

Management of Type 2 Diabetes Mellitus

Diabetes Mellitus Guideline Team

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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

Screening. Although little evidence is available on screening for diabetes, one may consider beginning screening at age 45 at 3-year intervals, earlier particularly if BMI ≥ 25 kg/m² [evidence: D].

Prevention. In individuals at risk for diabetes (see Table 1), diet, exercise, and pharmacologic interventions can delay or prevent type 2 diabetes [A].

Diagnosis. Either two separate fasting glucoses ≥ 126 mg/dL, or if symptoms, a glucose ≥ 200 mg/dL confirmed on a separate day by a fasting glucose ≥ 126 mg/dL, or 2-hour postload glucose ≥ 200 mg/dl during an oral glucose tolerance test [B]. (See Table 1.) HbA1c has low sensitivity, but high specificity, for the diagnosis of diabetes, and most experts feel that it should not be used as a primary diagnostic test.

Treatment. Diet, exercise, and pharmacologic interventions should be initiated for:

- Hypertension control [A]
- Glycemic control [A]
- Lipid control [A]
- Cardiovascular risk reduction [A]

Ongoing screening and management. 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 tables.

| Each regular diabetes visit | Every 3 to 6 months | Annually (see Table 2) |
|--|--|---|
| <ul style="list-style-type: none"> • Diabetes visit every 3 months for patients on insulin; every 6 months for patients on oral agents or diet only [D]. • Blood pressure measured and controlled [A]. (See Table 2) • Weight checked [D]. • Inspect feet each visit if presence of neuropathy; otherwise annually [A]. (See Tables 2 and 8) • Smoking cessation counseling provided for patients with tobacco dependence [B]. (See Table 2) • Very important self-management goals reviewed and reinforced. (See Table 8) [A] | <ul style="list-style-type: none"> • Check HbA1c and optimize glycemic control [A]. (See Table 4) | <ul style="list-style-type: none"> • Dilated retinal examination by an eye care specialist [B] and treatment of retinopathy [A]. (Biannually if previous eye exam was normal, see Table 2.) • Screen for microalbuminuria if not on an ACE inhibitor or ARB [B]. Prescribe an ACE-I or ARB for microalbuminuria or proteinuria [A]. • Serum creatinine and estimated glomerular filtration rate (eGFR) [D] • Monofilament testing of feet (see Table 9) [A] • Lipids measured [B] and treated [A]. (see Table 2) • Smoking status assessed. • Other important self-management goals reviewed and reinforced. (See Table 8) |

Special considerations: Pregnancy. Preconception counseling and glycemic control in women with diabetes mellitus results in optimal maternal and fetal outcomes [B].

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

(Continued on page 8)

Table 1. Diagnosis of Diabetes: Diagnostic Tests and Glucose Values

| Diagnostic Test | Normal | At risk for diabetes | Diabetes |
|--|-------------|----------------------|-----------------------------|
| Fasting plasma glucose * | < 100 mg/dL | 100-125 mg/dL | ≥ 126 mg/dL |
| Random plasma glucose † | < 130 mg/dL | 130-199 mg/dL | ≥ 200 mg/dL (with symptoms) |
| Oral glucose tolerance test (OGTT) 2hrs after a 75 gm oral glucose load | < 140 mg/dL | 140-199 mg/dL | ≥ 200 mg/dL |

* For fasting glucose, there must be two tests with ≥ 126 mg/dL

† A random glucose ≥ 200 mg/dL (with symptoms) must be confirmed with a fasting glucose ≥ 126 mg/dL or the OGTT.

Table 2. Prevention, Screening, and Treatment of Complications in Patients with Diabetes Mellitus

| Cardiovascular Risk Factors | Microvascular Complications |
|--|---|
| <p>Hypertension Check <u>blood pressure</u> (BP) (each visit)</p> <ul style="list-style-type: none"> If not on therapy and BP ≥ 135/80 [A*†] (see text & Table 3) <ol style="list-style-type: none"> Check electrolytes and serum creatinine Check for microalbuminuria Consider therapy if repeated BP measurements are elevated. Thiazide diuretics are recommended for patients without microalbuminuria and ACE inhibitors or ARBs (if ACE-I not tolerated) for patients with microalbuminuria, adding other agents as needed. Second line agents are beta-blockers and long-acting dihydropyridine calcium channel blockers. Other agents may also be necessary but have less supporting data. Recommend DASH diet, exercise and dietary referral If on therapy and BP ≥ 135/80 [A*†], adjust medication <p>Hyperlipidemia Check <u>lipid profile</u> – fasting or with direct LDL (annually)</p> <ul style="list-style-type: none"> Prescribe moderate dose statin (e.g. simvastatin (generic) 40 mg/d) in patients age 40 years or older [A**], While LDL target levels have not been clearly defined in trials, general recommendations are for LDL < 100 mg/dL. Statins are optional for patients < 40 years old as they are marginally cost-effective (~\$80,000 per QALY) <p>Smoking Check <u>smoking status</u> (at least annually). If non-smoker, reinforce nonsmoking.</p> <ul style="list-style-type: none"> If a smoker <ol style="list-style-type: none"> Educate about increased CV risk (diabetes + tobacco) Encourage smoking cessation [B**] <p>Cardiac Risk Reduction</p> <ul style="list-style-type: none"> Most patients with diabetes will benefit from low dose aspirin therapy <p>-----</p> <p>Levels of Evidence A = randomized controlled trials B = controlled trials, no randomization C = observational studies D = opinion of expert panel</p> | <p>Retinopathy Perform <u>dilated retinal exam</u> by eye care specialist [B**] every 2 years if previous eye exam was normal otherwise annually or more frequently as recommended by the eye care provider</p> <ul style="list-style-type: none"> If retinopathy <ol style="list-style-type: none"> Treatment per ophthalmology [A**] Consider improving glycemic control [A**] <p>Nephropathy Check <u>spot urinary albumin/creatinine ratio</u> (annually) if not on an ACE-I/ARB and without diagnosis of diabetic nephropathy. If > 30 mg/gm, check UA to rule out asymptomatic UTI.</p> <ul style="list-style-type: none"> Repeat spot urine ratio twice within 6 months. If 2 of 3 spot urine albumin/creatinine ratios > 30 mg/dL: <ol style="list-style-type: none"> Check creatinine, electrolytes and estimated glomerular filtration rate (eGFR) [D*] Begin ACE inhibitor or ARB [A**] (if electrolytes allow use of ACE inhibitor). Recheck creatinine and electrolytes within 1–2 weeks. Aggressive hypertension control [A**] <p>Neuropathy Perform <u>foot exam</u>: (1) inspect and check pulse (each visit if patient has a history of neuropathy; otherwise annually), and (2) monofilament (annually), see Table 9.</p> <ul style="list-style-type: none"> If structural abnormality <ol style="list-style-type: none"> Prescription for customized shoe and/or orthotics Consider podiatry referral If neuropathy <ol style="list-style-type: none"> Optimize glycemic control [A**] Treatment of painful neuropathy if indicated If not sensitive to monofilament <ol style="list-style-type: none"> Education regarding proper foot care and increased risk of ulceration If foot ulcer: <ol style="list-style-type: none"> Prescription for customized shoe and/or orthotics Aggressive wound care with close follow up Refer to a multidisciplinary team specializing in the care of diabetic foot ulcers [A**] <p>-----</p> <p>* studies in general population ** studies in patients with diabetes</p> |

† BP ≥ 130/80 is recommended for treatment by the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC 7) and by the American Diabetes Association, although there is no level A evidence for the systolic BP.

Table 3. Steps in Pharmacologic Treatment of Hypertension in Patients with Diabetes Mellitus
(Detailed information on hypertension medications can be found in Table 2 of the UMHS Hypertension Guideline)

| |
|--|
| <p>Step 1. Elevated BP (systolic BP \geq 135¹ and/or diastolic BP \geq 80) uncontrolled by prior lifestyle modifications</p> <p>Without microalbuminuria</p> <p>Thiazide diuretic – initiate therapy. <u>Hydrochlorothiazide</u> 12.5 mg daily. Titrate by doubling dose in 2-4 weeks if BP goal NOT met. (maximum dose: 25 mg)</p> <p>With microalbuminuria</p> <p>ACE-I (Angiotensin-Converting Enzyme Inhibitor) – initiate therapy unless contraindication (hypersensitivity reaction, angioedema) or documented persistent cough. <u>Lisinopril</u> 10 mg daily.² Titrate by doubling dose every 2-4 weeks until the BP goal is met (maximum dose: 40 mg)</p> <p>If ACE-I contraindicated: Angiotensin II Receptor Blocker (ARB) <u>Irbesartan</u> (Avapro ®) 150 mg daily.² Titrate by doubling dose in 2-4 weeks if BP goal NOT met (max dose: 300 mg)</p> |
| <p>Step 2. If dose is optimized on agent from Step 1 and patient BP remains \geq 135/80¹</p> <p>Add a Thiazide diuretic or ACE-I/ARB to the first agent. Consider combination therapy to reduce cost (e.g., lisinopril/HCTZ, irbesartan/HCTZ, atenolol/chlorthalidone)</p> |
| <p>Step 3. If above agents are contraindicated or dose is optimized and patient BP remains \geq 135/80¹</p> <p>Add a Beta-Blocker to the first two agents. Initiate therapy with either metoprolol (preferred) or atenolol: <u>Metoprolol tartrate</u> 25 to 50 mg BID.³ Titrate by doubling dose every 2-4 weeks until BP goal met (max dose: 200 mg) <u>Atenolol</u> 25 mg daily.³ Titrate by doubling dose every 2-4 weeks until BP goal met (maximum dose: 100 mg)</p> |
| <p>Step 4. If above agents are contraindicated or dose is optimized and patient BP remains \geq 135/80¹</p> <p>Add a Dihydropyridine Calcium Channel Blocker – initiate therapy <u>Amlodipine</u> (Norvasc ®) 5 mg daily. Titrate by doubling dose in 2-4 weeks if BP goal is NOT met (max dose: 10 mg)</p> |

¹ Systolic BP \geq 130 recommended for treatment by JNC 7 and ADA, although there is no level A evidence for this upper limit.

² Check serum creatinine and potassium levels 1-2 weeks after starting medication or increasing its dose.

³ Check heart rate 1-2 weeks after starting the medication or increasing dose.

Table 4. Monitoring Glycemic Control in Patients with Diabetes Mellitus

| |
|---|
| <p>Check HbA1c (every 3–6 months) [Interval expected by Health Plan Employer Data and Information Set (HEDIS)]</p> <ul style="list-style-type: none"> • If HbA1c \geq 7% and patient does not have factors that limit benefit of tight control * or heighten risk of tight control**: <ol style="list-style-type: none"> 1. Assess treatment regimen 2. Diabetes/dietary education or referral 3. Start or increase medication 4. Recheck HbA1c in 3 months; if adjusting medications, patient may check fasting blood sugar |
|---|

* Factors limiting benefit of tight control

- Comorbidities (e.g., end-stage cancer, severe heart failure, advanced age)
- Advanced diabetes complications (e.g., proliferative retinopathy, renal failure)
- Inability to carry out treatment regimen (e.g., financial constraints, availability of needed supplies)
- Limited life expectancy

** Factors heightening risk of tight control

- History of severe hypoglycemia (inability to treat without assistance): any episodes within the past year and/or more than 2 episodes ever
- Hypoglycemia unawareness
- Advanced cardiovascular or cerebrovascular disease
- Autonomic neuropathy (especially cardiac)
- Comorbidities / medications that impair the detection of hypoglycemia (e.g., CNS-acting drugs, alteration in mental status)
- Lack of mobility or lives alone

Table 5. Oral Agents for Glycemic Control in Patients with Type 2 Diabetes [UMHS Preferred Agents in Bold]

| Generic (Brand Name) | Strength (mg) | Initial Dose (mg) | Max Daily Dose (mg) | Usual Daily Dose (mg) | Cost ^a 30 days(range) | |
|---|--------------------------------|--|---|---|----------------------------------|-----------|
| | | | | | Generic | Brand |
| <i>Biguanide</i> | | | | | | |
| Metformin (Glucophage) | 500, 850, 1000 | 500 BID or 850 daily | 2550 | 1000-2550 divided (BID) | \$11-23 | \$54-136 |
| Metformin extended release (Glucophage XR) | 500, 750 | 500 daily with evening meal | 2000 | 1500-2000 daily with evening meal | \$18-23 | \$82-109 |
| <i>Sulfonylureas (Second Generation)^b</i> | | | | | | |
| Glimepiride (Amaryl) | 1, 2, 4 | 1-2 daily | 8 | 4 daily | \$15 | \$40 |
| Glipizide (Glucotrol) | 5, 10 | 2.5, 5 daily | 40 | 10 - 20 daily or divided (BID) | \$6-9 | \$29-57 |
| Glipizide SR (Glucotrol XL) | 2.5, 5, 10 | 5 daily | 20 | 5 - 20 daily or divided (BID) | \$12-36 | \$15-60 |
| Glyburide (Diabeta, Micronase) | 1.25, 2.5, 5 | 2.5-5 daily | 20 | 5 - 20 daily or divided (BID) | \$8-21 | \$27-105 |
| Glyburide, micronized (Glynase) | 1.5, 3, 4.5, 6 | 0.75-3 daily | 12 | 3 - 12 daily or divided (BID) | \$10-20 | \$34-107 |
| <i>Thiazolidinedione^c</i> | | | | | | |
| Pioglitazone (Actos) | 15, 30, 45 | 15-30 daily | 45 | 15 - 45 daily | NA | \$110-191 |
| Rosiglitazone (Avandia) | 2, 4, 8 | 4 daily or divided (BID) | 8 | 4 - 8 daily or divided (BID) | NA | \$102-186 |
| <i>Alpha-glucosidase inhibitor</i> | | | | | | |
| Acarbose (Precose) | 25, 50, 100 | 25 daily with meal | 300 | 50 - 100 TID before meals | NA | \$82-98 |
| Miglitol (Glyset) | 25, 50, 100 | 25 daily with meal | 300 | 25 - 100 TID | NA | \$70-91 |
| <i>Non-sulfonylurea insulin secretagogues</i> | | | | | | |
| Repaglinide (Prandin) | 0.5, 1, 2 | 0.5 with meals | 16 | 0.5 - 4 AC to QID | NA | \$123-330 |
| Nateglinide (Starlix) | 60, 120 | 60–120 with meal | 360 | 60 - 120 AC | NA | \$124-129 |
| <i>Combination formulations [Less dosing flexibility]</i> | | | | | | |
| Glipizide/metformin (Metaglip) | 2.5/250, 2.5/500, 5/500 | 2.5/250 daily- 2.5/500 BID ^d or 2.5/500-5/500 BID ^e | 10/2000 ^e or 20/2000 ^d | Titrate to effective dose (not over max) | \$22-93 | \$27-126 |
| Glyburide/metformin (Glucovance) | 1.25/250, 2.5/500, 5/500 | 1.25/250 daily- BID ^d or 2.5/500- 5/500 BID ^e | 10/2000 ^e or 20/2000 ^d | 2.5/500 – 10/1000 daily-BID | \$11-33 | \$35-141 |
| Pioglitazone/metformin (Actoplus Met) | 15/500, 15/850 | 15/500-15/850 daily-BID | 45/2550 | Titrate to effective dose (not over max) | NA | \$89-253 |
| Rosiglitazone/metformin (Avandamet) | 1/500, 2/500, 4/500 | 2/500 BID | 8/2000 | Titrate to effective dose (not over max) | NA | \$121-204 |
| Rosiglitazone/glimeperide (Avandaryl) | 4/1,4/2,4/4 | 4/1-4/2 daily | 8/4 | Titrate to effective dose (not over max) | NA | \$109-217 |

^a Cost = Average wholesale price -10% for brand products and Maximum Allowable Cost + \$3 for generics on 30-day supply.

^b Second generation sulfonylureas have a better safety profile compared to first generation sulfonylureas.

^c Pioglitazone is preferred over rosiglitazone (see Table 6 and page 13 for details).

^d Dose for initial therapy, i.e., starting both agents for the first time.

^e Dose for second line therapy, i.e., previously treated with one or both of the agents.

Table 6. Sequential Pharmacologic Steps to Achieve Glycemic Control in Patients with Diabetes

Short-term goal of glucose < 130 mg/dL (fasting and preprandial) **Long-term goal** of A1c < 7.0%

| <p>1. Start with diet and exercise for all patients. Add a single oral medication. The new guidelines call for metformin from the beginning.</p> <p><u>Metformin</u>¹ is preferred for patients with normal Glomerular Filtration Rate (GFR) <u>Sulfonylurea</u> (glipizide, glyburide) is preferred for those with contraindications to metformin</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p><u>Metformin</u>¹</p> <ol style="list-style-type: none"> Start metformin 500 mg daily or BID with breakfast and dinner Double initial starting dose every week as tolerated by side-effects up to 1000 mg BID </td> <td style="vertical-align: top;"> <p><u>Sulfonylurea</u> (e.g., glipizide or glyburide)</p> <ol style="list-style-type: none"> Start glipizide extended release (ER) 5 mg daily or glyburide 2.5 mg daily before breakfast or dinner Titrate² as needed to a maximum of glipizide ER 20 mg daily or glyburide 10 mg BID </td> </tr> </table> | | <p><u>Metformin</u>¹</p> <ol style="list-style-type: none"> Start metformin 500 mg daily or BID with breakfast and dinner Double initial starting dose every week as tolerated by side-effects up to 1000 mg BID | <p><u>Sulfonylurea</u> (e.g., glipizide or glyburide)</p> <ol style="list-style-type: none"> Start glipizide extended release (ER) 5 mg daily or glyburide 2.5 mg daily before breakfast or dinner Titrate² as needed to a maximum of glipizide ER 20 mg daily or glyburide 10 mg BID | | |
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| <p>2. Add a second oral medication if A1c remains above goal on a single medication</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p><u>Add sulfonylurea to metformin</u> (Use sulfonylurea dosing schedule above)</p> </td> <td style="vertical-align: top;"> <p><u>Add metformin to sulfonylurea</u> (Use metformin dosing schedule above)</p> </td> </tr> </table> | | <p><u>Add sulfonylurea to metformin</u> (Use sulfonylurea dosing schedule above)</p> | <p><u>Add metformin to sulfonylurea</u> (Use metformin dosing schedule above)</p> | | |
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| <p>3. Add an injectable medication or a third oral medication (thiazolidinedione)^{3,4} if A1c is above goal on both a sulfonylurea and metformin</p> <table border="1"> <thead> <tr> <th style="text-align: left;">Injectable Medication Options (Insulin or Byetta)</th> <th style="text-align: left;">Third Oral Medication</th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top;"> <p><u>Insulin</u></p> <ol style="list-style-type: none"> Start with NPH, detemir, glargine, or premixed insulin. The choice may vary depending on concerns regarding endogenous insulin secretion, need for meal-time insulin coverage, cost and convenience. All patients started on insulin should demonstrate use of a glucose meter and be educated on symptoms and treatment of hypoglycemia <p><i>NPH or detemir insulin (bedtime)</i></p> <ol style="list-style-type: none"> Continue metformin +/- sulfonylurea depending on preprandial glucose Add 10-20 units of NPH insulin at bedtime Then increase insulin by 10% or at least 2 units every 3 days until the goal of a fasting blood glucose (FBG) < 130 mg/dL without hypoglycemia Once fasting glucose is at goal, check preprandial glucoses; if > 140 mg/dL consider adding either rapid or regular insulin OR restarting sulfonylurea <p><i>NPH or detemir insulin (BID)</i></p> <ol style="list-style-type: none"> Continue metformin, discontinue sulfonylurea Add 5-10 units of NPH insulin at breakfast and dinner Then increase insulin by 10% or at least 2 units every 3 days until the goal of a fasting blood glucose and pre-dinner glucose < 130 mg/dL without hypoglycemia <p><i>Glargine (Lantus®) insulin (typically given at bedtime)</i></p> <ol style="list-style-type: none"> Continue metformin +/- sulfonylurea depending on preprandial glucose Add 10-20 units of glargine insulin at bedtime Increase bedtime insulin by 10% or at least 2 units every 3 days until the goal of a fasting blood glucose < 130 mg/dL without hypoglycemia Once fasting glucose is at goal, check preprandial glucose, if > 140 mg/dL consider adding either rapid or regular insulin OR restarting sulfonylurea <p><i>Premixed insulin (intermediate & short-acting mixtures)</i></p> <ol style="list-style-type: none"> Continue metformin, discontinue sulfonylurea Add 10 units of pre-mixed insulin at breakfast and dinner Increase pre-breakfast and/or pre-dinner insulin by 10% or at least 2 units every 3 days until the goal of a fasting and pre-meal glucose level < 130 mg/dL without hypoglycemia </td> <td style="vertical-align: top;"> <p><u>Thiazolidinedione</u>⁴</p> <p>Pioglitazone is recommended due to possible increased cardiovascular events with rosiglitazone</p> <ol style="list-style-type: none"> Add pioglitazone 30 mg daily <i>or</i> rosiglitazone 4 mg daily Titrate² as needed to pioglitazone 45 mg daily <i>or</i> rosiglitazone 8 mg daily Use with caution in patients with CHF (Class III and IV). Serum ALT should be checked prior to beginning therapy, and periodically thereafter <p><u>Exenatide (Byetta®)</u></p> <p>Works well for overweight or obese patients. Approved for non-insulin treated patients who failed metformin and sulfonylurea.</p> <ol style="list-style-type: none"> Continue metformin and/or sulfonylurea and add exenatide 5 mcg SQ BID, after 1 month consider reducing sulfonylurea dose Titrate exenatide if needed, to 10 mcg SQ BID if no nausea <p>Note: FDA warns that Byetta may be associated with an increased risk for pancreatitis</p> </td> </tr> </tbody> </table> | | Injectable Medication Options (Insulin or Byetta) | Third Oral Medication | <p><u>Insulin</u></p> <ol style="list-style-type: none"> Start with NPH, detemir, glargine, or premixed insulin. The choice may vary depending on concerns regarding endogenous insulin secretion, need for meal-time insulin coverage, cost and convenience. 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Serum ALT should be checked prior to beginning therapy, and periodically thereafter <p><u>Exenatide (Byetta®)</u></p> <p>Works well for overweight or obese patients. Approved for non-insulin treated patients who failed metformin and sulfonylurea.</p> <ol style="list-style-type: none"> Continue metformin and/or sulfonylurea and add exenatide 5 mcg SQ BID, after 1 month consider reducing sulfonylurea dose Titrate exenatide if needed, to 10 mcg SQ BID if no nausea <p>Note: FDA warns that Byetta may be associated with an increased risk for pancreatitis</p> |
| Injectable Medication Options (Insulin or Byetta) | Third Oral Medication | | | | |
| <p><u>Insulin</u></p> <ol style="list-style-type: none"> Start with NPH, detemir, glargine, or premixed insulin. The choice may vary depending on concerns regarding endogenous insulin secretion, need for meal-time insulin coverage, cost and convenience. All patients started on insulin should demonstrate use of a glucose meter and be educated on symptoms and treatment of hypoglycemia <p><i>NPH or detemir insulin (bedtime)</i></p> <ol style="list-style-type: none"> Continue metformin +/- sulfonylurea depending on preprandial glucose Add 10-20 units of NPH insulin at bedtime Then increase insulin by 10% or at least 2 units every 3 days until the goal of a fasting blood glucose (FBG) < 130 mg/dL without hypoglycemia Once fasting glucose is at goal, check preprandial glucoses; if > 140 mg/dL consider adding either rapid or regular insulin OR restarting sulfonylurea <p><i>NPH or detemir insulin (BID)</i></p> <ol style="list-style-type: none"> Continue metformin, discontinue sulfonylurea Add 5-10 units of NPH insulin at breakfast and dinner Then increase insulin by 10% or at least 2 units every 3 days until the goal of a fasting blood glucose and pre-dinner glucose < 130 mg/dL without hypoglycemia <p><i>Glargine (Lantus®) insulin (typically given at bedtime)</i></p> <ol style="list-style-type: none"> Continue metformin +/- sulfonylurea depending on preprandial glucose Add 10-20 units of glargine insulin at bedtime Increase bedtime insulin by 10% or at least 2 units every 3 days until the goal of a fasting blood glucose < 130 mg/dL without hypoglycemia Once fasting glucose is at goal, check preprandial glucose, if > 140 mg/dL consider adding either rapid or regular insulin OR restarting sulfonylurea <p><i>Premixed insulin (intermediate & short-acting mixtures)</i></p> <ol style="list-style-type: none"> Continue metformin, discontinue sulfonylurea Add 10 units of pre-mixed insulin at breakfast and dinner Increase pre-breakfast and/or pre-dinner insulin by 10% or at least 2 units every 3 days until the goal of a fasting and pre-meal glucose level < 130 mg/dL without hypoglycemia | <p><u>Thiazolidinedione</u>⁴</p> <p>Pioglitazone is recommended due to possible increased cardiovascular events with rosiglitazone</p> <ol style="list-style-type: none"> Add pioglitazone 30 mg daily <i>or</i> rosiglitazone 4 mg daily Titrate² as needed to pioglitazone 45 mg daily <i>or</i> rosiglitazone 8 mg daily Use with caution in patients with CHF (Class III and IV). Serum ALT should be checked prior to beginning therapy, and periodically thereafter <p><u>Exenatide (Byetta®)</u></p> <p>Works well for overweight or obese patients. Approved for non-insulin treated patients who failed metformin and sulfonylurea.</p> <ol style="list-style-type: none"> Continue metformin and/or sulfonylurea and add exenatide 5 mcg SQ BID, after 1 month consider reducing sulfonylurea dose Titrate exenatide if needed, to 10 mcg SQ BID if no nausea <p>Note: FDA warns that Byetta may be associated with an increased risk for pancreatitis</p> | | | | |

¹ For metformin, verify serum creatinine < 1.5 for males, < 1.4 for females; if serum creatinine > 1.3, or patient is elderly, verify creatinine clearance. Use caution in patients at risk for acidosis (e.g., heart failure, renal failure, liver failure)

² Titrate as needed: increase dose every 2 weeks for patients who self-monitor blood sugars if short-term goal is not achieved

³ Alpha-glucosidase inhibitors (e.g., Acarbose) tend to be less popular due to GI side effects and frequent dosing

⁴ All thiazolidinediones are associated with an increased risk of CHF; rosiglitazone may also increase the risk of myocardial infarction

Table 7. Injectable Agents for Glycemic Control in Patients with Type 2 Diabetes

| Type of Injectable | Examples | Onset of Action | Peak of Action | Duration of Action | Cost ¹ – 30 days |
|---|--------------------------------------|--|----------------|--------------------|-----------------------------|
| Incretin mimetic | Exenatide (Byetta) ² | n/a | n/a | n/a | \$190-222 |
| Amylinomimetic | Pramlintide (Symlin) | n/a | n/a | n/a | \$102 |
| Rapid-acting insulin | Lispro (Humalog) | 15 min | 0.5-2.5 hrs | 3-5 hrs | \$79 |
| | Aspart (NovoLog) | 15 min | 1-3 hrs | 3-5 hrs | \$86 |
| | Glulisine (Apidra) | 20 min | 1-2 hrs | 5-6 hrs | \$76 |
| Short-acting | Regular | 30-60 min | 2-3 hrs | 3-6 hrs | \$37 |
| Intermediate-acting | NPH | 2-4 hrs | 4-10 hrs | 10-16 hrs | \$37 |
| | Detemir (Levemir) | 3-4 hrs | 6-8 hrs | 6-23 hrs | \$81 |
| Long-acting | Glargine (Lantus) | 2-4 hour | None | 20-24 hrs | \$76 |
| Intermediate- and short-acting mixtures | 75/25 NPL/lispro (Humalog Mix) | Varies according to types and Percentages of insulin | | | \$79 |
| | 50/50 NPL/lispro (Humalog Mix) | | | | |
| | 70/30 NPH/aspart (NovoLog Mix) | | | | \$86 |
| | 70/30 NPH/regular (Humulin, Novolin) | | | | \$37 |
| | 50/50 NPH/regular (Humulin) | | | | \$34 |

¹ Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + \$3 for generics on 30-day supply, *Amerisource Bergen item Catalog 3/07 & Blue Cross Blue Shield of Michigan Mac List, 1/2/07*.

² The FDA warns that exenatide (Byetta®) may be associated with an increased risk for pancreatitis. If pancreatitis is suspected, exenatide should be discontinued. If pancreatitis is confirmed, exenatide should not be restarted unless an alternative etiology is identified.

Table 8. -Self-Management TopicsBased upon expert opinion**


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

- **Active responsibility for own care.** What do you do each day to take care of your diabetes? What is hardest for you to do? (Demonstrate through words and actions that diabetes is a serious illness.)
- **Progress toward blood pressure, glucose, and cholesterol goals.** Do you know your most recent blood pressure level, HbA1c level, and LDL cholesterol levels and your progress toward your goals for these levels?
- **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?
- **Symptoms and treatment of hyperglycemia and hypoglycemia.** What are the (1) symptoms and treatment for hyperglycemia? (2) symptoms and treatment for hypoglycemia? (3) when should you contact your health care provider?
- **Complementary therapies.** What herbal supplements, over-the-counter medicines, or other treatments do you use?
- **Exercise.** What exercise do you do to help keep your blood glucose level close to normal?
- **Meal plan.** Do you have a meal plan? Are you able to use your meal plan? Do you count carbohydrates?
- **Weight reduction.** (If overweight:) What strategies for weight loss are you following?
- **Stress and Coping.** Are you feeling more stressed than usual? How do you cope with this stress?
- **Psychological status.** How is diabetes affecting you emotionally? Are your emotions interfering with your ability to manage your diabetes? How do you handle these feelings?
- **Family planning/birth control.** Are you considering pregnancy? If so, are you at your glucose control goal? If not, are you using birth control?

At least annually ask about:

- **Identification.** Do you wear or carry diabetes identification?
- **Complications screening.** Do you know (1) your results on screening tests? (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 for insulin.** Do you rotate your injection sites around your abdomen and inspect sites?

Table 9. How to Use a Monofilament

| | |
|---|--|
|  <p>The diagram shows two line drawings of a human foot. The left drawing is labeled 'Bottom' and shows the sole of the foot with five circles indicating testing sites: one on the heel, one on the ball of the foot, and three on the forefoot. The right drawing is labeled 'Top' and shows the top of the foot with one circle on the first metatarsal head and one circle on the fifth metatarsal head.</p> | <ul style="list-style-type: none"> • Show the monofilament to the patient. Place the end of the monofilament on his/her hand or arm to show that the testing procedure will not hurt. • Ask the patient to turn his/her head and close his/her eyes or look at the ceiling. • Hold the monofilament perpendicular to the skin. • Place the tip of the monofilament on the sole of the foot. Ask the patient to say 'yes' when s/he feels you touching his/her foot with the monofilament. DO NOT ASK THE PATIENT 'did you feel that?' • If the patient does not say 'yes' when you touch a given testing site, continue on to another site. When you have completed the sequence, RETEST the area(s) where the patient did not feel the monofilament. • Push the monofilament until it bends, then hold for 1-3 seconds. • Lift the monofilament from the skin (Do not brush or slide along the skin). • Repeat the sequence randomly at each of the testing sites on each foot. |
|---|--|

Clinical Problem and Current Dilemma

Prevalence. Type 2 diabetes is a common condition, affecting 2–3% of the population overall, and up to 20–25% of the elderly population. Type 2 diabetes typically occurs in patients who are over 30 years old and weigh \geq 120% of ideal body weight. Conversely, type 1 diabetes occurs in patients under 30 who weigh $<$ 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 2 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. Optimizing blood pressure has the most impact on preventing macrovascular complications and is the most cost-effective intervention for diabetes. Moderate dose statins in all patients with diabetes age \geq 40 or LDL \geq 100 mg/dL has been shown to decrease macrovascular complications. 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, especially diabetic retinopathy, but the effect of glycemic control on cardiovascular disease remains uncertain. Minorities have a prevalence of type 2 diabetes mellitus that is 2 to 6 times greater than that of Caucasians. The morbidity and mortality are higher for minorities than for Caucasians. 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 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, standards for self-management education and patient goals.

Rationale for Recommendations

Diabetes Diagnosis, Screening, and Prevention

Diagnosis. The American Diabetes Association (ADA) recommendations for the diagnosis of diabetes include a

fasting glucose level greater than or equal to 126 mg/dL (7.0 mmol/l), confirmed on a separate day. Diabetes may also be diagnosed on the basis of symptoms (polydipsia, polyuria, unintentional weight loss) and elevated glucose level (\geq 200 mg/dL), but should be confirmed on a separate day by a fasting glucose \geq 126 mg/dL.

The oral glucose tolerance test (OGTT) is a reasonable diagnostic alternative, and in the view of many experts remains the diagnostic test of choice; however, it is somewhat limited by concerns about inconvenience for patients. A 2-hour glucose level of 200 mg/dL or greater is considered diagnostic for type 2 diabetes.

At this time, the ADA does not recommend the use of HbA1c for the diagnosis of diabetes, in part due to lack of standardization of the assay, and in part due to concerns about test sensitivity.

Screening for diabetes. The population burden of type 2 diabetes continues to increase due to the changing demographics and increasing obesity of the US population. Furthermore, type 2 diabetes often has a long (up to 10 year) pre-symptomatic phase, and national studies suggest that as many as 1/3 of subjects with type 2 diabetes are unaware of the disease. As a result, many experts feel that screening may be beneficial for the US population. However, the studies of screening do not clearly suggest that screening will lead to significant improvements in diabetes outcomes; therefore the effectiveness (or cost-effectiveness) of screening on a population-wide basis is not clear.

Individuals with hypertension ($>135/80$) should be screened for diabetes (USPSTF level B recommendation). In adults who have hypertension and diabetes, lowering blood pressure below conventional target values reduces the incidence of cardiovascular events and cardiovascular mortality. The optimal screening interval is not known, but the ADA (based on expert opinion) recommends a 3-year interval. [Text in italics added 10/10/08]

Women who have had gestational diabetes mellitus (GDM) should be screened for diabetes, as about 50% of these women will have DM within 10 years of having GDM. While the long-term benefits of earlier diagnosis in this population are uncertain, both expert opinion and the epidemiology of diabetes post-GDM support screening. The optimal test for screening in this group is not clear. Screening may be performed with either a 2 hour, 75 gram oral glucose tolerance test (OGTT) or fasting plasma glucose (FPG). Although the initiation and frequency of screening are debated, a general recommendation is to screen sometime after the 6–week postpartum visit, then with either FPG regularly (e.g., yearly) or OGTT every three years. [Text in italics added 10/10/08]

Screening other at-risk subjects (e.g., those with obesity, family history, and high-risk ethnic minorities) may be reasonable, although few studies have examined the benefits of screening, even in high risk groups, and the optimal frequency of this type of screening remains

uncertain. Based on expert opinion the ADA currently recommends that screening be considered at 3-year intervals beginning at age 45, particularly in those with a BMI \geq 25 kg/m². The ADA also suggests considering earlier or at more frequent screening for those with other risk factors, including family history, physical inactivity, minority ethnicity, previously identified impaired fasting glucose or impaired glucose tolerance, a history of HDL cholesterol \leq 35 mg/dL, and/or a triglyceride level of \geq 250 mg/dL, polycystic ovarian disease, or a history of vascular disease. *Lifestyle modification and metformin have both been shown to reduce the progression of pre-diabetes to diabetes. Screening may also identify patients with previously unrecognized diabetes. The effect of such screening on long-term diabetes-related morbidity and mortality is currently being examined in clinical trials.* [Text in italics added 10/10/08]

If a provider elects to screen for diabetes, the tests outlined in the “diagnosis” section should be used (see Table 1).

One possible additional benefit of screening for diabetes is the identification of people with impaired fasting glucose or impaired glucose tolerance. These people carry substantially increased risks of developing atherosclerotic disease, and have a high risk of developing diabetes (about 5% per year). Those with a fasting glucose of 100-125 mg/dL, a random glucose of 130-199 mg/dL, or a 2-hour OGTT of 140-199 mg/dL are considered at risk for diabetes.

Diabetes prevention. Several clinical trials have now demonstrated that interventions can delay or prevent the development of type 2 diabetes. Studies from China, Finland, and the United States have shown that diet (7% reduction in body weight) and exercise (150 minutes of brisk walking per week) can reduce the risk of progression from impaired glucose tolerance (IGT) to diabetes by 42-58%. A trial of metformin 850 mg twice daily demonstrated a 31% risk reduction in progression from IGT to diabetes. A trial of acarbose 100 mg TID demonstrated a 25% risk reduction in progression from IGT to diabetes. The DREAM study also showed that rosiglitazone can delay or prevent progression from impaired fasting glucose (IFG) or IGT or both to diabetes by about 60%. These studies suggest that a pharmacologic approach to diabetes prevention may also be feasible, although lifestyle modification is still considered preferable by most experts.

Cardiovascular Disease

Screening and prevention should address cardiovascular risk factors.

Hypertension. Hypertension (HTN) is the predominant predictor of adverse events in patients with type 2 diabetes. Treatment of blood pressure reduces risks of major cardiovascular events such as myocardial infarction, stroke, or cardiovascular death, and also reduces the risk of microvascular outcomes such as visual loss, photo-coagulation for retinopathy, and the development of end-

stage renal disease. Aggressive treatment of HTN in patients with type 2 diabetes should be a high priority for clinicians.

The majority of patients with diabetes and HTN have essential hypertension. 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.

Blood pressure should be measured at all clinic visits for patients with diabetes, and treatment is more aggressive than for patients without diabetes. If diastolic blood pressure is \geq 80 mmHg or systolic blood pressure is \geq 135 mmHg on two visits, antihypertensive therapy should be instituted (Tables 2 and 3). Lifestyle modification with dietary alteration, exercise, and weight loss should be advocated. However, expert opinion from The Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) recommends that in patients with diabetes, lifestyle measures should nearly always be augmented by pharmacologic therapy.

The goals for blood pressure treatment in diabetes have been evaluated in several randomized trials. For diastolic blood pressure, it is clear that a target of 80 mmHg provides marked benefits. Systolic blood pressure has not been evaluated as rigorously; few studies have targeted or achieved systolic pressures below 140 mmHg. However, the available data suggest that a systolic target of 135 mmHg is reasonable, and more aggressive control may be warranted, particularly in patients with renal disease. Some organizations, including the National Committee of Quality Assurance, which establishes the Health Plan Employer Data and Information Set (HEDIS), and the ADA promote a systolic pressure below 130 mmHg, but there are no data from Randomized Controlled Trials to support this.

There is much confusion over the choice of first-line antihypertensive drugs for patients with diabetes. In the ALLHAT trial, the largest and most representative direct drug-vs.-drug comparison to date, a strategy beginning with a thiazide diuretic reduced myocardial infarction as much as, and stroke and congestive heart failure more than, strategies beginning with other agents. That result held across all subgroups, including patients with diabetes. Angiotensin-converting enzyme (ACE) inhibitors reduce progression of diabetic renal disease. Evidence is conflicting in regard to whether ACE inhibitors have beneficial effects beyond blood pressure. Angiotensin II receptor blockers (ARBs) probably provide blood pressure benefits similar to ACE inhibitors, but evidence thus far is still limited. ARBs have more clear evidence than other agents that they are effective in preventing progression of established renal disease (see “nephropathy” below). ACE inhibitors in presence of microalbuminuria are recommended as first-line therapy. Calcium-channel blockers and beta-blockers are also effective agents, but should probably be added after thiazides and ACE/ARB (see Table 3). Other classes of agents have not been as

rigorously evaluated in patients with diabetes. We would not encourage the use of alpha-blockers as they appear to deliver less improvement in outcome than other agents.

Low-dose thiazide diuretics (e.g., 12.5 to 25 mg of hydrochlorothiazide) do not appear to have clinically important 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, so thiazides should be used at low doses. Patients with coronary disease or congestive heart failure (CHF) should receive beta-blockers unless a clear contraindication exists. Beta-blockers may decrease high density lipoprotein (HDL) and increase triglyceride levels, and in one major trial beta-blockers were more frequently discontinued, led to more weight gain and higher doses of glucose-lowering agents than ACE inhibitors. If a beta-blocker is used, it should be cardioselective to minimize side-effects. Patients with CHF or coronary disease with diminished left ventricular function should receive an ACE inhibitor, or an ARB if ACE inhibitors is are tolerated. ACE inhibitors can lead to cough. ACE inhibitors and ARBs can lead to renal insufficiency and hyperkalemia; careful monitoring of serum electrolytes is therefore warranted with these agents.

Regardless of initial agent, most patients with type 2 diabetes will require multiple agents in order to achieve their blood pressure goal. Indeed, many patients will not achieve their goal even with the use of 3 or 4 agents.

Lipid screening and treatment. Hyperlipidemia is common in patients with type 2 diabetes; characteristically, they have elevated triglyceride levels, while HDL levels are low, and LDL levels are typically normal or elevated. Given the high prevalence (up to an 80% lifetime risk) of vascular disease in patients with diabetes, the National Cholesterol Education Program (NCEP) suggests that diabetes should be considered a cardiovascular disease equivalent.

Optimal screening and follow-up intervals for cholesterol testing have not been evaluated in patients with type 2 diabetes. Expert opinion suggests that annual testing is reasonable for screening purposes, with more intensive testing reserved for those who are being actively managed.

Treatment goals for various types of cholesterol abnormalities have been evaluated with differing levels of rigor. Most of the literature is focused on LDL cholesterol. In a meta-analysis of available studies, there were consistent effects of HMG Co-A reductase inhibitors ("statins") in reducing the risk of cardiovascular events. However, few studies have established a specific LDL target level. Expert opinion from the NCEP suggests an LDL target of 100 mg/dL. However, recent studies have suggested that patients with diabetes benefit regardless of starting LDL level (even if baseline LDL levels are less than 100 mg/dL); it could therefore be argued that putting most patients with diabetes on moderate dose statins, (e.g.,

simvastatin [generic] 40 mg/d or lovastatin [generic] 40-80 mg/d) without specific LDL targets, is a viable strategy. For secondary prevention, essentially all patients with diabetes should be on statins. For primary prevention, younger patients who are otherwise at lower risk may receive less benefit. Trials have not firmly established an age threshold for initiating therapy, but delaying use until age 40 may be reasonable if patients do not have other cardiovascular risk factors as statin use in this population is marginally cost-effective (~\$80,000 per Quality Adjusted Life Year [QALY]).

Low HDL levels are also a known cardiovascular risk factor. One well-conducted RCT has shown that gemfibrozil is effective in reducing cardiovascular events in patients with diabetes, an HDL of 40 mg/dL or less, and an untreated LDL of 140 mg/dL or less. There are no data on whether combination therapy with statins and fibrates improves cardiovascular outcomes. At this point, we would favor the use of statins over fibrates as first-line agents in patients with diabetes.

In patients with diabetes, observational data suggest that triglycerides are also an independent risk factor for the development of atherosclerotic disease. However, there are very limited trial data evaluating the effectiveness of lowering triglycerides on cardiovascular outcomes. There are preliminary data suggesting that fibrates can reduce angiographic disease progression, but no long-term outcome data are available. The first-line of treatment for hypertriglyceridemia is optimization of glucose control. Fibrates can be used if triglycerides remain elevated, although again we would favor the empiric use of statins given the stronger outcome data. If triglycerides are markedly elevated (e.g., over 1000 mg/dL), then treatment may be warranted to avoid pancreatitis. If triglyceride levels are between 500 mg/dL and 1000 mg/dL, treatment may be considered to avoid other adverse outcomes.

The effectiveness of combination therapy with statins and fibrates has not been reported, although there are ongoing trials to assess safety and effectiveness. If providers do elect to use combination therapy, careful monitoring of liver function tests and for symptomatic myopathy is warranted until long-term safety data is available.

Aspirin. People with diabetes receive the same cardiovascular protection from aspirin as patients without diabetes. The ADA recommends use of aspirin in all patients with diabetes who have known coronary artery disease; in those 40 or older; or in those who are younger than 40 and have additional cardiac risk factors. However, the clinical trial data do not clearly support specific age cutoffs for those with diabetes. An alternative recommendation, particularly for those at risk of adverse effects, is that aspirin be used in those with a risk of cardiovascular disease greater than 3% in five years. Nearly all patients with diabetes who are 50 and older will meet these criteria.

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 patients to stop smoking. 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. Retinopathy and macular edema affect a substantial proportion of patients with type 2 diabetes. Between 10 and 30% of subjects have retinopathy at the time of diabetes diagnosis, and most will eventually develop some level of retinopathy. Severe retinopathy requiring treatment is somewhat less common, but still makes diabetes one of the leading causes of visual loss in US adults. Prevention of retinopathy is best achieved by optimizing blood pressure and glucose control.

Dilated retinal examination reduces the incidence of severe visual loss by allowing timely treatment (laser photocoagulation) of proliferative retinopathy and macular edema. Optimal screening intervals for retinopathy depends on the risk of the individual patient. Patients who have been diagnosed with retinopathy should be screened at least annually, and many will require much more frequent examination depending on the degree of retinal abnormality. Patients have a low risk of developing retinopathy requiring treatment over the short term if they (a) have no retinopathy on a baseline retinal exam by an expert and (b) have reasonable glucose and blood pressure control. These patients can be screened less frequently, at 2 to 3 year intervals. For measuring quality of care for diabetes, the HEDIS interval for retinal examinations is biannually for patients with previous normal eye exam and at least annually for patients with abnormal eye exam.

Unless the primary caregiver has been specifically trained to perform dilated diabetes eye examinations, the accuracy of fundoscopic examination is poor. Thus, all screening should be performed by a trained eye-care professional. 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 1 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. Albuminuria is defined as protein excretion greater than 300mg/day. Patients who are taking an ACE-I or ARB or who have a

diagnosis of diabetic nephropathy do not require yearly screening for 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. If screening microalbumin is >30 mg/dL, check UA to assess for other causes.

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, patients with diabetes with a creatinine of 2-2.5 mg/dL with or without nephrotic range proteinuria should be referred to a nephrologist for evaluation for other causes of nephropathy and for discussion of potential treatment options.

Dietary protein restriction has been proven to be beneficial in patients with type 1 diabetes with proteinuria. This has not been clearly proven in patients with type 2 diabetes. 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. ARBs show similar benefits to ACE inhibitors in patients with type 2 diabetes and microalbuminuria and diabetic nephropathy. Direct comparisons between ACE inhibitors and ARBs have not been performed in patients with type 2 diabetes, there is however better evidence in the literature for protection against progressive diabetic nephropathy with an ARB and therapy with an ARB continues to show benefit even up to the development of end stage renal disease. An ACE inhibitor or an ARB should be used in all patients with microalbuminuria. If proteinuria continues to increase, combining an ACE with an ARB should be considered as combination therapy appears to be more effective than either alone.

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 dihydropyridine class of calcium channel blockers (e.g., nifedipine, felodipine) may increase urinary albumin excretion, and should be avoided in patients with microalbuminuria.

In all cases, aggressive control of blood pressure is mandatory, with an ideal target being less than 135/80 mmHg. In non-hypertensive 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.

Neuropathy. Optimal glycemic control can prevent diabetic 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. There are three simple tests to detect peripheral neuropathy: Pressure sensation, vibration sensation and temperature/pain perception.

Diabetic foot examination and care. At each regularly scheduled diabetes visit, all patients need foot inspection. Inspection should identify 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; most insurance plans including Medicare cover therapeutic footwear for patients with diabetes. For others with less deformity, athletic shoes with sufficient room for the toes and forefoot and cushioned socks are appropriate.

Monofilament testing. Sensory testing with a 5.07 (10g) nylon monofilament should be done yearly to identify sensory loss. Instructions on "How to Use a Monofilament" are in the Figure. Individuals with insensitive feet are considered to be at high risk of developing ulcers and other related complications. Education regarding appropriate foot care should be emphasized regularly. For patients with mechanical deformities, customized shoes and/or orthotics have been shown to reduce the new foot problems.

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 painful peripheral neuropathy. Optimizing glycemic control is of paramount importance in slowing the progression of established diabetic neuropathy.

- Nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs may be helpful as first-line agents in treating painful peripheral neuropathy. Exercise caution when using NSAIDs in combination with ACE inhibitors or aspirin. NSAIDs can reduce the efficacy of ACE inhibitors, may lead to increased blood pressure, may be

associated with increased cardiovascular events, and can precipitate acute renal failure in patients with impaired renal function. Some NSAIDs may also interfere with the anti-platelet activity of aspirin.

- Tricyclic antidepressants (TCAs). TCAs started at low doses at bedtime may also be used as therapy in patients with painful neuropathy. They can be titrated to maximize pain relief while minimizing side effects.
- Other antidepressants. Duloxetine, a norepinephrine and serotonin reuptake inhibitor, has been shown relieve painful neuropathy. Serotonin Slow-Reuptake Inhibitors (SSRI's) and trazodone, while used to treat diabetic neuropathy, are not felt to be as effective.
- Anti-seizure medications. These medications may be helpful.
 - Gabapentin has been shown to alleviate painful diabetic neuropathy. Its efficacy is similar to amitriptyline and while it has significantly fewer side effects it is considerably more expensive.
 - Carbamazepine has been used successfully to treat painful diabetic neuropathy. It has potentially severe side effects and monitoring blood counts and serum levels of carbamazepine is recommended.
 - Lamotrigine has been shown to relieve painful diabetic neuropathy.
 - Pregabalin has been shown to relieve neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Other Agents. Several other agents might help.
 - Capsaicin cream may be a useful adjunct in patients whose pain is not adequately controlled by TCA, particularly in those with severe contact dyesthesias.
 - Tramadol is a weak opioid with an additional monoaminergic activity and has shown efficacy in treatment of painful diabetic neuropathy.
 - Dextromethorphan (an N-methyl -d- aspartate antagonist) has shown promise in preliminary efficacy studies.
 - ACE inhibitors have shown modest benefits in treating peripheral neuropathy.
 - Narcotics may be considered if the above agents are ineffective.
- Acupuncture. Several studies have shown the efficacy of using traditional acupuncture for the treatment of painful diabetic neuropathy. Transcutaneous Electrical Nerve Stimulation has also been evaluated for the treatment of peripheral neuropathy, and has been shown to reduce lower extremity pain associated with diabetic peripheral neuropathy.

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 that 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, 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.

Common Comorbidities

Diabetes may be associated with an increased prevalence of several comorbid conditions.

Coronary artery disease. Diabetes increases an individual's risk of coronary artery disease. Identifying such patients is important and cardiovascular risk factors should be assessed annually. These risk factors include hyperlipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of micro- or macroalbuminuria. In patients without suggestive symptoms a risk factor-based approach is useful. Candidates for screening exercise stress (electrocardiogram [ECG]) testing include those with 1) typical or atypical cardiac symptoms; 2) an abnormal resting ECG; 3) a history of peripheral or carotid occlusive disease; 4) sedentary lifestyle, age >35 years, and plans to begin a vigorous exercise program; or 5) those with two or more risk factors noted above.

Autonomic neuropathy and cardiovascular disease. Although less common in type 2 than type 1 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 and consideration should be given to risk assessment and stress testing.

Depression. Screening should also address depression. Recent meta-analyses and reviews of RCTs indicate that depression is twice as common among people with diabetes. Depression is associated with hyperglycemia and decreased self-care behaviors, such as medication-taking and meal planning. All patients with diabetes should therefore be evaluated for depression. Successful treatment of depression is associated with improved glycemic control. Better glycemic control is associated with improved quality of life, vitality and fewer days missed from work.

Screening questions for depression from the PHQ-2 are "Over the past month, have you been bothered by: (a) little interest or pleasure in doing usual things? (b) feeling down, depressed or hopeless?" If the patient indicates yes to either question, further assessment is needed with standardized tools such as the full PHQ-9 (see UMHS clinical guideline on depression for PHQ-9 questionnaire and references), Zung Depression Scale or the Center for Epidemiologic Studies Depression Scale.

Cognitive dysfunction. Epidemiological evidence indicates an association between diabetes and cognitive dysfunction but the quality of these studies is poor and no firm conclusions were reached in a recent metanalysis.

Immunizations. Annually provide an influenza vaccine to all patients with diabetes 6 months of age or older.

Provide at least one lifetime pneumococcal vaccine for adults with diabetes. A one-time revaccination is recommended for individuals 65 years of age or older who were previously immunized when they were younger than 65 years of age if the vaccine was administered more than 5 years ago. Other indications for repeat vaccination include nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as post-organ transplantation.

Glycemic Control

HbA1c is an accurate measurement of long-term glycemic control. Current recommendations are that HbA1c be checked at least every 6 months if the patient is well controlled (HbA1c < 7%) and on a stable hypoglycemic regimen, otherwise every 3 months.

Improving blood glucose control leads to reductions in the risk of microvascular diabetes complications such as retinopathy and nephropathy. However, these improvements must be sustained for many years (about 10 years in the major trial of glucose lowering) before advantages in outcomes are apparent. Targets for glucose control should be based upon HbA1c levels. In general, this target should be 7.2%, although lower targets will lead to further (albeit small) improvements in outcomes. However, targets should be discussed with patients, and providers should weigh patient-specific factors when considering glycemic goals (see Table 4). Factors that may modify target levels include limited life expectancy (advanced age or significant comorbidity), advanced diabetes complications, a history of being unaware of hypoglycemia, or limitations in the ability to carry out a treatment regimen (e.g., financial constraints, unwillingness to take insulin therapy).

Since type 2 diabetes is typically a progressive disease, glycemic control often deteriorates over time. Providers should expect that medication requirements will increase with duration of disease. Combining different classes of oral agents is often effective in improving blood glucose control. Combinations of oral agents and basal insulin preparations (e.g., insulin NPH, glargine) may also be effective. These approaches are discussed below.

Glycemic management. In type 2 diabetes, diet and exercise remain first line therapies. If a patient does not show improvement in glycemic control within one month, or does not achieve glycemic goal within three months, pharmacologic therapy should be instituted. Tables 5 and 7 summarize available oral agents and injectables for the management of type 2 diabetes and their costs. Even after instituting pharmacologic therapy, careful attention should still be given to diet and physical activity.

Self-monitoring of blood glucose is recommended for patients with *insulin-treated* type 2 diabetes, with the frequency individualized to need. Self-monitoring of blood glucose may be useful for patients with type 2 diabetes on *oral agents*, but the value of regular monitoring has not been established.

Metformin. Metformin is often selected as a first-line pharmacologic treatment for patients with type 2 diabetes initiated at diagnosis along with lifestyle interventions. Metformin may be especially useful for patients who are overweight (greater than 120% of ideal body weight for age and gender) or dyslipidemic (triglyceride level greater than 600 mg/dL). Also, metformin, as a single agent, does not cause hypoglycemia. Gastrointestinal side effects, including diarrhea, are seen in up to 30% of patients; a beginning dose of 500 mg metformin per day usually reduces these side effects. Metformin XR formulation may decrease diarrhea compared to the immediate release. The dosage may be increased by 500 mg per week to 2000 mg per day as 2 or 3 divided doses. Metformin therapy should be considered inadequate if the patient has not achieved his or her glycemic goal after four weeks of therapy at a maximum dose. Metformin should be avoided in patients with reduced creatinine clearance or at risk for acidosis (e.g. cirrhosis or CHF). It should be withheld in clinical settings such as IV contrast administration, surgery, or dehydration.

Sulfonylureas. Sulfonylureas may also be used as first line agents in type 2 diabetes. Patients are typically 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 glycemic goal after four weeks of therapy at a maximal sulfonylurea dose, sulfonylurea therapy should be considered inadequate.

Thiazolidinediones. The thiazolidinediones (TZD) reduce insulin resistance and lower blood glucose levels by improving sensitivity to insulin in muscle and adipose tissue. These medications may take up to 4 weeks before seeing improvements in glycemic control. TZDs reduce both glucose and insulin levels, and do not cause hypoglycemia when used as single agents (or in combination with metformin). If a TZD is indicated, the available evidence would suggest pioglitazone is preferable over rosiglitazone, due to possible increased risk of myocardial infarction with rosiglitazone. Both TZDs are associated with fluid retention and peripheral edema, which occur in at least 15% of patients. The FDA has issued a black box warning for TZDs due to an increased risk of congestive heart failure (CHF); therefore these drugs should be avoided in patients with significant CHF. TZDs have also been noted to worsen diabetic macular edema. Although few cases of hepatotoxicity have been reported with currently available thiazolidinediones, the FDA recommends that all patients started on thiazolidinediones have ALT levels evaluated prior to the initiation of therapy, and periodically thereafter per clinical judgment.

Alpha-glucosidase inhibitors. Alpha-glucosidase inhibitors may also be used as monotherapy in conjunction with diet 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 initial dose is 25 mg three times a day and should be taken with the first bite of each meal. Gastrointestinal side effects including abdominal pain, flatulence, and diarrhea are common. These effects usually diminish over time (4-8 weeks), but 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.

Non-sulfonylurea insulin secretagogues. These medications may reduce the risk of hypoglycemia in the event of skipped or delayed meals, but require more frequent dosing and are more expensive than sulfonylureas.

Dipeptidyl peptidase-4 (DPP-4) inhibitor. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones that stimulate insulin secretion and suppress glucagon. These incretin hormones are rapidly degraded by DPP-4. Sitagliptin (Januvia®) enhances the effect of these incretin hormones by inhibiting DPP-4. Sitagliptin is approved for use in patients with type 2 diabetes as monotherapy or adjunctive therapy in combination with metformin, a sulfonylurea, or a thiazolidinedione. The usual dose for Sitagliptin is 100mg daily with dosage adjustments for renal insufficiency (50mg for CrCl \geq 30 to < 50 ml/min; 25mg for CrCl < 30 ml/min). Post-marketing reports of hypersensitivity reactions have been noted.

Combination oral therapy. Each class of oral agents (metformin, insulin secretagogues, thiazolidinediones, and alpha-glucosidase inhibitors) works by a different mechanism, and may therefore be combined to achieve optimal glucose control. Table 6 presents the typical steps in combining oral medications. Typically, patients with type 2 diabetes are started on either metformin or a sulfonylurea, with a second agent added as needed. Thiazolidinediones, insulin, or exenatide (Byetta) may be added as a third line agent. In general, the addition of an oral agent will reduce HbA1c by an additional 1.0%. Patients who require additional therapy will need to begin insulin (see below). At this point, one or more of the oral agents may be discontinued. However, no consensus exists as to which (or how many) oral agents should be stopped. (see Table 6 for suggestions).

Tablets combining two classes of oral agents are now available. See the bottom of Table 5 for examples. At maximum doses the number of combination tablets a patient takes per day is about the same as the number of tablets for agents separately. Combinations offer less dosing flexibility but cost is not necessarily greater compared to single-agent tablets.

Combination oral/insulin therapy. Patients with type 2 diabetes who do not have adequate glucose control on oral

agents will need to start insulin therapy (see bottom of Table 6). The addition of bedtime NPH remains a traditional approach. However, therapy with once daily Lantus has become increasingly popular due to its lack of an insulin peak and its near 24-hour duration of action. Therapy may be intensified as needed with twice daily split/mixed insulin, three times daily insulin therapy, or multiple daily injections to achieve glycemic goals.

Insulin. Insulins are categorized by their duration of action (see Table 7). Rapid acting insulins (Lispro [Humalog], Aspart [NovoLog], Glulisine [Apidra]) or short-acting insulin (Regular) are used in conjunction with meals or to treat acute episodes of hyperglycemia. Since the onset and duration of rapid acting insulins are more physiologic than Regular insulin, most experts now prefer their use. However, in type 2 patients, Regular insulin would be an appropriate choice and cost effective.

Intermediate insulins (NPH and Detemir [Levemir]) are typically given twice daily. An AM dose provides for daytime basal insulin requirements, and the post-lunchtime peak of action may reduce the need for short-acting insulin at lunchtime. A PM dose, often given at bedtime, is titrated to fasting blood glucoses, while avoiding nocturnal hypoglycemia.

Long acting insulin, Glargine (Lantus) has a duration of action of nearly 24 hours, and can be used as a ‘basal’ insulin in both type 1 and type 2 diabetes.

Mixtures of NPH and short acting insulins are available in many forms. The two mixtures most frequently used by diabetes specialists are 75/25 NPL/lispro (Humalog mix) and 70/30 NPH/aspart (Novolog mix). Twice daily injections (before breakfast and supper) of these mixtures may provide good control for patients with type 2 diabetes. However, their use is rarely successful in patients with type 1 diabetes.

Exubera was the first inhaled insulin approved for adults with type 1 and type 2 diabetes. Although Exubera was found to be as effective as short-acting insulin injections there was little interest in using it by patients or physicians for several reasons including the large size of the inhaler device, the need perform pulmonary function testing prior to initiating and during treatment, the limited amount of insulin supplied with inhalation, and prohibitions on its use in patients who are smoking or stopped smoking less than six months previously. Given these barriers, Pfizer, the manufacturer, elected to stop producing Exubera.

Other injectables. Other injectables include exenatide (Byetta) and symlin.

Exenatide (Byetta) is an incretin mimetic agent approved for type 2 diabetes. It is typically used with metformin or sulfonylurea or both. It enhances insulin release in presence of hyperglycemia, slows the gastric absorption of glucose and suppresses appetite which can lead to weight loss in overweight individuals. The most common side

effects are nausea and vomiting. The incidence of these side effects decreases with continuation of therapy.

Symlin is an amylinomimetic agent approved as adjunct therapy in patients with type 1 and type 2 diabetes who use mealtime insulin but who are not achieving optimal control. Symlin is used at mealtimes to augment the effects of insulin on glycemic control. This can cause severe hypoglycemia which can occur within 3 hours after a symlin injection. Symlin and insulin should never be mixed. Symlin can also suppress appetite and lead to weight loss. Nausea is the most common side effect but improves with time in most patients.

Diabetes self-management. Diabetes self-management refers to all of the activities in which patients engage to care for their diabetes, promote health, augment physical, social and emotional resources and prevent long and short-term effects from diabetes. Diabetes self-management education (DSME) is the essential first step in becoming an effective self-manager. DSME is designed to help patients make informed decisions and evaluate the costs and benefits of those choices. Table 8 summarizes self-management topics that clinicians should address at each visit and annually. Appendix A lists useful handouts available over the internet for patient education.

DSME has evolved from primarily traditional, didactic programs based on information-transfer and compliance or adherence as outcomes, to more patient-centered, empowerment based approaches to education. Recent findings related to DSME include:

- Diabetes self-management education is effective for improving psychosocial and health outcomes.
- Diabetes self-management education is effective for improving HbA1c and other outcomes among people with type 2 diabetes, especially in the short-term. Greater time with the educator increases the effects.
- Traditional knowledge based DSME is essential but not sufficient for sustained behavior change.
- No single strategy or programmatic focus shows any clear advantage, but interventions that incorporate behavioral and affective components are more effective.
- Effective DSME is tailored to the patient’s preferences, social and cultural situation.
- DSME is most effective when coupled with appropriate care and reinforcement by all health care professionals.

While patients need DSME, it is unreasonable to believe that a one-time educational program will be adequate to manage diabetes for a lifetime. Self-management support is defined as the on-going assistance and resources patients need in order to make self-management decisions and sustain behavioral changes. Office-based practices providing multiple interventions in which patient education was included or the role of the nurse was enhanced reported favorable outcomes. Organizational interventions that improve diabetes self-management include computerized

tracking systems, regular recall and review of patients by nurses, the addition of patient-centered educational and counseling approaches, and behavioral goal-setting. Effective strategies to incorporate on-going self-management support include the use of case or care managers, use of information technologies, and group or cluster visits.

Diabetes self-management behaviors are affected by the psychological status of the patient. In the DAWN study, a large majority of the patients reported a high level of distress at the time of diagnosis, including feelings of shock, guilt, anger, anxiety, depression and helplessness. Many years after diagnosis, problems of living with diabetes remained common, including fear of complications and immediate social and psychological burdens of caring for diabetes. Forty-one percent of patients reported poor well-being, however only 10% reported receiving psychological treatment.

DSME is increasingly available through group programs and reimbursement structures are more available. DSME programs that achieve Certification from the Michigan Department of Community Health are reimbursable by Medicaid and state regulated health plans, including many Managed Care Organizations. A list of these programs is available at www.Michigan.gov. In addition, DSME programs that are recognized by the American Diabetes Association are reimbursable by Medicare. A list of these programs by state is available at www.diabetes.org.

Special Considerations

Pre-Conception Counseling

All women with diabetes who are of child-bearing potential should be counseled regarding the increased risks of pregnancy in the setting of diabetes to both mother and fetus. Family planning and contraception should be emphasized, as unplanned pregnancy has an even higher risk of poor outcome. A significantly higher incidence of miscarriage and congenital anomalies occur when maternal HbA1c is elevated in the first trimester. Specific preconception care for women with diabetes who are currently planning pregnancy is of critical importance to achieve optimal outcomes for both mother and baby. Unfortunately, fewer 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 critical importance 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 planning to become pregnant should

be counseled regarding the increased risks of pregnancy. They should be referred to specialists in caring for pregnancy in women with diabetes mellitus. Care will involve counseling regarding the genetics of diabetes, necessary changes in lifestyle of the woman and her family, the critical importance of optimal glucose control before and after conception, and therapies that are appropriate until they become pregnant

Complementary and Alternative Therapies

Individuals with diabetes are using complementary and alternative (CAM) therapies in ever-increasing numbers. Often, the health care provider is unaware of such use, and such interventions may interact with conventional therapy, for example the addition of a glucose-lowering herbal supplement to a sulfonylurea leading to hypoglycemia. The importance of asking individuals which supplements or complementary therapies they use cannot be overemphasized. This information can then lead to a dialogue regarding safety and efficacy issues. A number of traditionally used supplements have shown promise in the treatment of diabetes and are in the process of undergoing large randomized trials. Research studies should continue investigating novel agents for diabetes management.

Supplementation with multivitamins and aspirin is generally considered safe; however, megavitamin therapy should be discouraged. Relaxation therapy, yoga, and spiritual healing are helpful to individuals and can be encouraged. Interventions that are potentially harmful or have no real evidence of efficacy clearly should be discouraged. Patients should be commended, however, on their self-determination and encouraged to direct their efforts in areas that have proven benefits.

Chromium picolinate. This substance is very common nutritional supplement often marketed to individuals with diabetes. Research into supplementation with chromium picolinate has shown variable success in improving diabetic control. The dietary reference intake for chromium is 25 mcg/day. The average US diet contains 15 mcg /1000 Kcal. Chromium picolinate at doses in excess of 1000 mcg daily may positively influence diabetic control. Larger randomized trials are currently in process. However, relatively little data are available regarding side effects or long term toxicity of chromium. The hexavalent form is a known carcinogen although this effect has not been noted for chromium picolinate the trivalent form of chromium, further studies regarding safety are warranted.

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 1 diabetes and frequent hypoglycemia or hyperglycemia or HbA1c level greater than glycemic goal. Patients with type 1 diabetes should be managed by a multidisciplinary team using a regimen of 3-4 insulin injections a day in conjunction with 3-4 times/day self-monitoring of blood glucose.
- 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

Literature Search

The literature search for this update began with the results of the literature searches performed for the previous updates of this guideline. When recent evidence reviews were not available for a topic, new searches of primary literature were performed. For these topics literature searches were conducted on Medline in February 2003. The searches were performed prospectively using the major key words of diabetes mellitus; consensus development conferences, practice guidelines, guidelines, outcomes and process assessment (health care); clinical trials, controlled clinical trials, multicenter studies; English language; and published from 1995 to present. Terms for specific topic searches within the major key words included: alpha-glucosidase inhibitors, thiazolidinediones, nonsulfonyluric secretagogues (repaglinide, nateglanide), new insulins (glargine, aspart, lispro); chromium, nephropathy (screening, treatment), and neuropathy (screening and treatment).

The search was conducted in components each keyed to a specific causal link in a formal problem structure. The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was single cycle. Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data. If randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Team members then identified major evidence searches and major clinical trials performed since that time. The evidence summary and clinical practice recommendations of the American Diabetes Association (ADA) [2004] were the basis for screening recommendations. The topic of impaired fasting glucose tolerance (“pre-diabetes”) was already addressed in a recent literature search and publication by one of the team members. Glycemic control was based on the UKPDS for control value [A] and the ADA recommendations for goal [C]. Life style

modifications (diet, exercise) were based on the UKPDS [A] and DPP [A] studies. Comments about treatment for type 1 diabetes and insulin use are based on the Diabetes control and Complications Trial (DCCT) [A]. Treatment for type 2 diabetes with sulfonylureas and metformin is based on the UKPDS [A]. Screening and treatment of hypertension and lipid levels in type 2 diabetes is based on an evidence review and recommendations performed by the American College of Physicians, which included a member of our team. Screening and treatment for retinopathy were based on a literature review performed by the U. S. Veterans Administration. Recent evidence reviews were not available for the remaining topics.

Related National Guidelines

This guideline generally conforms to:

- American Diabetes Association: Clinical practice recommendations (2004)
- American Diabetes Association: Report of the Expert Committee on the diagnosis and classification of diabetes mellitus (1997)
- American College of Physicians, Clinical Efficacy Assessment Subcommittee: The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus (2003)
- Lipid control in the management of type 2 diabetes mellitus: A Clinical Practice Guideline from the American College of Physicians, Clinical Efficacy Assessment Subcommittee (2004)

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Annotated References

Guidelines

American Diabetes Association. Clinical practice recommendations 2004. *Diabetes Care*. 2004;27(Suppl 1):S1–S140.

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.

Snow V, Weiss KB, Mottur-Pilson C. The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus. *Annals of Internal Medicine* 2003; 138(7): 587-592.

The Clinical Efficacy Assessment Subcommittee of the American College of Physicians oversaw this summary of evidence and recommendations regarding the benefits of tight blood pressure control, target levels for blood pressure, and effectiveness of agents.

Snow V, Aronson MB, Hornbake ER, Mottur-Pilson C, Weiss KB. The evidence base for pharmacologic lipid lowering therapy in the management of type 2 diabetes

mellitus. *Annals of Internal Medicine* 2004; 140(8): 644-649.

The Clinical Efficacy Assessment Subcommittee of the American College of Physicians oversaw this summary of evidence and recommendations regarding the benefits of pharmacologic lipid-lowering therapy in type 2 diabetes.

Some Major Clinical Trials

UK Prospective 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: 837-53.

UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854-65.

These two reports from the UKPDS study are the only long-term trials showing the benefits of glucose control in type 2 diabetes. The findings show that intensive glucose control reduces the risk of early microvascular disease (retinopathy, nephropathy, neuropathy) but does not affect cardiovascular outcomes. The results also suggest that metformin monotherapy is superior to either sulphonylureas or insulin for overweight individuals with type 2 diabetes.

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; 317 (7160) 703-12.

Hansson L., Zanchetti A., Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principle results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group, *Lancet* 1998; 351: 1755-62.

These two studies demonstrated the importance of blood pressure control. UKPDS 38 (and 33, listed earlier) showed that control of hypertension was more important in prevention of macrovascular complications of type 2 diabetes than tight glycemic control.

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

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neuropathic complications, and treatment of hyperglycemia delays or prevents those complications.

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.

The Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle modification or metformin. *N Engl J Med* 2002; 346:393-403.

This report summarizes the proactive prevention of diabetes by treating individuals with borderline high levels of glucose, i.e. those most at risk for continuing on to develop diabetes.

Skovlund SE, Peyrot M on behalf of the DAWN International Advisory Panel: The Diabetes Attitudes, Wishes and Needs (DAWN) program: A new approach to improving outcomes of diabetes care. *Diabetes Spectrum* 2005; 18:136-142.

Peyrot M, Rubin RR, Lauritzen T, Snoek FJ, Matthews DR, Skovlund SE: Psychosocial problems and barriers to improved diabetes management: Results of the cross-national Diabetes Attitudes, Wishes and Needs study. *Diabetic Medicine* 2005; 22:1379-1385.

These two papers summarize the results of the Diabetes Attitudes, Wishes and Needs (DAWN) survey, a cross-sectional international study initiated in 2001 by Novo Nordisk in collaboration with the International Diabetes Federation. The purpose of the survey was to identify a broad set of attitudes, wishes and needs among persons with diabetes and care providers in order to lay a foundation for efforts to improve diabetes care nationally and internationally. Structured interviews were conducted in person or by telephone in 11 regions (representing 13 countries), including the United States. Survey participants consisted of 250 randomly selected generalist and specialist physicians per region (n=2,705), 100 randomly selected generalist and specialist nurses per region (n=1,122) and 250 randomly selected patients with self-reported type 1 diabetes per country and 250 patients with self-reported type 2 diabetes (n=5,104). In general, patients and providers identify a great deal of distress associated with diabetes and its management, but also

identify that our current health care systems and care guidelines do little to address these issues.

Other References

Vijan S, Hofer TP, Hayward RA. Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. *JAMA*. 2000;283:8889-896.

This article evaluates the relative costs and benefits of more versus less frequent screening for retinopathy in patients with type 2 diabetes. For lower-risk patients who do not have retinopathy at baseline, there is little benefit from screening every year versus every 2-3 years.

Amerisource Bergen Item Catalog (3/07) & Blue Cross Blue Shield of Michigan Maximum Allowable Cost (MAC) List (1/2/07).

These sources provide information on pharmaceutical costs.

Appendix A

Patient Education Resources for Diabetes Available on the Internet

(associated with UMHS Clinical Care Guideline Management of Type 2 Diabetes Mellitus)

Patients with diabetes require instruction and reinforcement to promote self-management. Diabetes educators or specially trained nurses or physicians can provide appropriate educational programs and ongoing assistance. In addition to individual instruction, the following handout materials may be helpful when clinicians address specific topics.

Health Topics A-Z (under Patient Education – access from CareWeb References or UMHS internal homepage)

Michigan Comprehensive Diabetes Center (MCDC) www.med.umich.edu/diabetes/patients/educate.htm

American Diabetes Association (under Patient Education – access from CareWeb References or UMHS internal homepage)

To access online patient education [www.diabetes.org], from the internal homepage or from CareWeb references:

- click on Patient Education
- click on Resources (far upper right corner)
- scroll down to “UMHS Endorsed External Sites”
- scroll down to locate the topic Diabetes. Click on the link American Diabetes Association.

On the American Diabetes Association home page [www.diabetes.org], from the menu on the left side of the page

- click on All about Diabetes
- click on Type 2 Diabetes
- click on the third link: Diabetes Learning Center [www.diabetes.org/all-about-diabetes/diabetes-learning-center.jsp]

The following topics and others can be located from this page.

Type 2 Diabetes [www.diabetes.org/all-about-diabetes/chan_eng/i2/i2p1.htm]

Treating Type 2 Diabetes for Life [www.diabetes.org/all-about-diabetes/chan_eng/i12/i12p1.htm]

Eating and Diabetes. [www.diabetes.org/all-about-diabetes/chan_eng/i3/i3p1.htm]

Factors Affecting Blood Sugar [www.diabetes.org/all-about-diabetes/chan_eng/i4/i4p1.htm]

Changing Habits [www.diabetes.org/all-about-diabetes/chan_eng/i7/i7p1.htm]

Emotions and Diabetes [www.diabetes.org/all-about-diabetes/chan_eng/i8/i8p1.htm]

Type 2 Diabetes and Exercise [www.diabetes.org/all-about-diabetes/chan_eng/i11/i11p1.htm]

Diabetes, Heart Disease, and Stroke [www.diabetes.org/all-about-diabetes/chan_eng/i23/i23p1.htm]

Long-Term Complications [www.diabetes.org/all-about-diabetes/chan_eng/i13/i13p1.htm]

National Diabetes Education Program <http://www.ndep.nih.gov/>

ACS Nursing Internal webpage

Internal access only. [www.med.umich.edu/i/acs/nursing/Clinical.practice%20Diabetes.htm]

Appendix B. Insulin Adjustment Protocol

For Pharm.D./RN

Insulin dosage adjustment: target range (< 130 mg/dl)

| | |
|--|---|
| If overnight or before breakfast glucoses are above/below target range, | adjust the supper* or bedtime dose of NPH or Lantus |
| If before lunch glucoses are above/below target range, | adjust the breakfast dose of Regular or Rapid Acting Insulin |
| If before supper glucoses are above/below target range, | adjust the breakfast dose of NPH or adjust the lunch dose of Regular or Rapid Acting Insulin |
| If before bedtime glucoses are above/below target range, | adjust the supper dose of Regular or Rapid Acting Insulin |
| If fasting glucose levels are significantly higher than bedtime levels (i.e., twice as high), consider nocturnal hypoglycemia. Have the patient check glucose level around 3:00am for 2 days during the week. If the glucose levels are: | |
| - normal in the middle of the night, | increase the NPH supper dose |
| - low in the middle of the night, | decrease the NPH supper dose. |

Basic principles:

- Adjust one insulin at a time
- Adjust no more than 10% of the total insulin units per day. Contact physician if an insulin adjustment of greater than 10% of total daily dose is warranted.
- Wait at least 3 days before adjusting further doses.
- Decrease insulin based on unexplained hypoglycemia.

For Patient

For NPH bedtime or Lantus dosing:

| | |
|--------------------------------------|---|
| 3 consecutive morning readings > 130 | increase bedtime NPH or Lantus by 2 units |
| 3 consecutive morning readings > 150 | increase bedtime NPH or Lantus by 4 units |

For NPH twice a day:

| | |
|--------------------------------------|---------------------------------|
| 3 consecutive morning readings > 130 | increase evening NPH by 2 units |
| 3 consecutive morning readings > 150 | increase evening NPH by 4 units |
| 3 consecutive evening readings > 130 | increase morning NPH by 2 units |
| 3 consecutive evening readings > 150 | increase morning NPH by 4 units |