRD in the United States.

It is estimated that about 20 to 30% of individuals with type 1 or type 2 diabetes develop evidence of nephropathy. Diabetic nephropathy and hypertension are the most significant contributors to chronic renal disease. Overall, clinically significant renal disease is less common in patients with type 2 diabetes, but its incidence approaches the levels observed for patients with type 1 diabetes among certain ethnic groups such as Native Americans, Mexican Americans, and African Americans.

Not all cases of nephropathy in patients with diabetes can be attributed to underlying diabetes.

The structural changes in vasculature associated with diabetic nephropathy and hypertension are similar in both type 1 and type 2 diabetes patients. They include renal hypertrophy, glomerular basement membrane thickening, mesangial expansion (expansion of phagocytic cells of the mesangium) and diffuse intercapillary glomerulosclerosis (degenerative process resulting in scarring of the renal glomeruli).

These changes are irreversible, progressive, and are identified as stages one through five.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:153.*

*American Diabetes Association. Position statement: Nephropathy in diabetes. Diabetes Care. 2004; 27(suppl 1):S79-83.*

*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:134-143.*

## Progression of Nephropathy

Stages	Characteristics	Onset	% Progressing to Next Stage (without treatment)
1	<b>Functional Changes</b> (Early hypertrophy and hyperfiltration)	Onset of diabetes	100%
2	<b>Structural Changes</b> (Renal lesions)	2 to 3 years	35% to 40%
3	<b>Incipient Nephropathy</b>	7 to 15 years	80% to 100%
4	<b>Overt Nephropathy</b> (Proteinuria)	10 to 30 years	50% to 75%
5	<b>Renal Failure or End-Stage Renal Disease (ESRD)</b>	20 to 40 years	75% to 100%

*Stage 1* is asymptomatic, characterized by hyper-filtration and renal hypertrophy. During this stage, tiny blood vessel deterioration due to atherosclerosis destroys some of the many nephrons within the kidney. Remaining nephrons increase in size and work capacity as they attempt to compensate. Renal function is reduced, but no accumulation of metabolic waste occurs.

During *Stage 2*, thickened and inflamed capillaries reduce blood flow to the glomerulus. This results in glomerular basement membrane thickening, mesangial expansion (expansion of phagocytic cells of the mesangium) and diffuse inter-capillary glomerulosclerosis (a degenerative process resulting in scarring of the renal glomeruli). This stage is also asymptomatic.

*Stage 3*, also referred to as incipient diabetic nephropathy (immediately prior to overt or symptomatic nephropathy), develops after 7 to 15 years of diabetes duration. This is when microscopic amounts of albumin (microalbuminuria) inadvertently slip through sclerosed glomerular membranes, signifying a progressive deterioration in kidney filtration. Metabolic waste begins to accumulate in the blood because unaffected nephrons can no longer compensate, and responsiveness to diuretic therapy decreases. This stage is also asymptomatic.

*Stage 4* is also referred to as overt or clinical diabetic nephropathy, and is characterized by significantly large amounts of protein detected in the urine (albuminuria or proteinuria). It is usually not until stage 4 that an individual becomes symptomatic. Symptoms include oliguria and edema. Significant amounts of metabolic waste begins to accumulate, particularly urea and creatinine.

Without aggressive treatment, and sometimes even in spite of aggressive treatment, deteriorating vasculature results in *Stage 5*, known as renal failure or end-stage renal disease (ESRD). Renal failure or ESRD develops in 75% to 100% of patients with overt nephropathy within 20 years.

Reference:

American Association of Diabetes Educators. *AADE core curriculum: Diabetes and Complications 5th ed.* Chicago, Illinois; American Association of Diabetes Educators; 2003:158-159.

# Kidney Function Tests

## Normal Reference Range

- Urinary Albumin < 30 mg/day
- Serum Creatinine<sup>1</sup> 0.5 to 1.4 mg/dL
- Blood Pressure < 130/80 mm Hg
- Creatinine Clearance<sup>2</sup> 100-125 mL/min

Levels vary according to laboratory

<sup>1</sup> Levels vary by body size and gender; males typically have higher levels

<sup>2</sup> For adult male on Western diet.

Throughout the early stages of diabetic nephropathy, individuals are usually asymptomatic. As with any microvascular complication, risk increases in the presence of poor glycemic control, poorly controlled hypertension, and duration of poorly controlled diabetes.

Diagnostic tests focus on early detection, and should be conducted at regular intervals in every individual with type 1 or type 2 diabetes. Diagnostic tests should include the following, with variable levels according to body size and gender as well as from laboratory to laboratory.

1. Test urine for the presence of proteinuria or albuminuria. The presence of protein in the urine is never normal. Measuring more than 30 mg per day indicates either systemic disease or intrinsic kidney disease.
2. Serum Creatinine - The daily rate of creatinine production is relatively constant in an individual. Elevated values indicate compromised kidney function.
3. Blood Pressure. The desired blood pressure range is a standing blood pressure of approximately 90-130/60-80 mm Hg. Supine hypertension and orthostatic hypotension can sometimes occur with autonomic neuropathy.
4. Creatinine clearance - Rate of creatinine clearance is an indirect measurement of one's glomerular filtration rate (GFR). Since the kidney can successfully adapt with almost 80% loss of nephrons, even subtle changes may indicate a major loss of renal function and should thus command attention.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:154-155,162.*

## Clinical Manifestations of Overt Nephropathy (Stage IV)

- Proteinuria
  - » 4-8 gm/day but can reach 20 to 30 gm/day
- Fluid retention
  - » Symptoms and signs:
    - ❖ Weight gain, peripheral edema, CHF and pulmonary edema
    - ❖ Fatigue and shortness of breath
    - ❖ Uncontrolled hypertension (secondary to volume overload)
- Uremia due to accumulation of metabolic wastes
  - » GI manifestations
  - » Neuromuscular disturbances
  - » Hematologic

The clinical course of nephropathy leading to symptomatic renal disease (stage IV) is variable, but intact and working nephrons within the kidney will significantly compensate for prolonged periods of time. Clinical manifestations of nephropathy do not become evident until the glomerular filtration rate (GFR) is 20 to 35% of normal. Once this happens, the cluster of symptoms results in uremia, a syndrome of renal failure characterized by elevated blood urea nitrogen (BUN) and creatinine levels. Uremia results when metabolic wastes accumulate and cannot be excreted. Primary metabolic wastes that accumulate include potassium and nitrogen. Other impaired and unbalanced systems involve calcium and phosphate metabolites.

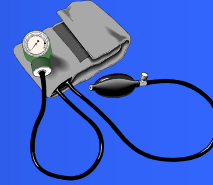
The usual gastrointestinal manifestations of uremia include anorexia, nausea, vomiting, and intractable hiccups. Neuromuscular disturbances include fatigue, muscle cramps, changes in cognitive function, seizures, coma, and asterixis (involuntary jerking movements accompanying metabolic dysfunction, especially in the hands; also known as flapping tremor). Hematologic symptoms include anemia and ensuing fatigue, decreased white blood cell count, increased risk of infection and of bleeding manifestations.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:164.*

## Diabetic Nephropathy Treatment /Prevention Interventions

- Strive for A1C < 7% (ADA), <6.5% (AACE)
- Control blood pressure
- ACE inhibitors or ARBs – indicated for renal “protection”
- Appropriate diet (low protein)
- Manage kidney infections
- Avoid nephrotoxic drugs
- Test regularly for microalbuminuria
- Smoking cessation



The results of the DCCT (1993) and UKPDS (1998) studies provided solid evidence showing that improved glycemic control could delay the onset and reduced the progression of nephropathy.

Treatment of hypertension requires careful individual assessment of current status. Practice guidelines generally include restricting sodium and diuretic therapy (to decrease extracellular water retention). Pharmacological agents include angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) that are given alone or with a conventional anti-hypertensive medication, alpha blockers, beta blockers, and calcium channel blockers. Many of these medications can produce adverse effects and so careful individual monitoring is required. Whenever anti-hypertensive therapy is undertaken, there may be side effects that include worsening of lipid levels or glycemic control, altered or masked symptoms of hypoglycemia, fluid retention, and hyperkalemia or azotemia.

Careful diet planning with a registered dietitian is necessary as decreased dietary protein is recommended based on the severity of the nephropathy and concomitant medication. Animal protein in the diet may increase glomerular filtration rate (GFR), so protein restriction may be able to reduce the hyperfiltration within the nephrons and also have a positive affect on lipid profile. However, the effect of dietary protein on nephropathy may be a subject of debate due to conflicting available evidence.

Additional recommendations for treatment and/or prevention include prompt recognition and treatment of kidney infections, avoidance of drugs that are known to be nephrotoxic, regular testing for microalbuminuria, and cessation of smoking.

### Reference:

American Association of Diabetes Educators. *AADE core curriculum: Diabetes and Complications 5th ed.* Chicago, Illinois; American Association of Diabetes Educators; 2003:167.

DeFronzo RA. *Current Therapy of Diabetes Mellitus.* St. Louis, MO: Mosby Yearbook; 1998:137-143.

Diabetes Control and Complications Trial (DCCT) Research Group. *The effect of intensive treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus.* *New England Journal of Medicine.* 1993; 329:14:977-986.

United Kingdom Prospective on Diabetes Study (UKPDS) Group. *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33).* *Lancet.* 1998; 352:837-853.

## Treatment Options for Renal Failure (End-Stage Renal Disease)

- Dialysis
  - » Hemodialysis
  - » Peritoneal
- Renal transplantation

Available treatment options for renal failure (ESRD) are aimed at replacing the diseased kidneys. While awaiting a kidney transplant, individuals can receive dialysis to cleanse the blood of nitrogenous waste and other metabolic waste using a semi permeable membrane filter. When hemodialysis is used, blood is circulated and cleansed outside the body using an external dialysis machine. Peritoneal dialysis takes place inside the body using the body's own peritoneal membrane that lines the abdominal cavity.

However patients with diabetes who receive dialysis or kidney transplants experience higher morbidity and mortality than patients without diabetes due to the coexistence of complications such as coronary artery disease, retinopathy and neuropathy.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:168.*

# Diabetic Retinopathy

- Retinopathy
- Other ophthalmic complications
  - » Blurred Vision
  - » Cataracts
  - » Glaucoma

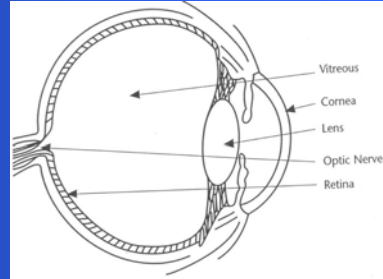


Figure from AADE Core Curriculum, 5<sup>th</sup> Edition, p. 128

Retinopathy occurs when the microvasculature that nourishes the retina is damaged, leading to the leakage of blood components through the thin vessel walls. Retinopathy is extremely common among persons with diabetes, and is the leading cause of blindness in the U.S. After 20 years duration of the disease, retinopathy is present in more than 90% of patients with type 1 diabetes and 55% to 80% of patients with type 2 diabetes.

Individuals with diabetes are also vulnerable to other ophthalmic complications. Transient blurred vision often occurs during times of hypoglycemia or hyperglycemia. Cataracts seem to develop at an earlier age and occur twice as frequently in individuals with diabetes. Additionally, the overall incidence of glaucoma is apparently 2 to 4 times greater in individuals with diabetes than in the general population.

The cause and progression of diabetic retinopathy can be directly traced to degree of structural abnormalities within the tiny vascular capillaries in the eye. *Non-proliferative retinopathy* is characterized by structural abnormalities, but growth of new blood vessels is not stimulated. *Proliferative retinopathy* is so named because of the new blood vessels that are formed within the eye.

## Reference:

American Association of Diabetes Educators. *AADE core curriculum: Diabetes and Complications 5th ed.*

Chicago, Illinois; American Association of Diabetes Educators; 2003:125-128.

American Diabetes Association. *Position statement: Retinopathy in diabetes. Diabetes Care 2004; 27(suppl 1):S84-87.*

DeFronzo RA. *Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:150-158.*

# Retinopathy

- Non-proliferative Diabetic Retinopathy (NPDR)
  - Mild NPDR
  - Moderate NPDR
  - Severe NPDR
- Proliferative Diabetic Retinopathy (PDR)

Non-proliferative Diabetic Retinopathy (NPDR) is the earliest stage of diabetes-related eye disease where structural changes begin to occur in various structures of the eye. Some of the changes associated with non-proliferative retinopathy are very common and generally occur without symptoms. Non-proliferative retinopathy is divided into 3 stages: *mild*, *moderate*, and *severe*.

*Mild NPDR* is characterized by microaneurysms (areas of weakness in vessel walls) appearing as sacular outpouchings along the weakened vascular walls. Also present are hard exudates, the residues of protein and lipid components that leak from the blood vessels, intra-retinal hemorrhage appearing as dots or flame shapes and soft exudates or “cotton wool spots”, areas of infarction in the nerve fiber layer of the retina.

*Moderate NPDR* is characterized by microaneurysms, dot and blot hemorrhages, and/or exudates. The retinal veins become dilated and tortuous (venous beading) and intra-retinal microvascular abnormalities (IRMA) which appear as clusters of micro-aneurysms and tortuous hypercellular vessels develop.

*Severe and Very Severe NPDR* is characterized by hemorrhages and microaneurysms in all 4 quadrants of the retina, IRMA in at least 1 quadrant, and venous beading in 2 quadrants signify high risk for development of proliferative diabetic retinopathy (PDR).

Proliferative Diabetic Retinopathy (PDR) is characterized by neovascularization, in which new blood vessels grow on the surface of the retina and may extend into the vitreous chamber. Pre-retinal or vitreous hemorrhage in combination with neovascularization of the disc covering > 25% of the surface area of the disc, is considered a high risk for progressive visual loss. Diabetic individuals with even mild NPDR are still at a risk for progressing to PDR within a relatively short period of time, and should be followed by a trained specialist at regular intervals.

## Reference:

American Association of Diabetes Educators. *AADE core curriculum: Diabetes and Complications 5th ed.* Chicago, Illinois; American Association of Diabetes Educators; 2003:126-128.

American Diabetes Association. *Position statement: Retinopathy in diabetes. Diabetes Care 2004; 27(suppl 1):S84-87.*

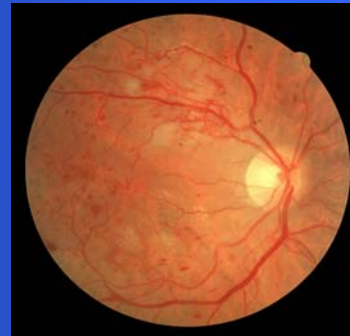
DeFronzo RA. *Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:154-156.*

# Retinopathy

Normal eye



Effect of Diabetes



Normal eye – Microvasculature is intact with no evidence of microaneurysms or hemorrhages. There is no sign of cotton wool spots or macular edema.

Effect of Diabetes – Microvasculature shows evidence of neo-vascularization, microaneurysms, and multiple hemorrhages. Cotton wool spots and macular edema can be detected.

## Diabetic Retinopathy Goals/Prevention

- Strive for A1C < 7% (ADA), < 6.5% (AACE)
- Regular visits to the health care team
- Eye exam (pupils dilated) at least once a year
- Prompt eye exam for any changes
- Avoidance of tobacco

Achieving A1C levels within goal range can reduce the risk of retinopathy. The diabetes-care team should work with patients to maintain blood glucose levels as close to normal as possible.

All persons with diabetes should receive routine ophthalmologic screening and follow-up. Blood pressure should be checked at each visit because of the close association between hypertension and retinopathy. Patients with type 1 diabetes who are  $\geq 10$  years of age should have their first comprehensive eye exam within 3-5 years after diagnosis, and patients with type 2 diabetes should have a comprehensive eye exam at the time of diagnosis with yearly follow-up. Routine ophthalmologic exams are especially important as eye changes can occur without any changes in vision. If eye changes are detected, an ophthalmologist should be consulted.

### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:131.*  
*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:154-159.*  
*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:67-99.*

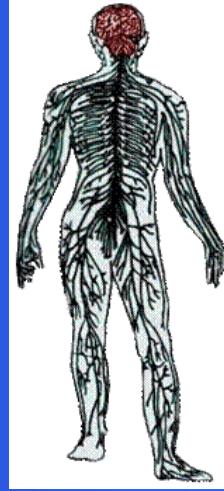
# Diabetic Neuropathy

## Diffuse Neuropathies

- Symptoms
  - Common
  - Insidious onset
  - Usually progressive

## Focal Neuropathies

- Symptoms
  - Sudden onset
  - Usually improves over time



Diabetic neuropathy is a descriptive term for a clinical or sub-clinical disorder that occurs in as many as 75% of all patients with diabetes. Diabetic neuropathy comprises a large group of sensory and autonomic syndromes with a wide range of manifestations. Diagnosis and staging of diabetic neuropathy are based on signs, symptoms and objective measures. Sub-clinical neuropathy is detected through objective measures (e.g., electrodiagnostic and sensory tests), while clinical neuropathy is defined by symptoms, clinical signs and objective measures.

Diabetic neuropathy is categorized as either *diffuse* (multiple nerve involvement) or *focal* neuropathy (single nerve involvement). Diffuse neuropathy is further classified as either *distal symmetric sensorimotor polyneuropathy* (affecting sensory and motor function) or *autonomic neuropathy* (affecting involuntary function).

Diffuse neuropathies are common, with an insidious onset that progresses over time. Focal neuropathies are less common, but tend to present with a sudden onset of symptoms that will often improve over time.

Reference:

American Association of Diabetes Educators. *AADE core curriculum: Diabetes and Complications 5th ed.* Chicago, Illinois; American Association of Diabetes Educators; 2003:192.

DeFronzo RA. *Current Therapy of Diabetes Mellitus.* St. Louis, MO: Mosby Yearbook; 1998:160-175.

## Distal Symmetric Sensorimotor Neuropathy

- Commonly referred to as peripheral neuropathy
- Type of diffuse neuropathy
- Most common form of neuropathy
- Usually occurs within 10 years of diabetes onset (average)

Most nerve damage from diabetes occurs in the peripheral nervous system (vs. central nervous system). Distal symmetric sensorimotor neuropathy, often referred to as peripheral neuropathy, is the most common long-term complication of diabetes. This form of neuropathy affects 72% of patients who are diagnosed with neuropathies, and involves progressive nerve fiber injury, atrophy, and loss. The lower extremities are more seriously affected. When present, distal symmetric polyneuropathy leads to deteriorating nerve function and worsening sensory motor deficits. On average, it occurs within 10 years after diabetes onset. However, it may occur as a presenting sign of diabetes at the time of diagnosis in patients with type 2 diabetes who have previously gone undiagnosed for many years.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:200.*

*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:160-175.*

## Distal Symmetric Sensorimotor Neuropathy

### Small Fiber Damage

- Loss of ability to detect temperature
- Pins and needles; tingling, or burning sensation
- Pain; usually worse at night
- Numbness or loss of feeling
- Cold extremities
- Swelling of the feet and ankles

Symptoms of small fiber damage include the loss of the ability to detect temperature, the persistent sensation of pins and needles and/or tingling or burning, numbness or loss of feeling, cold extremities, and swelling of the feet. Individuals also report pain which is usually worse at night, and sometimes pain on contact with even light objects such as bedsheets or clothing.

#### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:198-199.*

*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:160-175.*

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:207.*

## Distal Symmetric Sensorimotor Neuropathy

### Large Fiber Damage

- Abnormal or unusual sensations
- Loss of balance
- Inability to sense position of the toes and feet
- Charcot's joint

### Motor Nerve Damage

- Loss of muscle tone in hands and feet
- Deformed toes and feet
- Callus formation
- Open sores with foot ulceration

The symptoms of large fiber damage are somewhat different from symptoms of small fiber damage.

Symptoms may include abnormal or unusual sensations, but individuals also report a loss of balance and sometimes an inability to sense parts of their toes and/or feet. A complication of diffuse sensory neuropathy is Charcot's joint, or neuropathic arthropathy. Affected persons may require surgery, have difficulty walking, and/or require special shoes to walk safely.

Motor nerve damage often causes muscle weakness and atrophy of intrinsic foot muscles, leaving the pull of the long muscles unopposed. Ankle weakness and foot drop can then result.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:199.*

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:207.*

## Symptoms of Diabetic Autonomic Neuropathies

### Gastrointestinal Neuropathies

#### Upper GI

- Difficulty swallowing
- Premature feeling of satiety
- Bloating/abdominal pain
- Hypoglycemia following meals
- Nausea
- Vomiting food eaten hours before

#### Intestinal

- Diarrhea (more frequent at night)
- Constipation

Diffuse autonomic neuropathy can occur with all types of diabetes and can affect any body system. Autonomic neuropathies and diffuse sensory neuropathies often co-exist, and 50% of patients who have peripheral neuropathies also experience autonomic neuropathy. Early diagnosis and treatment is critical since morbidity and mortality rates are closely linked to diabetic autonomic neuropathies. Most commonly identified autonomic neuropathies affect the gastrointestinal system, genitourinary system, sexual function, cardiovascular system, impaired insulin counterregulation, sudomotor autonomic function, and pupillary function.

*Gastrointestinal neuropathies* affect both gastroparesis and intestinal motility. Gastroparesis symptoms include early satiety, postprandial hypoglycemia (hypoglycemia that occurs when pre-prandial antidiabetic medications are taken, but food is not absorbed). Motility problems affecting the upper GI tract include difficulty swallowing, nausea and vomiting of food eaten hours before. Motility problems affecting the intestines include diarrhea (more frequent at night), and constipation.

#### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:200-205.*  
*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:160-175.*  
*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:221.*

## Symptoms of Diabetic Autonomic Neuropathies

### Genitourinary Neuropathies

#### Bladder

- Less frequent urination
- Frequent infections of the urinary tract
- Difficulty emptying bladder completely
- Weak urinary stream
- Difficulty in starting to urinate; dribbling; incontinence

One form of *genitourinary neuropathy* is neurogenic bladder. Symptoms include diminished urinary frequency, incomplete or difficulty emptying bladder, and frequent urinary tract infections (UTI). Intervention /education includes scheduling urination every 2 to 4 hours during waking hours, prevention/immediate treatment of UTIs, palpitation for bladder distention, and self catheterization.

#### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:200-202.*

*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:160-175.*

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:221.*

## Symptoms of Diabetic Autonomic Neuropathies

### Genitourinary Neuropathies

#### Sexual Dysfunction - Males

- Erectile dysfunction
- Retrograde ejaculation

#### Sexual Dysfunction - Females

- Diminished vaginal lubrication
- Decreased frequency of orgasm

Another form of autonomic neuropathy involves *sexual dysfunction*. Symptoms in males include erectile dysfunction and retrograde ejaculation. Symptoms in women include diminished vaginal lubrication and decreased frequency of orgasm. Intervention and/or education strategies include reporting symptoms to appropriate members of the diabetes-care team and referrals to a urologist or gynecologist.

#### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:200-202.*

*DeFronzo RA. Current Therapy of Diabetes Mellitus. St. Louis, MO: Mosby Yearbook; 1998:160-175.*

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:221.*

## Symptoms of Diabetic Autonomic Neuropathies

### Other Neuropathies

#### Cardiovascular

- Swelling in feet
- Severe dizziness on standing
- Fixed (invariable) heart rate
- Shortness of breath with exertion

#### Insulin Counterregulation

- Hypoglycemia unawareness

Cardiovascular neuropathies include orthostatic hypotension and cardiac denervation syndrome. The primary recognizable symptom of orthostatic hypotension is postural hypotension. To promote safety and prevent falls, intervention/education includes safety measures such as teaching the patient to rise to a standing position in stages and increasing venous pressure in dependent lower extremities with support elastic body stockings that are applied while supine.

Cardiac denervation syndrome involves symptoms such as painless MI, sudden death, and fixed heart rate. The absent or blunted sensory responses to cardiac ischemia blunt the early warning sign of chest pain that prompts most individuals to seek medical attention, and so this syndrome is potentially fatal. Intervention should include avoiding heavy exercise or straining and monitoring glucose levels to avoid hypoglycemia which can cause cardiac arrhythmias.

Impaired insulin counterregulation is another autonomic neuropathy. Symptoms include: hypoglycemia unawareness which can occur in patients with diabetes of a long duration caused by the lack of classic adrenergic warning signs of hypoglycemia such as anxiety, tremulousness, and palpitations. Intervention/education includes avoidance of hypoglycemia, frequent glucose monitoring, wearing of medical identification, and teaching significant others about the signs, symptoms and treatment of hypoglycemia.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:205-206.*

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:218-230.*

# Symptoms of Diabetic Autonomic Neuropathies

## Other Neuropathies

### Sweating (Sudomotor)

- Dry hands and feet
- Increased upper body sweating
- Sweating when eating certain foods

### Pupillary (eye)

- Delayed or absent light/dark response/adaptation
- Small, irregular pupil size

The symptoms of *sudomotor autonomic neuropathy* include dry hands and feet, increased upper body sweating, and sweating when eating certain types of food. Intervention/education includes daily foot inspection and care, and reporting excessive sweating to the diabetes-care team. Affected individuals should avoid high temperatures and high humidity to prevent heatstroke.

*Pupillary (eye) neuropathy* involves the iris; the iris is innervated by both parasympathetic and sympathetic nerve fibers. Slow dilation of pupils may be observed during clinical examination. Symptoms may include decreased or absent response to light and small, irregular pupil size. Intervention primarily focuses on patient education regarding the use of night lights, and safety measures such as turning on lights when entering a dark room. Clinicians should emphasize safe and cautious behavior when driving at night.

#### Reference:

American Association of Diabetes Educators. *AADE core curriculum: Diabetes and Complications 5th ed.* Chicago, Illinois; American Association of Diabetes Educators; 2003:206-207.

Levin ME, Pfeifer MA. *The Uncomplicated Guide to Diabetes Complications.* Alexandria, VA: American Diabetes Association; 1998:218-230.

## Focal Neuropathies

- **Mononeuropathy:** damage to a single nerve
- **Mononeuropathy multiplex:** damage to a nerve cluster
- **Plexopathy:** damage to nerve roots
- **Radiculopathy:** damage to nerve roots in trunk of body
- **Cranial neuropathy:** damage to a single nerve from the brain

Focal Neuropathy is not always specific to diabetes or related to the duration of the disease. The primary symptom of focal neuropathy is often acute pain and onset can be unpredictable. Basic types of focal neuropathies include:

*Mononeuropathy* (damage to a single nerve). This form of focal neuropathy may involve cranial, thoracic, and peripheral nerves. It is often associated with sudden pain and often resolves in 6 to 8 weeks.

*Mononeuropathy multiplex* (damage to a nerve cluster). This form of focal neuropathy is associated with compression or entrapment neuropathies. Common entrapments include the median nerve of the wrist (carpal tunnel syndrome), ulnar nerve entrapment in the elbow, lateral cutaneous nerve of the thigh, and medial and lateral planar nerves in the foot. Onset is slow and symptoms persist and progress without intervention. Diagnosis is based on pain distribution and treatment usually consists of surgical release of the nerve, physical therapy, or protection from trauma.

*Plexopathy* (damage to nerve roots). This form of focal neuropathy is uncommon but may occur in older patients with sudden onset. Femoral neuropathy is one example which is caused by damage to the motor and sensory nerves in the thigh; symptoms include pain which is usually worse at night; muscle weakness and wasting are common. Simple analgesics are used to relieve pain; patients normally recover but it may take several years for muscle strength to return.

*Radiculopathy* (damage to nerve roots in the chest or abdomen). This form of focal neuropathy involves damage to the nerves or nerve root in the trunk of the body. Primary symptom is pain in the chest (or abdomen); onset is sudden and is usually worse at night. Pain does not get worse upon exertion, but other conditions should be ruled out. This type of neuropathy generally resolves in 6 months to 2 years.

*Cranial neuropathy* (damage to a single nerve directly from the brain). The third cranial nerve is most often affected, resulting in ptosis (the patient may not be able to open an eyelid). This form of focal neuropathy is not painful, and often resolves spontaneously in days or months.

Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:207-208.*

*Levin ME, Pfeifer MA. The Uncomplicated Guide to Diabetes Complications. Alexandria, VA: American Diabetes Association; 1998:230-233.*

## Prevention/Detection of Clinical Neuropathies

Encourage patients to:

- Report unusual sensations, numbness or pain
- Report digestive, urinary or sexual problems
- Take care to avoid injury to areas with decreased sensations
- Take medications as directed
- Inspect feet daily and practice good foot care

### Patient Education to Prevent or Detect Neuropathies

Clinicians can find numerous opportunities to provide and reinforce the importance of education to report tingling, numbness, loss of feeling, muscle weakness, pain, or other unusual sensations. Persistent digestive, urinary, or sexual problems should be explored, and safety measures should be stressed. Medications may or may not offer symptomatic relief, and so persons with diabetes can be encouraged to pursue other coping strategies if needed.

Patients that present with diffuse sensorimotor neuropathy should be encouraged to practice good foot care.

Clinicians should review the steps needed for daily care and thorough inspection. Referral to a podiatrist may be indicated.

### Reference:

*American Association of Diabetes Educators. AADE core curriculum: Diabetes and Complications 5th ed. Chicago, Illinois; American Association of Diabetes Educators; 2003:67-79,208-211*  
*American Diabetes Association. Position statement: Standards of medical care in diabetes. Diabetes Care. 2004; 27(suppl 1):S15-35.*

## Members of a Diabetes-Care Team

- Physician
- Dietitian
- Pharmacist
- Certified Diabetes Educator (CDE)
- Nurse
- Clinical nurse specialist
- Podiatrist
- Ophthalmologist
- Psychologist or counselor

Regular visits to members of the healthcare team can provide consistent and effective care. Healthcare team members can include the primary care physician, endocrinologist, diabetes educator, dietitian, pharmacist, podiatrist, ophthalmologist, psychologist or counselor, and other licensed and unlicensed professionals who contribute to overall care.

Reference:

*American Diabetes Association. Position statement: Standards of medical care in diabetes. Diabetes Care. 2004; 27(suppl 1):S15-35.*

## Resources

- Diabetes Education Center
- Community Based Diabetes Care Network
- Organizations
  - » American Diabetes Association
  - » Juvenile Diabetes Foundation
- Support groups
- Journals

Diabetes management requires commitment from the patient and the combined efforts of the diabetes care team. Individuals with diabetes should be encouraged to participate in their own care. Providing pamphlets and other informational resources is a valuable way to reinforce guidelines for prevention and treatment. Other support strategies include encouraging access to community resources (local, regional, national, international, and web-based). Joining local support groups, the American Diabetes Association (ADA) or the Juvenile Diabetes Foundation (JDF), and subscribing to diabetes magazines are all helpful strategies to motivate and encourage optimal self-care. Patients who are newly diagnosed with diabetes, or those requiring individualized and/or specialized teaching and support, should be referred to a diabetes education center.