Diabetes and Vascular Disease

A Continuing Education Monograph

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GOALS

The purpose of this monograph is to educate the community pharmacist on the relationship between diabetes mellitus and atherosclerotic vascular disease, and to empower the pharmacist to play an active role in the prevention and treatment of macrovascular complications.

LEARNING OBJECTIVES

After completing this article, the pharmacist will be able to:

1. Explain the relationship between diabetes mellitus and macrovascular disease.
2. Describe the typical lipid profile present in people with diabetes.
3. Apply principles of diabetes management according to standards of care recommended by the American Diabetes Association.
4. Compare and contrast the various classes of medication for treating hypertension, hyperlipidemia and hyperglycemia.
5. State specific goals for blood pressure, blood glucose, and serum lipids in people with diabetes.

INTRODUCTION

Diabetes mellitus is one of the most common, costly and damaging diseases in the United States. According to 1995 estimates, approximately 16 million Americans have diabetes, half of whom are undiagnosed. Of the eight million diagnosed patients, more than seven million have Type-II, non insulin-dependent diabetes (NIDDM), which usually develops after age 40. Individuals with NIDDM can survive without insulin injections, but may require a special diet, exercise, oral agents or insulin to control their blood glucose levels.

Nearly one million Americans have Type-I, insulin-dependent diabetes (IDDM), which usually presents during childhood, adolescence or early adulthood. Individuals with IDDM require insulin injections to survive.

Diabetes is a chronic metabolic condition in which the body does not properly transfer sugar from the bloodstream to the body's cells for metabolism. The underlying cause of diabetes can be either cessation of insulin production by the beta cells of the pancreas (IDDM), or insufficient insulin production related to insulin resistance at the cellular level (NIDDM). In either case, the resulting elevation in blood glucose levels produces frequent urination, extreme thirst, excessive hunger, lethargy, and a tendency toward weight loss.

The cause of Type-I diabetes is still under intense investigation. The current consensus is that destruction of the insulin-producing beta cells of the pancreas is triggered by an auto-immune defect. Type II diabetes is caused by a combination of hereditary and environmental factors. While a family history of Type-II diabetes greatly increases a person's risk of developing the disease, an unhealthy lifestyle (poor dietary habits, lack of exercise, obesity) plays a major role as well. Type-II diabetes is more common among ethnic minorities (African

Americans, Mexican Americans, Native Americans) than among White Americans.

Uncontrolled diabetes leads to elevated blood glucose levels (hyperglycemia) which, in the short term, can lead to a reduced level of energy and productive capacity. In the long-term, hyperglycemia contributes to a variety of devastating complications.

According to the National Center for Health Statistics, diabetes is the sixth leading cause of death by disease. Total direct and indirect costs of diabetes are estimated at $92 billion annually – representing more than 10% of total health costs in the U.S. Diabetes is the leading cause of new cases of blindness, end stage renal disease and lower limb amputation. Two thirds of people with diabetes have nerve disease with manifestations ranging from chronic pain and numbness in the extremities to impaired digestion and impotency. [1]

MACROVASCLUAR DISEASE AND DIABETES

Cardiovascular disease is two to four times more common in people with diabetes than in non-diabetics, and is present in four out of five diabetes-related deaths. [2] Each year, coronary heart disease and other vascular diseases account for one million hospital admissions among people with diabetes. [7]

The 16-year follow-up to the Framingham study population found that individuals with diabetes, compared to age- and sex-matched non-diabetics, are 1.8 times more likely to have coronary heart disease; 2.4 times more likely to experience a stroke; and 4.5 times more likely to suffer from intermittent claudication in the legs. In the study, people with diabetes were 2.9 times more likely to die from heart disease, and the risk is generally greater for pre-menopausal women than it is for men.[3] Survival from heart attacks is also significantly lower in people with diabetes.[4]

Why all the macrovascular problems? People with diabetes commonly have multiple risk factors for atherosclerotic vascular disease, including glucose intolerance, hypertension, upper-body obesity and hypertriglyceridemia. This combination of conditions, termed "The Deadly Quartet" or "Syndrome X", occurs more together more often than by chance. Hypertension, hypertriglyceridemia and diabetes are 2-3 times more common in the obese than in the nonobese. Obesity and diabetes are also more common among those with hypertension, and the combination of hypertriglyceridemia and low HDL cholesterol levels are often seen in the obese. [6]

A leading physician and researcher in the field of diabetes and cardiovascular disease stated, "The common coexistence of these four conditions suggests a shared pathogenesis for at least some of those who suffer from two or more of these conditions." [6] Dyslipidemia, in particular, plagues those with diabetes. People with NIDDM are two to three times more likely to show a pattern of elevated triglycerides, depressed HDL cholesterol and small/dense LDL particles compared to non-diabetic patients. [5] It is likely that this dyslipidemic pattern plays a major role in causing macrovascular disease in people with diabetes.

Community-based pharmacists are in an opportune position to help improve clinical outcomes in people with diabetes. The majority of Americans with diabetes receive no basic instruction on diabetes management. [8] With the length of physician visits squeezed by managed care, pharmacists can and should play a key role in educating both patients and health professionals on the latest pharmacological and non-pharmacological means for preventing and treating risk factors for atherosclerotic vascular disease.

BENEFITS OF CONTROL

Diabetes can be controlled through the use of insulin injections, oral medications, diet, exercise and self monitoring of blood glucose levels. Research has clearly indicated that intensive management of blood glucose levels can reduce both the incidence and progression of diabetic complications.

The Diabetes Control and Complications Trial (DCCT) was a 10-year, multi-center study designed to answer the question: Does blood sugar control matter? The results of the study indicated that people with diabetes can prevent and slow the progression of diabetic complications through intensive blood glucose control.

In the study, more than 1400 individuals with Type-I diabetes were assigned to either an "intensive therapy" group or a "conventional therapy" group (see below). The mean blood glucose level for the intensive therapy group was 155 mg/dl (HbA1c 7.2%). The conventional therapy group averaged 231 mg/dl (HbA1c 9.0%).

Intensive Therapy Group

- ≥ 3 injections of insulin a day or use of an insulin pump
- blood glucose monitoring ≥ 4 times/day
- dosage adjustments based on blood glucose levels/diet/anticipated exercise
- monthly visits with the health care team with phone contact between visits

Conventional Therapy Group

- 1-2 daily insulin injections with constant doses
- daily self-monitoring of blood glucose
- basic diet/exercise education
- quarterly examinations

The results of the study were consistently in favor of intensive therapy. Intensive therapy reduced the risk for developing retinopathy by 76%; for those with pre-existing retinopathy, progression was slowed by 54%. Intensive therapy reduced the appearance of microalbuminuria (≥ 40 mg albumin excretion per 24 hours) by 39%, and the appearance of albuminuria (≥ 300 mg albumin excretion per 24 hours) by 54%. The incidence of clinical neuropathy was also 60% lower in the intensive therapy group.

Despite the age the subjects (average age 27 years at onset), the intensive therapy group had a 24% lower incidence of elevated LDL cholesterol (>160 mg/dl) and 41% less macrovascular disease. [9]

To project the results of the DCCT to the Type-II (NIDDM) population, a study using similar protocols was applied to Japanese patients with NIDDM.

The results were similar to those found in the DCCT: Intensive therapy reduced the risk of developing retinopathy by 76% and worsening retinopathy by 69%. The intensive therapy group had 73% less occurrence of nephropathy, and the risk of worsening nephropathy was reduced by 70%. The intensive therapy group also showed significant improvements in peripheral sensory and cardiovascular autonomic nerve conduction, while the conventional group showed deterioration. The total number of cardiovascular, cerebrovascular and peripheral vascular events was also reduced by 50% in intensive therapy group. [10]

It is important to remember that blood glucose control is only one method for preventing and slowing the progression of diabetic complications. Control of blood pressure, blood lipids and other manageable risk factors also plays a key role.

A study evaluating the effectiveness of Captopril, an angiontensin-converting enzyme (ACE) inhibitor provides a good example of the role of pharmacotherapy. Elevations in serum creatinine, need for dialysis or transplantation, and death due to renal failure can be reduced by almost 50% through use of Captopril in patients showing early signs of kidney damage due to diabetes. Furthermore, Captopril appears to slow the progression of diabetic nephropathy by a mechanism that is independent of its antihypertensive properties. [11]

DIABETES: A DISEASE OF SELF-MANAGEMENT

Physicians often instruct their patients with diabetes to "think like a pancreas." Remember, a healthy pancreas maintains euglycemia by producing the appropriate amounts of insulin at the appropriate times. Blood glucose levels can be affected by many factors, including dietary intake of carbohydrates, fats, protein and fiber; levels of physical activity; frequency and severity of emotional stress; illness and injury; basal metabolic rate; prescription and OTC drugs; and a host of environmental factors such as ambient temperature and humidity. Given all of these sources of glycemic variability, it is substandard medical practice to expect a standard dose of insulin of oral medication to do the job of controlling blood sugar levels from day-to-day. Furthermore, it is unrealistic to expect physicians to be able to make their patients' many day-to-day decisions regarding medication doses and timing.

Many patients with NIDDM are also instructed to lose weight in order to control their diabetes. Weight loss is a complex physical and emotional process that requires extensive education, discipline and decision-making on the part of the patient. It is extremely rare that the physician has the time and resources to enable patients to lose weight effectively.

In almost every case, diabetes management involves ***choices***: day-to-day, and minute-to-minute decisions that affect blood sugar and weight control. The patient must be trained and properly equipped to make sound decisions. Each patient needs to know how and when to monitor blood glucose levels, and more importantly, what to do with the results. Self-monitoring and record-keeping will help guide both the patient and health professional in making appropriate adjustments to medications, diet and physical activities. Self-empowerment can help most patients achieve better control of their diabetes and enjoy a healthy, active, flexible lifestyle.

GOALS OF THERAPY

The overall goal in the management of both IDDM and NIDDM is to maximize quality of life by preventing acute and long-term complications. Acute complications include severe or persistent hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic syndrome, fatigue, vaginitis, polyuria, polydipsia and polyphagia. Long-term complications include diabetic retinopathy, nephropathy, neuropathy and atherosclerotic vascular disease.

Goals for glycemic control, as determined by the American Diabetes Association, are as follows:[12]

Fasting glucose: 80-120 mg/dl
Preprandial glucose: 80-120 mg/dl
2-hr. Postprandial glucose: <180 mg/dl
Bedtime glucose: 100-140 mg/dl
Hemoglobin A1c (normal range 4-6%):
<7%

For hypertensive individuals, blood pressure reduction is critical for the prevention of long-term complications. A blood pressure goal of <130/85 mmHg applies to most hypertensive individuals. For those with isolated systolic

hypertension of ≥ 180 mmHg, the goal is to achieve a pressure of <160 mmHg. For those with a systolic pressure of 160-179, the goal is a reduction of at least 20 mmHg. [12]

Due to the high incidence of cardiovascular disease in people with diabetes, the following blood lipid goals have been established: [12]

LDL: <130 mg/dl
≤ 100 mg/dl (with known CHD)
< 160 mg/dl (children with multiple cardiac risk factors)
HDL: > 35 mg/dl (men)
> 45 mg/dl (women)
Triglycerides: ≤ 200 mg/dl

ACHIEVING BLOOD GLUCOSE GOALS

Diabetes management is best achieved through an approach that balances factors that raise and lower blood sugar levels. Insulin (endogenous and exogenous), oral diabetes agents and physical activity must be balanced against food consumption (primarily carbohydrate intake) and hepatic glucose output, which is increased by stress and illness. The diabetes management plan should be individualized and emphasize patient self-management. [12]

Even with the ongoing development of newer and more effective forms of medicinal therapy for treating diabetes, effective management still hinges on the basics: a healthy diet and regular exercise. "The initial treatment of choice in patients with NIDDM is optimization of the meal plan and enhancement of physical activity." [13]

For patients with IDDM, learning to make adjustments for food and physical activity are cornerstones to effective management. All people with diabetes, for whom hypertriglyceridemia, hypertension and obesity are common problems, a healthy diet and regular exercise should be considered effective forms of therapy.

Proper nutrition is an essential component of successful diabetes management. An effective meal plan can optimize blood glucose control, improve serum lipid levels, aid in weight management, prevent hypoglycemia and improve overall health status. [14]

In general, the same healthy nutrition recommendations outlined in *Dietary Guidelines for Americans* and the *Food Guide Pyramid* are applicable to people with diabetes. For those with IDDM, the meal plan should be designed to match the timing and amounts of exogenous insulin in order to prevent hypo- and hyperglycemia. [14]

Nutrition therapy for those with NIDDM should emphasize glucose, lipid and blood pressure goals rather than weight reduction. Initially, the nutrition plan should focus on improving food choices so as to reduce total fat intake, especially saturated fat. Moderate caloric reduction (250-500 calories less than usual daily intake) is recommended. Serotonergic appetite suppressants may be helpful to those with refractory obesity. [14]

Protein intake for people with diabetes should be approximately 10-20% of total calorie intake. With the onset of nephropathy, daily intake of no more than .8 g protein per kg body weight is recommended.

Reducing intake of fat (particularly saturated fat) and cholesterol have been shown to reduce the risk of cardiovascular disease. It is recommended that fat make up less than 30% of total daily calories, and saturated fat represent less than 10% of daily calories. Cholesterol intake should be no more than 300 mg daily. If LDL cholesterol is elevated, less than 7% of total calories should come from saturated fat, and dietary cholesterol should be limited to no

more than 200mg/day. If triglycerides and VLDL cholesterol are elevated, an increase in monounsaturated fats (up to 20% of total daily calories) may be beneficial; saturated and polyunsaturated fats should each account for less than 10% of total daily calories. With triglyceride levels above 1000 mg/dl, a reduction in all types of dietary fat is recommended. [14]

Although the effect of dietary fiber on glycemic control is minimal, soluble fiber intake can have a beneficial effect on serum lipids. Daily consumption of 20-35 grams of dietary fiber is recommended.

Carbohydrate intake may vary from individual to individual and from day to day. In general, carbohydrates should make up 50-70% of daily calorie intake. Since carbohydrates are the primary determinant of postprandial blood glucose levels, carbohydrate gram counting has become a popular and practical method for managing blood glucose levels. And since little difference has been found in the glycemic effects of simple and complex carbohydrates (sugar and starch), emphasis should be given to the total amount of carbohydrate consumed rather than the nature of the carbohydrate. [14]

The timing of carbohydrate intake should be based on the pharmacokinetics of diabetes medications. Quantities should be fine-tuned based on the outcome of self blood-glucose measurement. For example, if a person who takes an oral agent for their diabetes finds that their blood glucose level rises every day between breakfast and lunch, they would probably benefit from reducing the amount of carbohydrate in their breakfast. A person who experiences low blood sugar in the late afternoon might benefit from having more carbohydrate in their lunch, or taking a carbohydrate-containing snack at mid-afternoon.

Sodium recommendations for people with diabetes are the same as for the general population. Sodium intake should be less than 3000 mg per day for those with no complications or additional risk factors for heart disease. For those with mild to moderate hypertension, less than 2400 mg/day is recommended. Individuals with hypertension and nephropathy should keep sodium intake below 2000 mg daily. [14]

Exercise, as well as nutrition, plays a key role in the management of diabetes and prevention and treatment of macrovascular complications. Individuals with IDDM should be encouraged to exercise in order to improve cardiovascular fitness and enhance psychological well-being. Self-monitoring of blood glucose levels before and after exercise can help guide adjustments to diet and insulin, and thus prevent hypoglycemia during exercise. [15]

For those with Type-II diabetes, an appropriate exercise program should be incorporated into the diabetes management plan in order to improve glycemic control, reduce cardiovascular risk factors, and enhance psychological well-being. 20-45 minutes of moderate cardiovascular exercise such as walking, swimming, or cycling can be very beneficial. An exercise stress test is recommended in all patients over 35 years old. [15]

Many of the benefits of exercise are secondary to improvements in insulin sensitivity. [16,17] Enhanced insulin sensitivity has the effect of reducing serum insulin levels, lowering blood pressure, reducing triglycerides and total cholesterol, and providing an acute reduction in blood glucose levels. In fact, regular exercise has been shown to reduce the risk of Type-II diabetes in non-diabetic men. Studies on University of Pennsylvania alumni [18] and US male physicians [19] showed a dose-dependent effect of exercise: The more calories burned

each week through physical activity, the lower the risk of developing Type-II diabetes. This protective effect of exercise stood even after adjusting for changes in body mass index.

The combined effects of diet and exercise in reducing risk factors for macrovascular disease cannot be understated. Participants with NIDDM or glucose intolerance who entered an intensive 3-week diet-and-exercise program experienced statistically significant reductions in fasting serum insulin (32%), fasting serum glucose (13%), total and LDL cholesterol (22% and 23%, respectively), triglycerides (26%), body weight (5%), and systolic and diastolic blood pressure (6% and 8%, respectively). Normalization of body weight was not a requisite for a reduction in other risk factors,[20] supporting the adage that improvements in risk factors can be obtained with even a modest amount of weight loss.

PHARMACOLOGICAL THERAPY

According to the results of the DCCT, the desired outcome of glycemic control is to lower the glycohemoglobin level in order to prevent the long-term complications of diabetes. Of course, realism must take precedence as the occurrence or recurrence of hypoglycemia may jeopardize patient safety. [12]

For individuals with Type-I diabetes, optimal control is usually achieved through the use of multiple injection therapy (MDI) or an insulin pump (CSII - Continuous Subcutaneous Insulin Infusion). MDI typically requires injections of fast- or short-acting insulin (Humalog or Regular) prior to meals, with one or two injections of intermediate-acting or long-acting insulin to provide background insulin through the night and possibly between meals. Because individuals with IDDM do not produce sufficient amounts of insulin to meet basic metabolic needs, 24-hour background insulin coverage is necessary to prevent ketogenesis.

CSII involves the use of an external pump that delivers a continuous "basal" rate of fast- or short-acting insulin at a level designed to match each individual's normal hepatic glucose output. The user programs the pump to deliver a "bolus" prior to each meal, usually based on anticipated carbohydrate consumption. In addition to offering the user significant flexibility in terms of meals and physical activities, CSII has been shown to reduce the incidence of severe hypoglycemia compared to MDI. It has also been proven effective for lowering HbA1c in individuals whose level was previously elevated. [21]

A summary of each type of commercially-available insulin is given below:

Insulin Type	Name	Appearance	Onset	Peak	Duration
Fast Acting	Humalog	Clear	0-15 minutes	30-90 minutes	3-5 hours
Short Acting	Regular	Clear	30-60 minutes	2-4 hours	5-7 hours
Intermediate Acting	NPH*, Lente*	Cloudy	2-4 hours	4-8 hours	12-16 hours
Long Acting	Ultralente*	Cloudy	4-8 hours	8-20 hours	24-36 hours

** Available in beef/pork as well as human insulin version. Beef/pork varieties usually have a longer peak time and duration of action than human insulin.*

Pharmacological therapy in the treatment of Type-II diabetes offers several options. In general, pharmacological intervention is appropriate in patients with ketosis or symptoms of hypoglycemia at the time of diagnosis, or if glycemic goals are not met through the use of diet and exercise within three months. [13]

The choice of medicinal therapy depends on a number of variables, including cost, frequency of dosing, mechanism of action, and potential side effects. Presently, there are four classes of oral agents available for the treatment of Type-II diabetes:

Sulfonylureas appear to act primarily by potentiating insulin secretion. Sulfonylureas are relatively inexpensive, and most can be taken just once a day. Because sulfonylureas will only work in the presence of endogenous insulin production, their effectiveness tends to diminish over the course of several years. The initial clinical response to sulfonylureas averages an approximate 60 mg/dl reduction in fasting plasma glucose (reduction in glycated hemoglobin by 1.5-2.0%). Hypoglycemia and weight gain are potential and common side effects of sulfonylureas. [13] Use of second-generation sulfonylureas (glyburide, glipizide, glimepiride) are preferred over older-generation sulfonylureas (Tolbutamide, tolazamide, Chlorpropamide, Acetohexamide) for individuals with impaired liver or kidney function.

1. **Metformin** has no direct effect on insulin secretion. Its primary mechanisms of action are inhibition of hepatic glucose output and, to a lesser extent, an increase in peripheral insulin sensitivity. Metformin has been used as monotherapy or in combination with sulfonylureas. As with sulfonylureas, metformin tends to lower fasting plasma glucose by approximately 60 mg/dl and reduce glycated hemoglobin by 1.5-2.0%. In subjects with fasting blood glucose over 200 mg/dl (or HbA1c over 8.0%), combining metformin with sulfonylureas may prove effective. Metformin also tends to produced a greater improvement in blood lipids than sulfonylureas. Metformin does not cause hypoglycemia and is not associated with weight gain. Gastrointestinal side-effects (usually diarrhea) are common, and the drug should not be used in patients with renal, liver or advanced cardiovascular disease. [13]

2. **Acarbose** inhibits enzymes that break down starches in the small intestine, thereby delaying carbohydrate absorption and reducing postprandial hyperglycemia. Its effect on glycated hemoglobin is less than that of sulfonylureas and metformin (.5-1.0% reduction), and dosing schedules require it to be taken before each meal. Gastrointestinal upset is a common side effect, but there is essentially no risk of hypoglycemia. The addition of acarbose to a sulfonylurea has resulted in significant reductions in postprandial hypoglycemia and modest decreases in HbA1c. In general, use of acarbose with metformin is discouraged due to the likelihood of gastrointestinal side effects. [13]

3. **Troglitazone** lowers blood glucose by improving target cell response to insulin. In this respect, decreases in hepatic glucose output and increases in glucose uptake by skeletal muscle are seen in most patients who use the drug. In clinical trials, glycemia fell by 34-35%, insulinemia fell by 50%, triglycerides fell by 20%, and HDL cholesterol rose by 20% among the 75% of patients who responded to the drug. Side effects were found to be comparable to placebo-control groups. (22) Troglitazone is intended primarily for individuals with significant insulin resistance; i.e. those with NIDDM who are taking large doses of insulin.

Use of exogenous insulin is usually considered a last line of defense in the treatment of NIDDM. Insulin therapy requires subcutaneous injection (which most patients prefer to avoid), more frequent blood glucose monitoring and physician visits, and possible weight gain. However, if glycemic goals are not achieved with oral agents alone, insulin administration (alone or in combination with oral agents) is indicated. Patients who are resistant to using syringes to administer insulin may benefit from using commercially-available insulin "pens" or needle-free insulin infusion devices.

When used in combination with oral agents, BIDS therapy (bedtime insulin, daytime sulfonylurea) usually produces better fasting blood sugar control, and hence improved function of the sulfonylurea during the day. When used alone, intermediate-acting insulin (with or without fast-acting insulin) should be administered at least twice a day to provide adequate insulin coverage through the day and night. [13]

Hyperinsulinemia appears to be a marker for other risk factors of cardiovascular disease. Many studies have suggested that patients with NIDDM receiving insulin have a higher rate of cardiovascular disease than those who manage with diet and exercise or oral agents. Once again, efforts to reduce insulin resistance through non-pharmacological means are crucial to the management of Type-II diabetes. [13]

EXAMINATION

1. The most common cause of death in people with diabetes is:

A. Kidney Failure
B. Ketoacidosis
C. Heart Disease
D. Infection

2. Which of the following patients is most likely to suffer from "metabolic syndrome"?

A. An obese woman with Type-II diabetes, high blood pressure and high HDL cholesterol.
B. An obese man with high blood pressure, Type-II diabetes and elevated triglycerides.
C. A moderately overweight woman with hypertension, hyperglycemia and osteoporosis.
D. A moderately overweight man with Type-I diabetes and a total cholesterol of 300.

3. The benefits of controlling blood glucose levels through intensive therapy apply to:

A. Individuals with Type-I diabetes only.
B. Individuals with Type-I or Type-II diabetes.
C. Individuals with Type-II diabetes only.
D. Only those patients who take insulin.

4. A patient tells you that despite taking her diabetes medication every day, her blood sugar levels remain very high. Which of the following would <u>not</u> be an appropriate recommendation?

A. Double up on the dosage.
B. Try doing some more walking each day.
C. Cut down on the amount of carbohydrates in the diet.
D. Educate the patient on some of the newer medications so that she can discuss them with her doctor.

5. Which of the following would be considered too high for a person with diabetes?

A. An after-meal blood sugar of 145 mg/dl.
B. An LDL cholesterol of 145 mg/dl.
C. A Triglyceride level of 145 mg/dl.
D. All of the above.

6. The "diabetic diet":

A. Should contain little or no simple sugars.
B. Should contain as little starch as possible.
C. Should contain as little soluble fiber as possible.
D. Is the same as the healthy diet recommended for most Americans

7. The effects of regular cardiovascular exercise such as brisk walking include:

A. Improvements in endogenous insulin production
B. Improvements in peripheral insulin sensitivity
C. Reduced risk of Type-I diabetes
D. All of the above.

8. Peggy has Type-I diabetes and takes three shots of insulin a day: NPH and Regular in the morning, Regular at dinner, and NPH at bedtime. Her pre-dinner blood sugar levels are consistently in the 200s. Which insulin probably needs to be increased?

A. The morning Regular
B. The morning NPH
C. The dinnertime Regular
D. The bedtime NPH

9. Which of the following oral agent side effects are correct?

A. Sulfonylureas tend to raise triglycerides.
B. Metformin can contribute to hypoglycemia.
C. Acarbose often causes gastrointestinal upset.
D. Troglitazone usually leads to weight gain.

10. A person with Type-II diabetes who has high blood sugar levels first thing in the morning but normal readings the rest of the day would probably benefit most from which oral agent?

A. Sulfonylurea
B. Metformin
C. Acarbose
D. Troglitazone

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