MISSOURI DUReport

Diabetes Mellitus Type 2

According to the American Diabetes Association (ADA), diabetes mellitus (DM) refers to a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Individuals with undiagnosed type 2 diabetes are also at significantly higher risk for stroke, coronary heart disease, and peripheral vascular disease than the non-diabetic population. They also have a greater likelihood of having dyslipidemia, hypertension, and obesity. Type 2 diabetes (DMII), the most prevalent form of the disease, is often asymptomatic in its early stages and can remain undiagnosed for many years. The onset, pathology and prevalence of DM are illustrated in Table 1.

Table 1 – Type 2 DM, Onset, Pathology and Prevalence

	Onset	Pathology	Prev
Diabetes Mellitus Type 1	childhood	Results from cellular-mediated autoimmune destruction of the pancreatic beta cells. Insulin-dependant. Prone to develop Diabetic Ketoacidosis	10%
Diabetes Mellitus Type 2	adulthood (earlier onset becoming more common)	Cellular resistance to insulin. Initially insulin hypersecretion leading to exhaustion of islet cell activity. Initially non-insulin dependant, but can progress to insulin dependence. Less prone to develop DKA, but increasing numbers of cases reported.	90%

Please send comments and suggestions regarding this newsletter to Jayne Zemmer,DUR Coordinator, Division of Medical Services, P.O. Box 6500 Jefferson City, MO 65102-6500

Epidemiology/Prevalence

Approximately 17 million people in the United States, or 6.2% of the population, have diabetes. While an estimated 11.1 million have been diagnosed, unfortunately, 5.9 million people (at least one-third and perhaps as many as 50%) are unaware that they have the disease.

Diabetes is the leading cause of blindness in adults 20 to 74 years of age, the leading cause by category of end-stage renal disease, and is responsible for 67,000 lower extremity amputations each year. Based on death certificate data, diabetes contributed to 209,664 deaths in 1999.

The estimated prevalence of diabetes among adults was 7.4% in 1995; and is expected to rise to ~9% by 2025.

Risk Factors for Disease Development/Prevention

The ADA's list of major risk factors for DM is as follows:

- Family history of diabetes (i.e., parents or siblings with Diabetes)
- Overweight (BMI ≥25 kg/m2, or 23 kg/m2 in Asians)
- Race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
- Habitual physical inactivity
- Previously identified impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
- Hypertension (≥140/90 mmHg in adults)
- HDL cholesterol ≤35 mg/dl (0.90 mmol/l) and/or a triglyceride level ≥250 mg/dl
- History of gestational diabetes mellitus or delivery of a baby weighing >9 lbs
- Polycystic ovary syndrome

All persons over age 45 should be tested for diabetes. Subsequent testing should occur every 3years if the blood glucose level is normal. **Those with risk factors for developing diabetes, as listed above, should be tested more frequently and at an earlier age.**

Prevention or delay of diabetes has been shown to be possible and beneficial for patients; a synopsis of recommendations is below in Table 2**.**

Table 2— Synopsis of Recommendations to Prevent or Delay Diabetes

- Individuals at high risk for developing diabetes need to become aware of the benefits of modest weight loss and participating in regular physical activity.
- Screening: based on current screening guidelines for diabetes, men and women ≥45 years of age are candidates for screening to detect IFG or IGT, particularly those with a BMI ≥25 kg/m^2. Screening should be *considered* in younger individuals with a BMI ≥25 kg/m^2 who have one of the following risk factors: a family history of diabetes, have had gestational diabetes or a baby weighing >9 lb, are not Caucasian, have dyslipidemia, or who have hypertension. In individuals with normoglycemia, rescreening at 3-year intervals is reasonable.
- How to screen: screening should be carried out only as part of a health care office visit. Both an FPG test or 2-h OGTT (75-g glucose load) is appropriate, and positive test results should be confirmed on another day.
- Intervention strategy: patients with IFG or IGT should be given counseling on weight loss as well as instruction for increasing physical activity. Follow-up counseling appears important for success. Monitoring for the development of diabetes should be performed every 1–2 years. Close attention should be given to, and appropriate treatment given for, other CVD risk factors (e.g., tobacco use, hypertension, dyslipidemia). Drug therapy should not be routinely used to prevent diabetes until more information is known about its cost-effectiveness.

Diagnostic Criteria:

Table 3 Criteria for the Diagnosis of Diabetes

1. Symptoms of diabetes and casual plasma glucose (PG) ≥200 mg/dl. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
OR
2. Fasting plasma glucose (FPG) ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 hours.
OR
3. 2-h PG ≥200 mg/dl during an oral glucose tolerance test (OGTT).

Treatment Goals

Growing evidence shows that increases in plasma glucose levels are associated with increases in macrovascular disease risk (e.g., myocardial infarction) beginning at glucose levels within the "normal" range, which is below the threshold for diagnosing impaired glucose control or diabetes mellitus. Microvascular disease is already present in many individuals with undiagnosed or newly diagnosed diabetes. Treatment objectives are to prevent symptoms of hyperglycemia, to prevent long-term microvascular and macrovascular complications (myocardial infarction, stroke, peripheral vascular disease, neuropathy, retinopathy, and nephropathy) and to minimize hypoglycemic events.

Use **ABC**'s approach with patients: **A**1C, **B**lood Pressure, and **C**holesterol, to convey a simple message of parameters to include in goals (target parameters shown in Table 4.

Table 4 – Target Goals for Monitoring Parameters

Parameter	Goal
A1C	= 7 %
LDL Cholesterol	= 100 mg/dl
HDL Cholesterol	= 45 mg/dl
Triglycerides	= 200 mg/dl
Preprandial (or fasting) Blood Glucose	Range = 80 to 120 mg/dl
Bedtime Blood Glucose	Range = 100 to 140 mg/dl
2 hour Postprandial	Range = 100 to 140 mg/dl
Blood Pressure w/o proteinuria	= 130 / 80 mm Hg
Blood Pressure with proteinuria	= 125 / 75 mm Hg, protein > 1 gm/24 hrs

Treatment

Once DMII is diagnosed, Medical Nutrition Therapy with a dietitian's guidance can be used to manage the disease along with an increase in physical activity; oral medication or insulin may or may not be required. Appropriate physical activity will improve insulin sensitivity, glucose tolerance and help maintain or reach ideal body weight.

If DMII cannot be managed through diet and exercise, pharmacological intervention becomes necessary. Most clinicians initiate monotherapy with either a sulfonylurea, a biguanide (metformin), or a meglitinide (repaglinide or nateglinide). Thiazolidinediones (rosiglitazone or pioglitazone), alpha-glucosidase inhibitors (acarbose or miglitol) and insulin are not usually initial therapy.

Primary care providers should take care not to portray insulin use as a "primary treatment failure," because most diabetics will eventually require insulin for control. The "punitive" approach (e.g. "If you don't start your diet and exercise, we're going to have to start you on insulin.") by primary care providers makes patients even more reluctant to start insulin when it is needed.

Please see attached **Addendum 1** for a list of the mechanism of action, precautions, side effects and other important information for the classes of oral anti-diabetic drugs.

Prevention of Long-term Complications

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

While too extensive to be included in this newsletter, detailed information on the standard of care for diabetics, including specific recommendations for the prevention and management of long term complications, along with specific information for children, adolescents, and older adults may be found in the ADA Position Statement: Standards of Medical Care for Patients With Diabetes Mellitus, Diabetes Care 25:S33-S49, 2002 by the American Diabetes Association, Inc., on the web at http://care.diabetesjournals.org/cgi/content/full/25/suppl_1/s33#top

Community Pharmacists as a Resource for Assisting with Implementation of Physician Recommendations - The Asheville Project

Risk reduction is something that is not attainable without prolonged improvement in blood glucose control. Unfortunately this level of control is often associated with high resource, high expense programs. Notably, the 1,400 patient, 10 year, landmark Diabetes Control & Complication Trial (DCCT) stated in their concluding paragraph, "Intensive therapy was successfully carried out in the present trial by an expert team of diabetologists, nurses, dietitians, and behavioral specialists, and the time, effort, and cost required were considerable. Because the resources needed are not widely available, new strategies are needed to adapt methods of intensive treatment for use in the general community at less cost and effort." At two years, the Asheville Project results continue to exceed ADA goals by using "widely available resources" with relatively little "time, effort, and cost."

The City of Asheville, NC agreed to partner with the North Carolina Center for Pharmaceutical Care (NCCPC), a goal of which was to demonstrate the value of utilizing community pharmacists to provide pharmaceutical care services in improving patient care.

Table 5 - Results, The Asheville Project (n = 40)

	Baseline	End of Year 1	End of Year 2
HgA1c (avg.)	7.6%	6.2%	6.8%
Total Cholesterol (avg.)	210mg/dl	198 mg/dl	190 mg/dl
LDL (avg.)	118mg/dl	98 mg/dl	94 mg/dl
City Expenditures	-	$20,000 savings on total healthcare costs	Not reported
Additional days worked	-	6.5 more days/year (savings estimated	Not reported

The primary concern of physicians has been that this was just another group "trying to tell them how to practice medicine," and that it would further "fragment care." It is emphasized that these were local pharmacists, who had received special training by local physician experts, and who were simply acting as an extra set of eyes and ears for the physician. Also of note is that patients already see pharmacists five times more often than any other health care provider and that in this program the participating pharmacists were committing to take time to make that interaction more useful to both the patient and physician. More information on The Asheville Project may be found at http://www.ncpharmacists.org/nccpc/frameset4.html.

Information on the upcoming Missouri Medicaid Disease State management Program may be found at http://www.dss.state.mo.us/dms .

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Addendum 1

Class	Method of Action	Precautions	Side Effects / Miscellaneous
Sulfonylureas Glyburide, Glipizide, Glimepiride are most commonly used. (Several first generation sulfonylureas exist but are seldom used due to more significant hypoglycemic side effects. Examples include acetohexamide, chlorpropamide, tolazamide, and tolbutamine.)	Increase pancreatic beta cell insulin secretion.	All should be administered 30 minutes prior to meals for maximum results; Glyburide comes in a micronized form (glynase) which provides a higher plasma level and more predictable absorption.	Advantages 75% to 90% of DMII patients respond to sulfonylurea therapy. Glipizide should be taken with meals. Glyburide and Glipizide are used as monotherapy; Glimepiride can be used as monotherapy or with metformin or insulin. Disadvantages Increased incidence of hypoglycemia compared with other oral agents. Special Instructions If patient experiences primary failure (fails to respond to initial dose), either increase sulfonylurea or change to a new drug class. If patient experiences secondary failure (fails to respond after initial positive response), then increase sulfonylurea dose or add a new class.* *It is inappropriate to d/c sulfonylurea and begin a new drug class with secondary failure as most studies show no improvement in glycemic control, therefore addition of additional agent is warranted.
Biguanide Metformin	1. Enhances peripheral muscle glucose uptake. 2. Inhibits glucose release from liver. Also induces insulin sensitivity	Should not be used with a serum creatinine = 1.5 in males or = 1.4 in females. Contraindicated in CHF requiring pharmacological treatment. Use with caution with ethanol abuse and hepatic insufficiency. Hold for 48 hours in patients receiving	Advantages When taken alone, metformin does not induce significant hypoglycemia. Can be used as monotherapy or with sulfonylurea or insulin. Disadvantages Can predispose patient to lactic acidosis when other conditions are present which cause a decrease in renal function. Special Instructions

Class	Method of Action	Precautions	Side Effects / Miscellaneous
Meglitinide repaglinide nateglinide	Stimulates insulin release from pancreatic islet cells.	Repaglinide should be used in caution in patients with liver impairment. Quicker onset of action and shorter half-life than sulfonylureas.	Advantages Can be used in combination with metformin. Disadvantages Highly protein bound, the potential for adverse events is increased when administered with other drugs that are highly protein bound (ceftriaxone, clindamycin, diazepam, ibuprofen, indomethacin, nafcillin, naproxen, phenytoin, valproic acid, warfarin). Patients may experience headaches Special Instructions Should be taken 15 minutes prior to meals.
Alpha-glucosidase inhibitor acarbose miglitol	Causes delay in the intestinal breakdown of complex carbohydrates into glucose.	Patients that are started on acarbose will need to limit both complex carbohydrate and alcohol consumption. Contraindicated in inflammatory bowel disease. Use of these drugs may result in weight gain and elevated LDL and HDL cholesterol.	Advantages Acarbose can be used as monotherapy or with sulfonylurea, metformin or insulin. Miglitol can be used as monotherapy or with a sulfonylurea. Disadvantages Significant flatulence. Special Instructions Titrate dose slowly to minimize GI adverse effects.
Thiazolidinediones Rosiglitazone pioglitazone	Lowers blood glucose by improving target cell response to insulin without increasing pancreatic insulin secretion.	If initial LFT's =2.5 times normal these drugs should not be used. Use in caution with CHF; may cause fluid retention.	Advantages Pioglitazone may be used as monotherapy, with a sulfonylurea, metformin or insulin. Rosiglitazone may be used as monotherapy, with a sulfonylurea or metformin.
Combination products Glucovance	metformin and sulfonylurea (glyburide)	When switching patients who are taking each component individually to Glucovance or Avandament choose dose which most closely matches the current individual doses of metformin and glyburide.	Special Instructions With conversion from metformin and glyburide to Glucovance, note that Glucovance contains micronized glyburide, (which differs from the original glyburide), providing a higher plasma level and more predictable absorption.

For recent, in-depth pharmacologic information, see:

- **Oral Antihyperglycemic Therapy for Type 2 Diabetes**
  Scientific Review
  ilvio E. Inzucchi
  JAMA. 2002;287:360-372
- **Oral Antihyperglycemic Therapy for Type 2 Diabetes**
  Clinical Applications
  Eric S. Holmboe
  JAMA. 2002;287:373-376

References

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2. Diabetes Care, Vol. 25, number 1, Jan 2002. 25(Suppl 1): S1-147.
   - *Diabetes Care* 25:S21-S24, 2002
   - *Diabetes Care* 25:S33-S49, 2002
3. Diabetes Care, Vol. 25, number 4, April 2002. 25(4):742-749.
4. Pharmacotherapy, a Pathophysiologic Approach, 5th edition.
5. Drug Information Handbook, 2001-2002 edition.
6. Pharmacist's Newsletter/Prescriber's Letter, Volume 18, Number 180608, June 2002.
7. Pharmacist's Directory, CD Rom, 2002 edition. APA/Roc
8. October 1998 Supplement to *Pharmacy Times*, Online at the North Carolina Center for Pharmaceutical Care Website at http://www.ncpharmacists.org/nccpc/frameset4.html

Table 6-Top 10 Drug Classes Ranked by Paid 10/2001 to 09/2002

DRUG CLASS DRUG	PAID	RX	USER MONTHS	PAID PUPM	PAID RX
Antipsychotis	$106,342,213	629,678	581,816	$182.78	$168.88
Analgesics	$84,724,878	2,073,980	1,868,064	$45.35	$40.85
Antidepressants	$73,878,090	1,277,833	1,282,117	$57.62	$57.82
AntiConvulsants	$51,068,545	711,313	693,577	$73.63	$71.79
Anti-Ulcer	$30,338,358	608,997	607,704	$49.92	$49.82
Antilipemics	$30,257,739	366,903	383,595	$78.88	$82.47
Antihistamines	$25,757,855	638,238	631,980	$40.76	$40.36
Antivirals	$23,389,556	72,908	73,108	$319.93	$320.81
Immmunological/ Biological Agents	$22,910,682	47,722	47,790	$479.40	$480.09
Angiotensin-Modulating	$21,500,043	569,231	584,255	$36.80	$37.77