Management of Diabetes Mellitus

Diabetes Mellitus Guideline Team

Team Leaders

Deryth Stevens, MD
Family Medicine

Sandeep Vijan, MD
General Internal Medicine

Team Members

Martha Funnell, MS, RN
Diabetes Research and Training Center

Douglas Greene, MD
Endocrinology and Metabolism

Van Harrison, PhD
Medical Education

William Herman, MD
Endocrinology and Metabolism

Roland Hiss, MD
Postgraduate Medicine

Catherine Martin, MS, RN
Endocrinology and Metabolism

Evelyn Piehl, MS, RN
Obstetrics and Gynecology

Barbara Ratliff, RN
Primary Care Nursing

Connie Standiford, MD
General Internal Medicine

Developed
May 1996

Updated
April 1998

Literature search service
Taubman Medical Library

For more information call
GUIDES: 936-9771

© Regents of the University of Michigan

These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

Patient population Adult

Objectives Improve adherence to important, morbidity-reducing recommendations for preventing, detecting, and managing diabetic complications.

Key points Routine screening and prevention efforts for cardiovascular risk factors (hypertension, hyperlipidemia, tobacco use) and for microvascular disease (retinopathy, nephropathy, neuropathy) are recommended to be performed in the following time frames. Management of risk factors, complications, and glycemia is summarized in the referenced figures.

Each regular diabetes visit

- Diabetes visit every 3 months for patients on insulin; every 6 months for patients on oral agents or diet only.
- Weight checked.
- Blood pressure measured and controlled. *[A*]* (See Figure 1)
- Diabetic foot examination performed and areas of concern discussed. *[A**]* (See Figure 2)
- Smoking cessation counseling provided for patients with tobacco dependence. *[B**]* (See Figure 1)
- Very important self-management actions reviewed and reinforced: (See Table 4)
  - active responsibility for own care
  - progress toward goal for hemoglobin A_{1c} or glycosylated Hgb level
  - blood glucose monitoring, if on insulin
  - regular exercise
  - medication compliance
  - meal plan
  - stress and coping mechanisms
  - family planning/birth control
  - preconception counseling/care*[B**]*

Every 3 to 6 months

- Hemoglobin A_{1c} or glycosylated hemoglobin measured and glycemic control optimized. *[A**]* (See Figure 3 and Table 1)

Annually

- Dilated retinal examination by an eye care specialist and treatment of retinopathy. *[A**]* (See Figure 2)
- Urine protein and, if normal, screen for microalbuminuria. ACE inhibitor for micro-albuminuria or proteinuria. *[A**]* (See Figure 2)
- Monofilament testing of feet. *[A**]* (See Figure 2)
- Lipids measured and controlled. *[A*, B**]* (See Figure 1)
- Smoking status assessed. (See Figure 1)
- Other important self-management actions reviewed and reinforced: (Table 4)
  - hypo and hyperglycemia
  - diabetes identification
  - complications screening
  - foot care
  - injection sites

Levels of evidence for the most significant recommendations:

A = randomized controlled trials; B = controlled trials, no randomization; C = observational trials; D = opinion of expert panel
*= studies performed in the general population and extrapolated to the diabetic population
** = studies performed in the diabetic population

Special Circumstances

- **Pregnancy.** Preconception counseling and glycemic control in women with diabetes mellitus results in optimal maternal and fetal outcomes *[evidence: B**]*. Before pregnancy, diabetic women should be started on insulin therapy and have their oral hypoglycemic agents and ACE inhibitors stopped.

(Continued on page 5)

FIGURE 1. Prevention, Screening, and Treatment of Cardiovascular Risk Factors in Patients with Diabetes Mellitus:Hypertension, Hyperlipidemia, Smoking

(If one present, consider use of aspirin.)

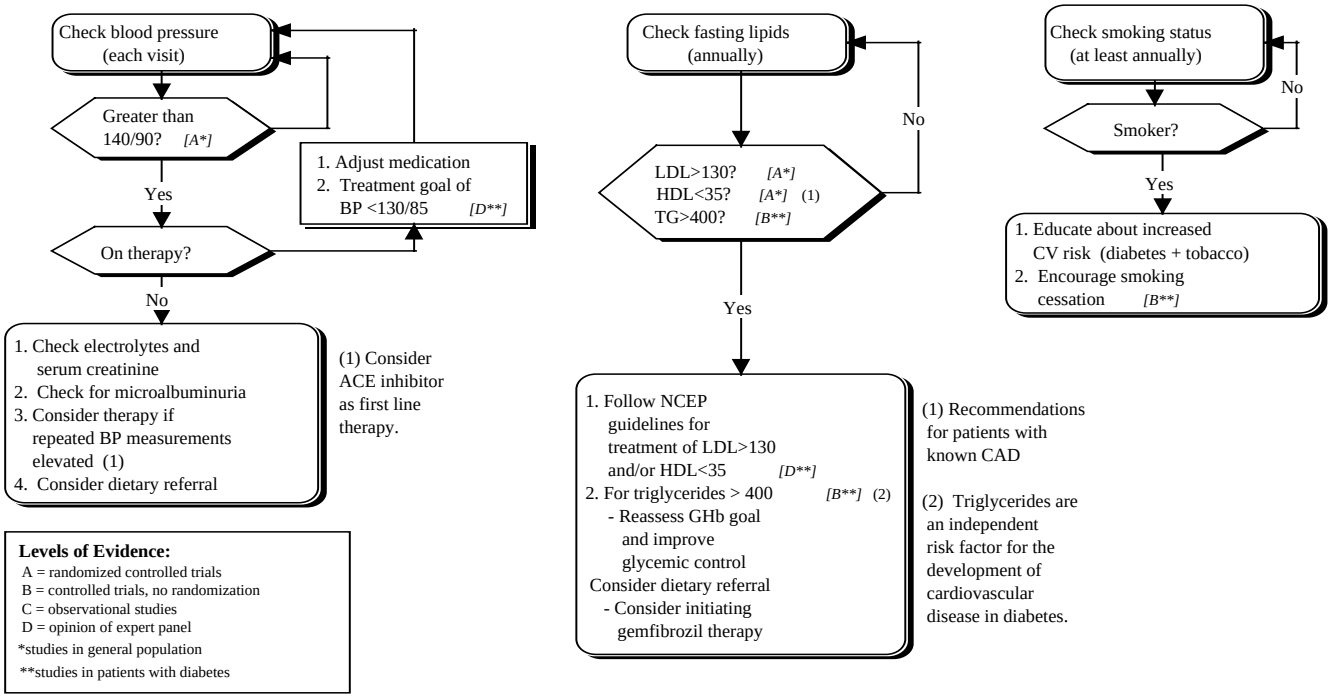


FIGURE 2. Prevention, Screening and Treatment of Microvascular Complications in Patients with Diabetes Mellitus: Retinopathy, Nephropathy, Neuropathy

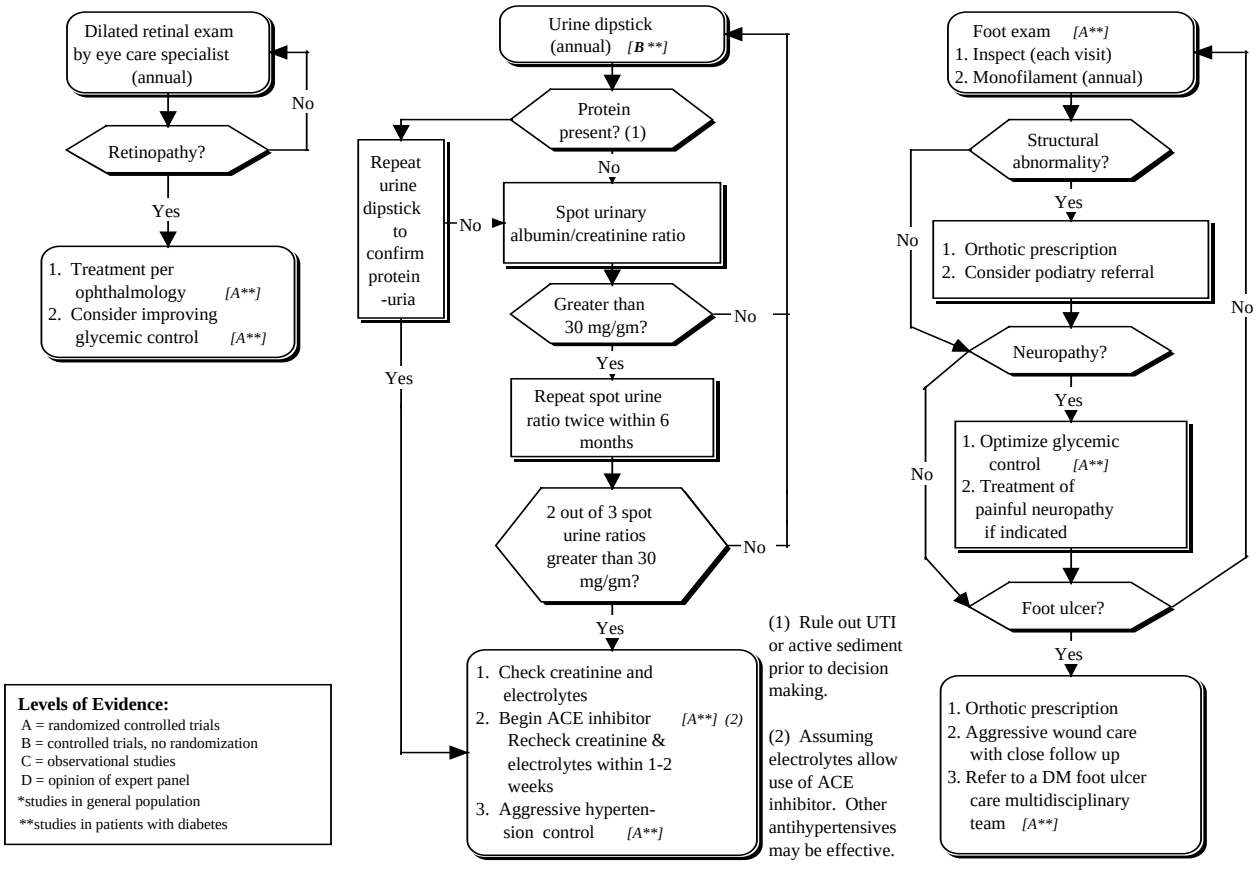


Figure 3. Monitoring Glycemic Control in Patients with Diabetes Mellitis

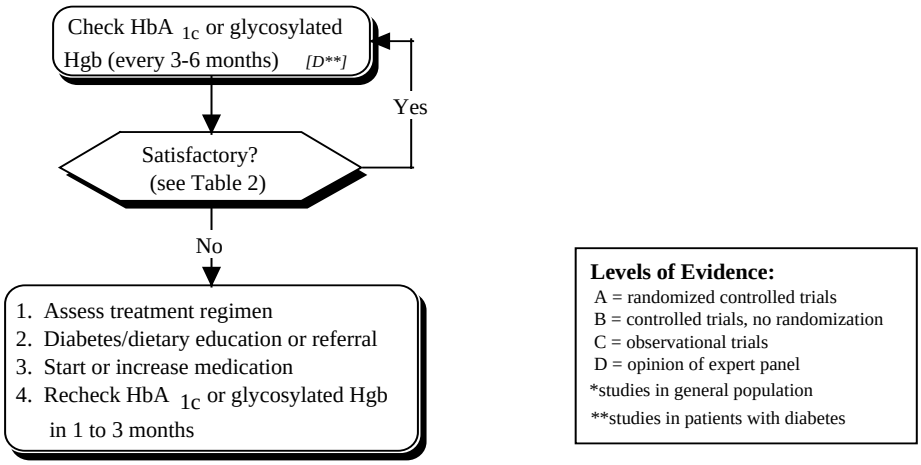


Table 1: Factors That Affect the Benefit and Risk of Tight Glycemic Control

Factors Limiting Benefit of Tight Control	Factors Heightening Risk of Tight Control
• Comorbidities (e.g., end-stage cancer, severe heart failure, advanced age)	• History of severe hypoglycemia (inability to treat without assistance): any episodes within the past year and/or more than 2 episodes ever
• Advanced diabetes complications (e.g., proliferative retinopathy, renal failure)	• Hypoglycemia unawareness
• Inability to carry out treatment regimen (e.g., financial constraints, availability of needed supplies)	• Advanced cardiovascular or cerebrovascular disease
• Limited life expectancy	• Autonomic neuropathy (especially cardiac)
	• Comorbidities / medications that impair the detection of hypoglycemia (e.g., beta-blockers, CNS-acting drugs, alteration in mental status)
	• Lack of mobility or lives alone

Table 2: Adequacy of Glycemic Control Based on Factors Affecting Benefit or Risk

Factors That Affect the Benefit or Risk of Intensive Glycemic Control	Percent Hemoglobin A_{1c} or Glycosylated Hemoglobin*				
	A_{1c} 3.6–6.5% GHb 4–8%	6.5–8.0% 8–11%	8.0–10% 11–15%	10–11.5% 15–18%	> 11.5% > 18%
Minimal	Excellent control	Good control	Fair control	Poor control	Poor control
Moderate		Excellent control	Good control	Fair control	Poor control
Substantial			Acceptable control	Fair control	Poor control

*The table shows the approximate correspondence of values of the two methods of determination.
UMHS Central Clinical Pathology Laboratories reports glycosylated hemoglobin levels. The Ann Arbor VA reports A_{1c}.

Table 3. Some Oral Agents For the Management of Type II Diabetes

Generic	Brand Name	Usual Daily Dose	Generic Cost ($)* (Range)	Brand Cost ($)*
Sulfonylureas				
First Generation				
Acetohexamide	Dymelor	500-750 mg once or divided	12-20	14-22
Chlorpropamide	Diabinese	250-375 mg once	2-6	25-37
Tolamide	Tolinase	250-500 mg once	11-12	19-37
Tolbutamide	Orinase	1000-2000mg once or divided	5-10	18-36
Second Generation				
Glimepiride	Amaryl	4mg once	NA	21
Glipizide	Glucotrol	10-20 mg once or divided	18-35	23-43
Glipizide, sustained release	Glucotrol XL	5-10 mg once or divided	NA	10-20
Glyburide	Diabeta, Micronase	5-20 mg once or divided	17-66	20-78
Glyburide, micronized	Glynase	3-12 mg once or divided	15-59	18-61
Alpha-glucosidase inhibitor				
Acarbose	Precose	50-100 mg t.i.d.	NA	41-53
Biguanide				
Metformin	Glucophage	1500-2550 mg, divided	NA	49-82
Thiazolidinedione				
rosiglitazone	Avandia	4 – 8 mg once or divided	NA	75-138**
pioglitazone	Actose	4.5mg – 45 mg	NA	45 – 149**

*Cost for 30 days treatment with lowest daily dosage based on wholesale price (AWP and HCFA) listings in *Drug Topics Red Book 1997* and May *Update.*

** *Drug Topics Red Book, 2000*

NA = generic not available

Table 4. Self-Management Topics*

At each regular visit (e.g. every 3-6 months) ask about:

- **Active responsibility for own care.** Do you take active responsibility for your own daily diabetes care? (Demonstrate through words and actions that diabetes is a serious illness.)
- **Progress toward glucose goal.** Do you know your most recent glycosylated hemoglobin level and your progress toward your goal level?
- **Blood glucose monitoring if on insulin.** Do you know (1) the rationale for monitoring your blood glucose (sick day management, insulin dose adjustments)? (2) your monitoring schedule? (3) how to use the results? How do you use this information in your daily diabetes care?
- **Medications.** What time of the day do you take your pills or insulin each day? Do you take them even if you are ill and unable to eat? What are your current doses?
- **Exercise.** What exercise do you do to help keep your blood glucose level close to normal?
- **Meal plan.** Are you able to use your meal plan?
- **Stress and Coping.** Are you feeling more stressed than usual? How do you cope with this stress?
- **Questions answered.** Do you (1) have unanswered questions? (2) want to see the dietitian or nurse educator? (3) have any concerns you would like to address?
- **Family planning/birth control.** Are you considering pregnancy? If so, are you working to optimize blood sugars? If not, are you using birth control?

At least annually ask about:

- **Symptoms and treatment of hyperglycemia and hypoglycemia.** What are the (1) symptoms and treatment for hypoglycemia? (2) symptoms and treatment for hyperglycemia? (3) when should you contact staff?
- **Identification.** Do you wear or carry diabetes identification?
- **Complications screening.** Do you know (1) your results on screening tests for complications? (2) when you should be tested next?
- **Foot care.** (1) What do you do to take care of your feet? (2) do you check your feet each day?
- **Injection sites.** Do you rotate your injection sites around your abdomen and inspect sites?

*Based upon expert opinion.

Clinical Problem and Current Dilemma

Prevalence. Type II diabetes is a common condition, affecting 2–3% of the population overall, and up to 20–25% of the elderly population. Type II diabetes typically occurs in patients who are over 30 years old and weigh greater than 120% of ideal body weight. Conversely, Type I diabetes occurs in patients under 30 who weigh less than 120% of ideal body weight. These patients require insulin to prevent diabetic ketoacidosis (DKA). Patients who do not fit exactly into either group should probably be classified as having Type II diabetes unless they have a history of DKA.

Outcomes. Diabetes has significant associated morbidity. There is a high rate of cardiovascular disease, resulting in an increased mortality rate among patients with diabetes compared to the general population. There are also microvascular complications, including retinopathy, nephropathy, and neuropathy, that can progress to end-stage outcomes such as blindness, renal failure, and amputation. Improving glycemic control decreases the incidence of microvascular disease, but the effect of glycemic control on cardiovascular disease remains uncertain. Minorities have a prevalence of Type II diabetes mellitus that is 2 to 6 times greater than that of white persons. The morbidity and mortality are higher for minorities than for white persons, and the rate is increasing. Therefore, in minorities with diabetes, more aggressive management may be indicated.

Inadequate screening. Screening and treatment for early diabetic complications is effective in reducing the incidence of end-stage complications. However, implementation rates of recommended screening procedures are low, leading to ineffective and/or delayed treatment of complications. This, in turn, increases the costs of medical care and adversely affects quality of life.

Need for self-management. Effective management of diabetes has many components which need to be addressed by clinicians. However, as diabetes is a largely self-managed disease, psychosocial and educational factors may affect outcomes. Therefore, these issues need to be addressed in detail by primary care providers to allow optimization of treatment and reduce the likelihood of adverse outcomes. Diabetes education should provide consistent, evidence-based teaching that conforms with treatment guidelines and patient goals.

Rationale for Recommendations

Diabetes Diagnosis and Screening

Recently, the American Diabetes Association recommended new standards for the diagnosis of diabetes. A *fasting* glucose level greater than or equal to 126 mg/dl (7.0 mmol) confirmed on a separate day is now the preferred diagnostic criterion for diabetes. As before, diabetes may also be diagnosed on the basis of symptoms (polydipsia, polyuria, unintentional weight loss) and elevated glucose level ($\geq$ 200 mg/dl) confirmed on a separate day (fasting glucose $\geq$ 126 mg/dl). The oral glucose tolerance test is generally not recommended for diagnosis of diabetes in nonpregnant adults. Use of glycosylated hemoglobin (or hemoglobin A_{1C}) to screen for diabetes is controversial due to lower sensitivity and lack of standardization of the assay.

Cardiovascular Disease

Screening and prevention should address cardiovascular risk factors.

Aspirin. People with diabetes receive the same cardiovascular protection from aspirin as nondiabetic patients. In the absence of contraindications, aspirin should be used for people with diabetes who are less than age 50 with cardiovascular risk factors, and for all individuals with diabetes age 50 or greater. The recommended dosage is 81 mg (1 baby aspirin) to 325 mg/d.

Hypertension. Hypertension (HTN) is a significant contributor to the development of atherosclerosis. Untreated HTN can also lead to worsening of albuminuria and an increase in the rate of decline of glomerular filtration rate. People with diabetes develop hypertension at twice the rate of nondiabetics. The majority of patients have essential hypertension or HTN as the result of diabetic nephropathy. However, it is important to identify secondary causes of HTN such as renal artery stenosis, Cushing's disease, and oral contraceptive usage in patients who remain refractory to therapy or who have clinical syndromes suggestive of these conditions.

If a patient has a blood pressure of greater than or equal to 140/90 on three separate occasions, intervention should be considered (Figure 1). Initially, nonpharmacologic measures including dietary alteration, exercise, restriction of alcohol, and weight loss should be attempted. In those with mildly elevated BP, a three-month trial of the above may be appropriate. In patients with moderate to severe hypertension or those who do not respond to nonpharmacologic intervention, pharmacologic therapy is indicated. Due to a lack of evidence, controversy exists regarding the optimal target BP for patients with diabetes. Expert opinion from The Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) recommends treatment to a BP of 130/85 or less based on the significantly elevated risk of cardiovascular disease in patients with diabetes. Aggressive treatment to a BP of 130/85 or less may be especially beneficial for patients with diabetic nephropathy.

Antiotensin-converting enzyme (ACE) inhibitors are a reasonable first-line agent for patients with diabetes because of their potential benefits on renal function and lack of adverse effects on lipid and glucose metabolism. The angiotensin II receptor antagonists are effective anti-hypertensive drugs and do not cause cough. Studies are in progress to assess whether they exhibit the same renal protective effects as ACE inhibitors.

Low-dose diuretics do not appear to have adverse effects, and have been proven to reduce mortality in patients with

diabetes. High-dose thiazide diuretics have been reported to have a variety of adverse effects including worsening of hyperlipidemia, deterioration of glycemic control, impotence, and increased mortality.

The use of other anti-hypertensive agents should be based on the specific needs of the patient. Beta-blockers have an important role after myocardial infarction. People with diabetes have increased postinfarction mortality when compared with nondiabetic subjects, and diabetic patients experience greater cardioprotection with beta-blockade. Beta-blockers may obscure some of the symptoms of hypoglycemia (although this is rarely a problem with cardioselective beta-blockers) and may decrease high-density lipoprotein (HDL) and increase triglyceride levels. If a beta-blocker is used, it should be cardioselective.

Calcium channel blockers are effective antihypertensive agents, although caution should be exercised in using the dihydropteridine class as this group does not appear to have the same renal protective effects as other calcium channel blockers. As a class, calcium channel blockers have less protective effect on the kidneys than do ACE inhibitors.

$Alpha_1$-adrenergic receptor blockers do not have adverse glycemic or lipid effects, but may aggravate postural hypotension in some persons with diabetes.

Studies reveal that 20-60% of patients are not well controlled on monotherapy. In these instances, addition of another antihypertensive medication is required. The combination of an ACE inhibitor with a low dose thiazide diuretic works well. The combination of a beta-blocker with a thiazide may lead to an increase in plasma glucose levels.

Lipid screening and treatment. Characteristically, people with Type II diabetes have elevated triglyceride levels, while HDL levels are low. LDL levels can also be elevated. Due to the high prevalence of coronary artery disease (CAD) in diabetic patients, the National Cholesterol Education Program (NCEP) guidelines recommend that diabetic patients be screened annually and be treated intensively like patients with known CAD, with target LDL levels of less than 100 mg/dl. However, optimal screening intervals and treatment goals have not been rigorously defined. Whether to perform annual screening and/or initiate drug therapy after intensive dietary therapy depends on a variety of factors and must be left to the judgment of the physician. The first line of therapy is dietary intervention, followed by the use of HMG CoA reductase inhibitors when necessary to achieve target LDL levels.

In diabetic patients, triglycerides are an independent risk factor for the development of atherosclerotic disease. Therefore, physicians should consider starting therapy for hypertriglyceridemia at a level of 400 mg/dL. Initial therapy should consist of improving glycemic control with a combination of exercise, dietary changes, and increased intensity of oral hypoglycemics or insulin. If this is ineffective, then pharmacologic therapy should be initiated. Gemfibrozil is usually the first line of therapy for isolated hypertriglyceridemia. Nicotinic acid should be used with caution because it may worsen hyperglycemia.

Smoking. Smoking and diabetes are synergistic risk factors for the development of atherosclerotic disease. People with diabetes should be counseled regarding these risks, and all possible measures should be used to encourage discontinuation of tobacco use. This includes enrollment in formal smoking cessation programs and use of alternative nicotine delivery systems or pharmacologic therapies when necessary.

Microvascular Disease

Screening and prevention should also address microvascular disease.

Retinopathy. Yearly dilated retinal examination reduces the incidence of blindness by allowing timely treatment (i.e. laser therapy) of proliferative retinopathy and macular edema. Current estimates indicate that only 35–50% of people with diabetes undergo annual screening, and even after enrollment in blindness prevention programs, only 60% report having received an eye examination in the prior year.

The treatment of proliferative retinopathy and macular edema are performed by ophthalmology. However, the primary care physician can improve glycemic control which has been strongly linked to the development and progression of diabetic retinopathy. Should evidence of retinopathy be found, the care provider should strongly consider lowering the target glycosylated hemoglobin level, if possible. Referral to an optometrist who performs pupil dilation and is appropriately trained and skilled in the diagnosis and classification of diabetic eye disease is acceptable, but may not be a covered benefit.

Nephropathy. Yearly screening for microalbuminuria and treatment in Type I diabetes mellitus can reduce the incidence of renal failure. There are numerous methods of testing for microalbuminuria; most are equivalent in their short-term predictive value. The spot urinary albumin-creatinine ratio is a simple method. Because of variation in urinary albumin excretion, it is recommended that, if the first test is positive, the test be repeated on at least two occasions. Two of three tests should be positive (greater than 30 mg albumin per gm of creatinine) before microalbuminuria is considered present. Ideally, a first morning urine should be used as the specimen is concentrated, allowing a higher sensitivity for detecting microalbuminuria.

Causes of elevated urinary albumin excretion in the absence of diabetic nephropathy include urinary tract infection, recent exercise, acute illness, hematuria related to urinary tract infection (UTI) or menses, and congestive heart failure. Screen for overt proteinuria and UTI via standard dipsticks before performing the albumin/creatinine ratio. One plus protein is significant. Trace protein on urinalysis should be followed up with urinary albumin-creatinine ratio measurements.

A clinical diagnosis of diabetic nephropathy may be made when an individual develops albuminuria and has had Type 1 diabetes for more than 5 years or has evidence of diabetic retinopathy. Because albuminuria may be caused by other complicating renal diseases, a person who does not meet one of the above criteria or has factors suggestive of other renal diseases (such as active urinary sediment, nephrotic range proteinuria, accelerated hypertension, or rapidly progressive renal insufficiency) will require further evaluation.

Based on expert opinion, diabetic patients with a creatinine of 2-2.5 mg/dl and nephrotic range proteinuria should be referred to a nephrologist for evaluation for other causes of nephropathy if indicated, and for discussion of potential treatment options and treatment planning.

Dietary protein restriction has been proven to be beneficial in Type I diabetic patients with proteinuria. This has not been clearly proven in Type II diabetic patients. Consider dietary referral to evaluate dietary protein in patients with proteinuria.

ACE inhibitors reduce the rate of progression from microalbuminuria to overt proteinuria and diabetic nephropathy, independent of their effect on blood pressure. Other antihypertensives (including Beta-blockers and calcium channel blockers), slow the progression but are less effective in preventing diabetic kidney disease. Some members of the dihydropteridine class of calcium channel blockers may increase urinary albumin excretion, and should be avoided in patients with microalbuminuria. ACE inhibitors should be used in all patients with microalbuminuria unless contraindications are present or side effects are intolerable.

In all cases, aggressive control of blood pressure is mandatory, with an ideal target being less than 130/85. In nonhypertensive patients with microalbuminuria, target dosages of ACE inhibitors are difficult to define. Some experts recommend titrating medications upward until a reduction in albumin excretion is seen or side effects occur.

Diabetic foot examination and care. At each regularly scheduled diabetes visit, all patients need foot inspection for skin and nail abnormalities, fissures, and ulcers. Inspection should also include identifying areas of callus formation, claw toe deformity, prominent metatarsal heads (or other bony prominences), and other structural changes.

All patients need education regarding optimal foot care which includes daily inspection by the patient and appropriately fitting shoes. To minimize the risk of trauma patients should be counseled to avoid walking barefoot and those with neuropathy should avoid high-impact exercise and the use of hot water.

Orthotic footwear should be prescribed to accommodate major foot deformities and cushion pressure areas; Medicare covers therapeutic footwear for diabetic patients. For others with less deformity, athletic shoes with sufficient room for the toes and forefoot and cushioned socks are appropriate.

Neuropathy. Diabetic neuropathy is reported in more than 50% of patients after 15 years of diabetes. Evidence indicates early detection of diabetic neuropathy results in fewer admissions for foot ulcers and amputations.

Monofilament testing. Sensory testing with nylon monofilament (10g) should be done yearly to identify sensory loss. Testing for vibration perception (128 Hz tuning fork) is also a reliable and sensitive indicator of neuropathy.

(Instructions on “How to Use the Monofilament” are in the box at the top of the next page.)

Treatment of painful peripheral neuropathy. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be helpful as first-line agents in treating painful peripheral neuropathy. Caution should be exercised in the use of NSAIDs in combination with ACE inhibitors, as NSAIDs can reduce the efficacy of ACE inhibitors and can precipitate acute renal failure in patients with impaired renal function.

Tricyclic antidepressants (TCA) started at low doses at bedtime may be used as second-line therapy in patients with painful neuropathy. They can be titrated to maximize pain relief while minimizing side effects. Doxepin is the TCA of choice in patients with cardiac disease.

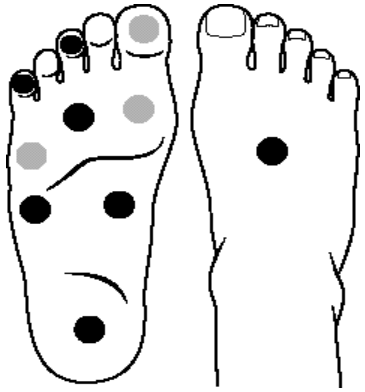
Capsaicin cream may be a useful adjunct in patients whose pain is not adequately controlled by TCA, particularly in those with severe contact dysthesias.

Careful attention should be paid to the etiology of pain in diabetic feet. Often, mechanical factors rather than neuropathy are the mechanism underlying pain. In these circumstances, NSAIDs can often be effective.

Treatment of diabetic foot ulcers. Detection and early treatment of foot ulcers is of paramount importance, as foot ulcers are among the most common reasons for hospitalization among people with diabetes. Ulcers are defined as any interruption of the integrity of the skin of the foot which extends through the entire dermis. Should a foot ulcer be found, circulation should be carefully evaluated and early treatment should be undertaken with aggressive wound care, orthotic prescriptions or casting,

How to Use the Monofilament

- Get the patient comfortable and relaxed.
- Show the patient the filament and touch his or her hand with it to show that it doesn't hurt.
- Ask the patient to say "yes" when he or she feels the filament on the foot. Don't ask, "Do you feel that?"
- Hold the filament perpendicular to the skin and use a smooth motion; touch until the filament bends, then lift off. Don't jab or bounce around.
- Touch designated parts of the feet randomly so the patient can't guess where the next point will be. Most critical are the great toe and the ball of the foot.
- If the patient doesn't say "yes" when you touch a particular spot, go to another site and come back to that one later.
- Keep the filament in its plastic case at all times when not in use. It can be cleaned with sodium hypochlorite 1:10 solution.



Source: The Gillis W. Long Hansen's Disease Center, Carville, La., and Dr. Charles Patout Jr.

pressure relief, and antibiotics when necessary. If rapid healing is not seen, immediate referral to a foot care specialist is warranted. Studies have shown that patients with diabetic foot ulcers have the best outcomes if managed by a multidisciplinary team which specializes in diabetic foot care.

Autonomic neuropathy and cardiovascular disease. Although less common in Type II than Type I diabetes, autonomic neuropathy can occur. This is primarily of concern in the detection of cardiovascular disease, as angina is often silent in the adult diabetic population. Care should be taken to elicit a history of possible atypical anginal symptoms or equivalents.

Glycemic Goal

Hemoglobin A_{1C} and glycosylated hemoglobin (GHb) are accurate measurements of long-term glycemic control. Current recommendations are that GHb be checked every 3-6 months in the patient on a stable hypoglycemic regimen, and every 1–3 months if changes are being made. Different laboratories use different measures and standard ranges; each laboratory should provide this information to clinicians.

A GHb goal or target level should be discussed and agreed upon by the patient and the primary care provider at the initial patient visit. Several factors should influence the GHb goal selected. The benefits of near-normalization of blood glucose levels in Type I diabetes are known: intensive therapy (which lowered HbA_{1C} by an average of 2%) reduced the rates of microvascular and neuropathic complications by approximately 50%. There appears to be an exponential relationship between the level of GHb and the rate of microvascular disease. In Type II diabetes, data suggest a similar relationship between glycemic control and complication rates. The major risk of intensive control is hypoglycemia, which has been an infrequent occurrence (2% requiring medical assistance per year) in an ongoing trial of aggressive glycemic control in Type II diabetes.

Factors affecting glycemic target levels. Several factors must be considered for each patient when selecting glycemic target levels. For young, healthy patients, the possibility of eventually developing advanced complications (i.e. blindness, renal failure) should be of major concern, and in general, tight control should be advocated. However, the chronic nature of some diabetes complications implies that any benefit in postponing or preventing their clinical occurrence may be delayed years or even decades.

In the presence of factors that affect the benefit and risk of glycemic control, it is less clear whether tight control is worth the risk and lifestyle modification necessary. Table 1 provides examples of factors which affect the risk/benefit ratio of tight control.

The actual target level of glycemic control selected for each person with diabetes must represent a balance between the patient's self-determined diabetes care goals, the likelihood of benefit from attaining those goals, and the risks associated with the therapy required to achieve those goals.

Determining individual glycemic control goal. Guidelines based on GHb have been used to categorize blood glucose control as either ideal (generally coincident with definitions of tight control), acceptable, or poor. These guidelines would categorize some patients as poorly controlled, despite agreement by patient and provider that more rigid (ideal or acceptable) glucose control would be undesirable, if not

frankly contraindicated. This creates a situation in which the patient must be assigned the status of "poor" control, despite agreement by patient and provider that the glycemic level may in fact be "ideal" given the patient's individual circumstances. One remedy to this problem is to use a classification scheme that adjusts the glycemic level associated with the categorization of ideal, acceptable or poor control, based on known factors that would limit the benefits, or heighten the risks of "ideal" blood glucose control. Ideal, acceptable (good or fair), or poor control can then be individually determined for each patient based on the factors present (see Table 2). In this way, patients and providers can set more realistic, attainable goals, giving the patient a greater likelihood of success. In almost all cases, at least good control should be sought.

The glycemic target ranges are shown in Table 2. The benefit-limiting and risk-heightening factors listed in Table 1 are given as an alternative guideline for goal-setting with the patient. It is an adjunct to, and not a substitute for careful ongoing assessment, treatment planning and follow-up. Once a glycemic target has been established, adjustment in diet and education, and if necessary, medications should be made until the target has been reached. Targets need to be reassessed on a regular basis, as the circumstances of each patient will change over time.

Glycemic management. In Type I diabetes, intensive insulin therapy as practiced in the Diabetes Control and Complications Trial should be regarded as the standard of care. Such care, delivered by a multidisciplinary team, involved 3 to 4 times daily insulin injections and 3 to 4 times daily self-monitoring of blood glucose.

If after implementing an individualized meal plan and negotiated exercise plan, a patient with Type II diabetes does not show improvement in glycemic control within one month, or does not achieve his or her glycemic goal within three months, then pharmacologic therapy should be instituted. Table 3 summarizes available oral agents for the management of Type II diabetes and their costs. Even after instituting pharmacologic therapy, careful attention must be paid to diet and physical activity.

Self-monitoring of blood glucose in recommended for patients with insulin-treated Type II diabetes with the frequency individualized to need. Self-monitoring of blood glucose may be useful for patients with non-insulin-treated Type II diabetes, but the value of regular monitoring has not been established.

- **Sulfonylureas.** Traditionally, sulfonylureas have been used as first-line therapy for patients with Type II diabetes in whom nonpharmacologic therapy has failed. Patients may be treated with a second-generation sulfonylurea starting at a low dose. Dose increments may be made every two weeks. If the patient has not achieved his or her glycemic goal after four weeks of therapy at a maximal sulfonylurea dose, sulfonylurea therapy should be considered a failure.

- **Metformin.** Metformin may also be selected as a first-line pharmacologic treatment for patients with Type II diabetes in whom nonpharmacologic therapy has failed. Metformin may be especially useful for patients who are overweight (greater than 140% of ideal body weight for age and sex) or dyslipidemic (triglyceride level greater than 600 mg/dL). Gastrointestinal side effects, including diarrhea, are seen in up to 30% of patients; a beginning dose of 500 mg metformin per day will reduce these side effects. The dosage may be increased by 500 mg per week to a maximum dose of 2.5 gm per day as 3 divided doses. Metformin therapy should be considered a failure if the patient has not achieved his or her glycemic goal after four weeks of therapy at a maximum dose.

- **Combination therapy.** Patients with Type II diabetes in whom therapy with sulfonylurea or metformin has failed are candidates for combination therapy with sulfonylurea and metformin. If the patient has not achieved his or her glycemic goals after four weeks of maximal dose combination therapy, a change of therapy is indicated.

- **Alpha-glucosidase inhibitors.** Alpha-glucosidase inhibitors such as acarbose (Precose) or miglitol (Glyset) may also be used as monotherapy in conjunction with diet to lower blood glucose or in combination with other oral agents or insulin. These drugs slow the digestion of ingested carbohydrates, delay glucose absorption into the bloodstream, and decrease postprandial blood glucose levels. The dosing for both acarbose and miglitol are the same. The initial dose is 25 mg three times a day and should be taken with the first bite of each main meal. Gastrointestinal side effects including pain, flatulence, and diarrhea are common; although these effects usually diminish over time (4-8 weeks), they frequently lead to discontinuation of the drug. Some experts advocate starting at a lower dose (25 mg once a day) to minimize the initial side effects and increase compliance. The maintenance dose may be titrated to 50 to 100 mg three times per day.

- **Thiazolidinediones.** The thiazolidinediones are a new class of oral agents designed to enhance the actions of insulin. Thiazolidinediones lower blood glucose levels by improving sensitivity to insulin in muscle and adipose tissue, and by inhibiting hepatic glucose production. Troglitazone, the first drug in this class marketed in the United States, was initially approved for use in patients with Type II diabetes on insulin therapy whose hyperglycemia was inadequately controlled despite large doses of insulin. However, troglitazone (Rezulin) has now been withdrawn from the market due to the occurrence of severe liver function abnormalities leading to death or transplant in some patients. Therefore, all patients on troglitazone should have the drug discontinued; substitution with another thiazolidinedione or alternative therapies is recommended.

There are two newer thiazolidinediones on the market, rosiglitazone and pioglitazone. There have been 2 case reports of hepatotoxicity associated with rosiglitazone; however, the relationships may not have been causal and liver function tests returned to normal when the drug was discontinued. All patients who are started on thiazolidinediones should have baseline AST and ALT levels, with follow-up levels at least every 2 months for at least 12 months.

The thiazolidinediones typically reduce HbA1c by 1-2% when added to other agents. The starting dose for rosiglitazone is 4 mg/d, and the drug should be titrated to a maximum dose of 8 mg/d (the dosage can also be split into twice daily dosing). The starting dose for pioglitazone is 7.5 or 15 mg/d, and the drug can be titrated to a maximal dose of 45 mg/d.

- **Bedtime insulin/daytime sulfonylurea (BIDS) therapy.** For patients with Type II diabetes who are hesitant to discontinue oral agents or to take more than one insulin injection per day, BIDS therapy may be considered. The patient is continued on daytime sulfonylurea at a maximum dose. Self-monitoring of blood glucose is intensified and NPH insulin is added at bedtime. The usual starting dose of insulin is 0.3 u/kg of body weight. Adjust therapy to achieve glycemic goals.

- **Insulin.** If four weeks of BIDS therapy fails to achieve the Type II diabetic glycemic goals, treatment should be changed to twice daily insulin injections. Therapy should be intensified as needed with twice daily split/mixed insulin, three times daily insulin therapy, or multiple daily injections to achieve glycemic goals.

Special Circumstances

Pregnancy / Pre-Conception Counseling

All female patients with diabetes who are of child-bearing potential should be counseled regarding the increased risk of diabetes and pregnancy. Family planning and contraception should be emphasized, as unplanned pregnancy has an even higher risk of poor outcome. Diabetes mellitus can significantly increase the risk of morbidity and mortality for the pregnant woman and the fetus/neonate. A significantly higher incidence of congenital anomalies occurs when maternal glycosylated hemoglobin in the first trimester is elevated. Specific preconception care for women with diabetes who are currently planning pregnancy is of prime importance to achieve the optimal outcome for both mother and baby. However, less than 20% of women with diabetes receive pre-pregnancy care.

Women not currently planning pregnancy. Women not currently planning pregnancy require general information regarding the risks of pregnancy and the need for pre-pregnancy planning. The importance of preventing pregnancy by establishing an acceptable method of birth control should be emphasized. Maintaining good glycemic control as a way of life can avoid preconception hyperglycemia in the event of an unplanned pregnancy.

Women who are or plan to become pregnant. Women with diabetes who are pregnant or who are planning to become pregnant should be counseled regarding the increased risks of pregnancy, the genetics of diabetes, the changes in lifestyle necessary (i.e. a personal commitment to diabetes care by the woman and family), and the possibility of hospitalization during pregnancy. These women require a GHb measurement in addition to the routine laboratory testing and examination done for all pregnant women. In addition to usual prenatal care, the management plan should include discontinuation of oral hypoglycemics and ACE inhibitors and initiation of insulin therapy, with a plan of achieving blood glucose or GHb in the normal range. Specific attention should be given to diet and exercise programs to allow adequate nutrition and optimal weight maintenance. ACE inhibitors are not teratogenic per se, but when used in pregnancy during the second and third trimesters, can cause injury and death to the developing fetus. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible. As with all pregnancies, folic acid (400 mcg. qd) should be prescribed and cessation of tobacco, alcohol, illicit drug, and caffeine use should be emphasized.

When to Consider Consultation or Referral

Consider consultation or referral for patients with:

- uncertain classification of diabetes, e.g., diabetes associated with endocrinopathies such as acromegaly, Cushing's syndrome, or pheochromocytoma; genetic defects of beta-cell function (MODY); genetic defects in insulin action (Type A syndrome of insulin resistance)
- Type I diabetes and frequent hypoglycemia or hyperglycemia or glycosylated hemoglobin level greater than glycemic goal
- plans for pregnancy
- multiple severe complications of diabetes
- chronic lack of adherence to their treatment regimen
- family problems or significant psychiatric problems interfering with treatment
- substantial disability despite adequate therapy
- frequent emergency room or hospital admission

Information the Patient Needs to Know

At the time the diagnosis of diabetes mellitus is made, the patient should be given extensive information about the disease and its management, including the importance of self-management. An important part of the primary care provider's role in the ongoing management of diabetes is to review and update the information the patient needs to manage the disease, to ascertain the patient's understanding of that information, to ascertain the extent to which the

patient is managing the disease appropriately, and to reinforce self-management behaviors.

Table 4 presents a list of important self-management topics and questions about them will help elicit the patient's understanding and actions. The entire list may be too long to go over at every visit, so items have been grouped to ensure that particularly important topics are checked frequently. However, any topic may be important at any visit.

Evidence Summary

Strategy for Literature Search

Preliminary evidence was identified using literature considered relevant by members of the panel. These articles and their bibliographies were used as a starting point. Further evidence was identified using a Medline search that included the following terms: Diabetes (all inclusive and non-insulin-dependent), retinopathy, nephropathy, neuropathy, lipids, cholesterol, triglycerides, blood glucose, glycemic control, hemoglobin A_{1c} glycosylated hemoglobin, foot care, proteinuria, microalbuminuria, and preconception care.

Evidence Regarding Specific Aspects of Care:

Aspirin therapy: The American Diabetes Association has recently published a comprehensive technical review on the indications for aspirin therapy in diabetes.

Blood pressure. No specific randomized, controlled trials identifying optimal blood pressure levels for patients with diabetes are available. A number of studies performed in the general population support a blood pressure cutoff of 140/90; JNC VI recommends a cutoff of 130/85 based on the significantly elevated risk of cardiovascular disease in patients with diabetes.

Lipids. No trials identifying cutoff or target levels for HDL and LDL have been performed specifically in patients with diabetes although some trials have now published subanalysis of their diabetic subjects showing benefit. The NCEP guidelines recommend treating patients with Type II diabetes as if they have existing cardiovascular disease, again based on the elevated risk in patients with Type II diabetes. Observational trials have shown that triglycerides are an independent risk factor for cardiovascular disease in patients with Type II diabetes.

Smoking. Many longitudinal cohort studies (non-randomized controlled trials) have shown the harmful effects of smoking among non-diabetic populations. In diabetic populations longitudinal cohort studies have shown that smoking adds to the diabetic populations' already elevated risk of CAD.

Retinal care. Multiple randomized, controlled trials have demonstrated the efficacy of laser therapy for proliferative retinopathy (60% reduction in blindness) and macular edema (50% reduction in blindness). Screening has been shown to be cost-effective in multiple models, although randomized, controlled trials of screening performed in true primary care settings have not been performed.

Urine protein. Microalbuminuria and proteinuria have clearly been identified to be early markers of eventual diabetic nephropathy. ACE inhibitors have been shown to reduce the rate of progression of early diabetic renal disease in randomized, controlled trials in both Type I and Type II diabetes. Based on this evidence, models have demonstrated the cost-effectiveness of screening and early treatment of patients who have microalbuminuria.

Foot care. The combination of patient education regarding foot care and increased surveillance from physicians regarding foot related risk factors for amputation have been examined in a randomized controlled trial and a non-randomized controlled trial. Both trials showed a significant reduction in serious foot lesions. Both trials used a comprehensive program of diagnosis (including monofilament testing) and intervention. The effectiveness of individual components of the comprehensive programs were not evaluated separately.

Glycemic control. Based on evidence from observational trials, it has long been known that level of glycemic control is associated with the development of microvascular diabetic complications. The DCCT demonstrated this association in a randomized, controlled trial of Type I diabetes. A single randomized, controlled trial of Japanese patients with Type II diabetes has confirmed that the rate of microvascular complications can be reduced by improving levels of glycemic control as measured by hemoglobin A1c (or glycosylated hemoglobin).

Preconception care. The effects of preconception care for diabetic mothers has been examined in at least five clinical trials (non-randomized) and three observational trials. All show a meaningful decrease in the percent of malformations in infants of diabetic mothers receiving preconception care.

Annotated References

Vijans S, Stevens DL, Herman WH, Funnell MM, Standiford CJ. Screening, Prevention, Counseling, and Treatment for the Complications of Type II Diabetes Mellitus. J Gen Intern Med 1997;12:567-580.

This review summarizes current knowledge of interventions that should improve the care of patients with Type II diabetes mellitus. Interventions lie within the realms of prevention, screening, and treatment, all of which are focused on office practice. The emphasis is on prevention of atherosclerotic disease, and prevention, screening, and early treatment of microvascular disease.

American Diabetes Association. Clinical practice recommendations 1995. Diabetes Care. 1995;18(Suppl 1):1–96.

The American Diabetes Association (ADA) has developed position statements on screening for diabetes, diagnosis and classification of diabetes, medical care for patients with diabetes, nutritional recommendations and principles for individuals with diabetes, diabetes and exercise, screening for diabetic retinopathy, diabetic neuropathy, foot care in patients with diabetes mellitus, detection and management of lipid disorders in diabetes, and hospital admission guidelines for diabetes mellitus, among others.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-1197.

This article reviews the scientific basis for the ADA's new recommendations for the diagnosis and classification of diabetes mellitus.

The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–986.

This is the first key report from the Diabetes Control and Complications Trial, a prospective randomized controlled clinical trial of intensive therapy for insulin-dependent diabetes mellitus. It conclusively demonstrated that intensive therapy, compared to conventional insulin therapy, reduced the development and progression of all of the microvascular and neuropathic complications of IDDM. The chief adverse event associated with intensive therapy was a two to three-fold increase in severe hypoglycemia. This study proved the glucose hypothesis: that hyperglycemia causes diabetic microvascular and neuropathic complications, and treatment of hyperglycemia delays or prevents those complications.

Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings. DRS report number 8. Ophthalmology. 1981;88:583–590.

The Diabetic Retinopathy Study, a randomized controlled clinical trial of photocoagulation treatment for proliferative diabetic retinopathy, demonstrated that photocoagulation as used in the study reduces the risk of severe visual loss by more than fifty percent. This report clearly outlines the high risk characteristics associated with more rapid progression to severe visual loss and advises prompt therapy for such patients. It also highlights the side effects associated with treatment; mild decreases in visual acuity and constriction of peripheral visual field.

Early Treatment of Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology. 1991;98:766–785.

This report summarizes the results of the Early Treatment Diabetic Retinopathy Study, a randomized controlled clinical trial of early photocoagulation in the treatment of mild to severe non-proliferative or early proliferative diabetic retinopathy. The ETDRS results demonstrated that for eyes with macular edema, focal photocoagulation is effective in reducing the incidence of moderate visual loss. Focal treatment also increased the chance of visual improvement, decreased the frequency of persistent macular edema, and caused only minor visual field losses.

Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329:1456–1462.

This randomized controlled clinical trial compared Captopril with placebo in patients with insulin-dependent diabetes mellitus and clinical nephropathy (urinary protein excretion > 500 mg per day and serum creatinine concentration < 2.5 mg/dL). It demonstrated that therapy with the angiotensin-converting enzyme inhibitor was associated with a fifty percent reduction in the risk of the combined end points of death, dialysis, and transplantation that was independent of the small disparity in blood pressure between the groups. In subsequent studies, these findings have been extended to patients with earlier stages of diabetic nephropathy and to patients with NIDDM. ACE-inhibitors protect against deterioration in renal function in diabetic nephropathy, act independently of their effect on blood pressure control, and are more effective than blood pressure control alone.

Colwell JA. Aspirin therapy in diabetes. Diabetes *Care* 1997:20;1767-1771.

This technical review summarizes the literature on the role of aspirin in diabetes.