Early Intervention to Prevent Type 2 Diabetes

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JCOM CME

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Program Audience

Primary care physicians.

Educational Needs Addressed

The growing prevalence of type 2 diabetes, with its high morbidity and excess mortality, is imposing a heavy burden on the U.S. health care system. Prediabetes, defined as impaired glucose tolerance and/or impaired fasting glucose, is a major risk factor for development of type 2 diabetes. The evidence is overwhelming that diabetes can be prevented or delayed in high-risk populations through lifestyle modification or pharmacologic interventions. Primary care physicians need to be aware of this information and be prepared to use nonpharmacologic and pharmacologic approaches to reach glycemic goals and to help promote weight loss.

Educational Objectives

After participating in this CME activity, primary care physicians should be able to

1. Identify patients at risk for developing diabetes
2. Explain the rationale for the treatment of prediabetes
3. Know the lifestyle interventions that are effective in preventing type 2 diabetes
4. Describe the pharmacologic agents that are used in the treatment of prediabetes

Diabetes mellitus is a global epidemic and a growing public health problem. The worldwide prevalence of diabetes is projected to increase from an estimated 171 million (2.8%) in 2002 to 366 million (4.4%) in 2030 [1]. The proportion of the U.S. population affected by diabetes is even greater. Based on data from the 1999–2002 National Health and Nutrition Examination Survey, 9.3% of those aged 20 years or older (19.3 million, 2002 U.S. population) had diagnosed or undiagnosed diabetes, and an additional 20.6% had impaired fasting glucose [2].

Diabetes was the sixth leading cause of death in the United States in 2002 [3]. The complications of diabetes—including heart disease, hypertension, stroke, blindness, renal disease, and peripheral neuropathy—contribute significantly to the morbidity and mortality associated with diabetes. The risk of death is roughly double in people with diabetes versus those without the disease [3]. The economic impact of diabetes also is enormous, with total (direct and indirect) costs estimated at $132 billion in 2002 [4].

In response to the clinical and economic burden of the diabetes epidemic, national guidelines call for strategies to prevent diabetes whenever possible. Although we refer to "prevention" in this article, we recognize that the diabetes prevention trials have shown that interventions more *delay* diabetes than prevent or reverse its pathophysiology. Thus, prevention of diabetes in this article should be understood to mean the delaying of the onset of diabetes. A case example will be used to examine the rationale for early, aggressive action on behalf of patients at risk for diabetes and its complications.

CASE STUDY

Initial Presentation

A 45-year-old Hispanic woman is referred by her family physician to an endocrinologist for evaluation of prediabetes. The referral was prompted by a recent set of blood tests that revealed a fasting blood glucose level of 95 mg/dL.

History

The patient has a history of gestational diabetes, and both of her parents have type 2 diabetes. Since the delivery of her last child, the patient has been unable to lose weight. Her primary care physician had recommended decreasing

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the carbohydrate content in her meals and increasing her physical activity. However, she has been unsuccessful in making significant changes over the past year. Because of the family's tight budget, rice and beans are the staple diet. Also, after working a full day at her desk job, doing household chores, and taking care of her children, the patient cannot find time for exercise. On the weekends, she tries to walk in her neighborhood. Currently, she does not take any medication and does not drink alcohol or smoke.

Physical Examination

The patient is obese, with a body mass index (BMI) of 36 kg/m^2. She has central adiposity. Blood pressure is 125/80 mm Hg, and heart rate is 72 bpm. Acanthosis nigricans is noted at the back of the neck and in the axilla. The cardiovascular examination is normal. The remainder of the physical examination is unremarkable.

An oral glucose tolerance test (OGTT) and fasting lipid profile reveal the following:

- Fasting glucose, 98 mg/dL (normal, 55–100 mg/dL)
- Glucose at 2 hours, 160 mg/dL (normal, < 140 mg/dL)
- Total cholesterol, 194 mg/dL (normal, 140–199 mg/dL)
- Low-density lipoprotein cholesterol, 120 mg/dL (normal, 50–129 mg/dL)
- High-density lipoprotein (HDL) cholesterol, 38 mg/dL (normal, 40–60 mg/dL)
- Triglycerides, 180 mg/dL (normal, 35–150 mg/dL)

A repeat OGTT reveals a fasting glucose of 96 mg/dL and glucose at 2 hours of 170 mg/dL.

- **Do these findings warrant concern? Is aggressive intervention indicated?**

This patient is at high risk for developing type 2 diabetes. She meets criteria for the diagnosis of impaired glucose tolerance (IGT), defined as a plasma glucose level between 140 and 199 mg/dL 2 hours after a 75-g glucose challenge. She does not have impaired fasting glucose (IFG), defined as a fasting plasma glucose level between 100 and 125 mg/dL.

Without aggressive intervention, progression to diabetes is very high. A comprehensive assessment of her risk factors, education about preventing diabetes and its complications, and interventions targeting the underlying mechanisms of glucose dysregulation are indicated for this patient. Although beyond the scope of the following discussion, the patient's high lipid levels should also be addressed.

In assessing risk for developing type 2 diabetes, it is important to investigate all possible risk factors to best gauge the level of risk in an individual patient. The case patient, for example, had diabetes while she was pregnant and has a strong family history of diabetes, in addition to being obese and physically inactive. Patients at such high risk require the most aggressive approach to preventing the onset of diabetes. For example, although the case patient has been unsuccessful in making lifestyle changes, the goal of patient education would be to emphasize the importance of making these changes and to encourage the patient to find even small ways to incorporate these changes into her life.

Rationale For Early Intervention To Prevent Diabetes

For individuals born in the United States in 2000, the estimated lifetime risk of developing diabetes is 33% for men and 39% for women [5]. Current estimates indicate that type 2 diabetes accounts for 90% to 95% of all diagnosed cases of diabetes [3]. Identifying individuals at risk for developing type 2 diabetes prior to the onset of disease and targeting risk factors that promote insulin resistance are integral to prevention. Easily recognizable risk factors include obesity, a sedentary lifestyle, 1 or more first-degree relatives with type 2 diabetes, non-Caucasian ethnicity, and medical conditions associated with insulin resistance (ie, gestational diabetes, polycystic ovary syndrome) [6].

When insulin resistance is accompanied by failure of pancreatic beta cells to hypersecrete insulin, compensation for insulin resistance falters and blood glucose rises, heralding the onset of IGT and, ultimately, diabetes. The majority of patients with IFG and/or IGT develop type 2 diabetes [7–12]. Therefore, individuals with IGT and IFG are now considered to have *prediabetes*. Inflammatory markers such as C-reactive protein and interleukin-6 may identify patients at especially high risk for both diabetes and cardiovascular disease [13,14]. Multiple epidemiologic studies have shown that IFG and especially IGT predict increased risk for cardiovascular disease [15,16].

IFG and IGT are associated with different pathophysiology. In IFG, the liver is the major site of insulin resistance; in IGT, skeletal muscle is the major site of insulin resistance [17]. Both IFG and IGT have reduced first-phase insulin secretion in response to a meal, but in IGT there may also be a decreased late-phase insulin response. IGT and IFG can exist independently. Therefore, it is important to check plasma glucose levels as well as do an OGTT to rule out the possibility of prediabetes.

- **Can lifestyle interventions prevent or lower the risk of type 2 diabetes?**

Benefits of Weight Loss and Exercise

The rising prevalence of obesity and sedentary lifestyle has helped to fuel the diabetes epidemic. Unlike race or genetic predisposition, obesity and physical inactivity are major risk factors for type 2 diabetes that can be modified. Indeed, interventions that promote weight loss and increase physical activity have proved to be the most effective strategies for preventing type 2 diabetes.

In the Finnish Diabetes Prevention Study, 522 overweight participants with IGT were randomized to an intervention of individualized diet and exercise counseling or to usual care [8]. The goals for the intervention group were a reduction in weight of at least 5%, a decrease in fat intake to less than 30% of total calories, a decrease in saturated fat intake to less than 10% of total calories, an increase in fiber intake to at least 15 g per 1000 kcal, and a daily "dose" of at least 30 minutes of moderately intense physical activity. After 4 years, there was a 58% risk reduction in diabetes in the intervention group compared with the usual care group. Study participants who did not develop diabetes were followed for an additional 3 years [18]. Without receiving any further counseling on lifestyle modifications, a 43% reduction in relative risk of diabetes was maintained over the 3-year period (for a total of 7 years) in the intervention group.

The Diabetes Prevention Program demonstrated that lifestyle changes were superior to metformin in reducing the risk of developing type 2 diabetes [9]. More than 3000 ethnically diverse patients with IGT or IFG were randomized to an intensive program of lifestyle modification, standard lifestyle recommendations plus metformin 850 mg twice daily, or standard lifestyle recommendations plus placebo. The goals for the intensive lifestyle modification group were 7% weight loss and 150 minutes of physical activity per week. Patients in the intensive lifestyle modification group lost significantly more weight and participated in more physical activity as compared with both the metformin and placebo groups (**Figure 1**). After an average follow-up of 2.8 years, intensive lifestyle changes decreased the incidence of diabetes by 58% and decreased fasting blood glucose by 63%, as compared with placebo. Lifestyle modifications were also more cost-effective than metformin. From a societal perspective, intensive lifestyle interventions cost $10,100 less to prevent 1 case of diabetes and $47,600 less for each quality-adjusted life-year compared with metformin [19].

In these clinical trials, recommendations for specific lifestyle interventions were accompanied by regular, time-intensive counseling personalized for each patient. By providing individualized coaching on how patients could improve their diet and increase their physical activity, patients were able to lose weight. As these trials demonstrated, even modest reduction in weight significantly reduces the incidence of type 2 diabetes [8,9]. Ideal body weight does not need to be attained to prevent diabetes. Furthermore, physical activity, even without weight loss, can reduce insulin resistance, as exercise increases insulin-mediated glucose uptake and promotes glycogen synthesis [20].

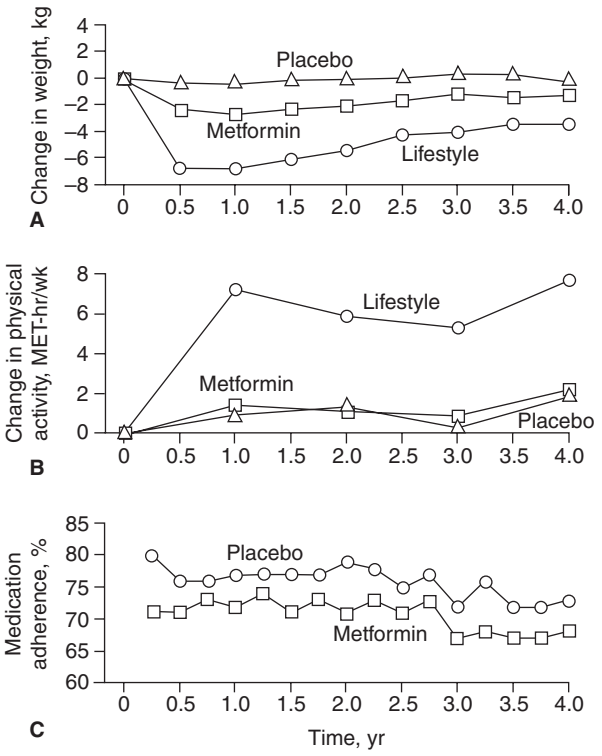

Figure 1. Changes in body weight (**A**) and leisure physical activity (**B**) and adherence to medication regimen (**C**) in the Diabetes Prevention Program, according to study group. Each data point represents the mean value for all participants examined at that time. The number of participants decreased over time because of the variable length of time that persons were in the study. For example, data on weight were available for 3085 persons at 0.5 year, 3064 at 1 year, 2887 at 2 years, and 1510 at 3 years. Changes in weight and leisure physical activity over time differed significantly among the treatment groups ($P < 0.001$ for each comparison). MET = metabolic equivalents. (Adapted with permission from Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program Research Group. N Engl J Med 2002;346:396. Copyright 2002, Massachusetts Medical Society. All rights reserved.)

- **Given that nonpharmacologic interventions are highly effective, would you consider pharmacologic measures to prevent diabetes?**

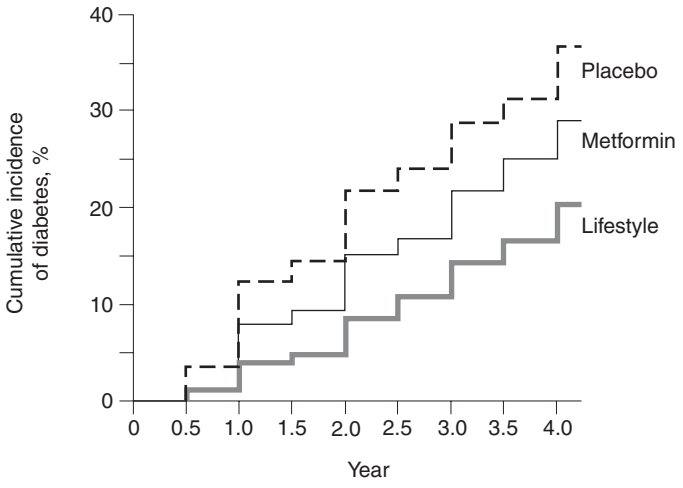

Figure 2. Cumulative incidence of diabetes according to study group. At 3 years, the cumulative incidence of diabetes was 29% in the placebo group, 22% in the metformin group and 14% in the intensive lifestyle intervention group. The cumulative incidence rates differed significantly among the 3 groups ($P < 0.001$ for each comparison). (Adapted with permission from Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program Research Group. N Engl J Med 2002;346:397. Copyright 2002, Massachusetts Medical Society. All rights reserved.)

Like the case patient, many patients seen in clinical practice attempt lifestyle changes but have difficulty achieving and maintaining the goals of these interventions. Adopting and adhering to a healthy diet and a regimen of regular physical activity can be challenging for many patients. The degree of individualized diet and exercise counseling achieved in clinical trials has not yet proven feasible in routine clinical care settings. Not surprisingly, the results of lifestyle intervention trials have not been replicated in clinical practice.

Although no medication has proven to be as effective or as well tolerated as lifestyle interventions, pharmacologic treatments may be an option for prevention of diabetes. The U.S. Food and Drug Administration has not approved the use of any medication for prevention of diabetes, but clinical trials have suggested that a few pharmacologic interventions are effective in preventing type 2 diabetes. Regardless of whether or not a medication is tried, it is important to continue to emphasize the importance of lifestyle changes and to encourage patient efforts to lose weight and increase physical activity.

- **What pharmacologic agents have been evaluated for reducing the risk of type 2 diabetes?**

Insulin-Sensitizing Agents

Metformin

In the Diabetes Prevention Program, metformin at 850 mg twice daily reduced the incidence of diabetes (7.8 cases/100 person-years vs. 11 cases/100 person-years in the placebo group, or 31%), although not as significantly as the intensive dietary and exercise counseling intervention (4.8 cases/100 person-years, or 58% compared with placebo) (**Figure 2**) [9]. Subgroup analysis revealed that metformin was most effective in young (age < 60 years) and obese (BMI ≥ 35 kg/m^2) patients with fasting plasma glucose levels of 110 to 125 mg/dL. Metformin decreased fasting blood glucose by 48% (compared with 63% for the intensive lifestyle group). Metformin was associated with a significantly higher rate of gastrointestinal (GI) symptoms, but there was no difference in rates of hospitalization or mortality compared with lifestyle intervention and placebo [9].

Acarbose

In the STOP-NIDDM trial, approximately 1400 patients with IGT and IFG were randomized to acarbose 100 mg or placebo 3 times daily [21]. All patients were encouraged to maintain or lose weight with diet and regular exercise. Intention-to-treat analysis revealed that acarbose decreased the progression from prediabetes to diabetes by 25% over 3.3 years, even though 25% of patients in the acarbose group discontinued the medication due to GI side effects. Thirty-two percent of acarbose-treated patients developed diabetes compared with 42% of placebo-treated patients.

Thiazoledinediones

Use of thiazoledinediones for diabetes prevention has been studied in various populations [22–24]. In the TRIPOD (Troglitazone in Prevention Of Diabetes) trial, troglitazone decreased the risk of diabetes by approximately 50% in Hispanic women with a history of gestational diabetes [22]. However, troglitazone was associated with significant hepatotoxicity, which prompted its withdrawal from the market. Women in the TRIPOD study who had not developed diabetes were then recruited for the PIPOD (Pioglitazone in Prevention Of Diabetes) study, which demonstrated that treatment with pioglitazone 45 mg daily continued to prevent the development of diabetes [23].

In the DREAM (Diabetes Reduction Assessment with

Table. Interventions to Prevent Type 2 Diabetes

Variable	Intervention				
	Lifestyle		Metformin	Acarbose	Rosiglitazone
Trial	FDPS [8,18]	DPP [9]	DPP [9]	STOP–NIDDM [21]	DREAM [24]
Mean follow-up, yr	3.2	2.8	2.8	3.3	3.0
Patient characteristics					
Mean age, yr	55.0	50.6	50.9	54	54.7
Body mass index, kg/m^2	31	33.9	33.9	31	31
Outcomes					
Weight change, kg*	–4.2	–5.6	–2.1	0.5	2.2
Relative reduction in occurrence of type 2 diabetes (95% CI), %	58 (30–70)†	58 (48–66)‡	31 (17–43)‡	25 (10–37)†	62 (56–67)†
Adverse events	None	Musculoskeletal symptoms	GI symptoms	GI symptoms	Peripheral edema, weight gain, heart failure
Persistence of effect	Confirmed	Pending	Pending	No	Pending

NOTE: Enrollment criteria for all trials included impaired fasting glucose, impaired glucose tolerance, or both. CI = confidence interval; DPP = Diabetes Prevention Program; DREAM = Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; FDPS = Finnish Diabetes Prevention Study; GI = gastrointestinal; STOP–NIDDM = Study to Prevent Non–Insulin-Dependent Diabetes Mellitus. (Adapted with permission from Nathan DM, Berkwits M. Trials that matter: rosiglitazone, ramipril, and the prevention of type 2 diabetes [editorial]. Ann Intern Med 2007;146:462.)

*All estimates are mean weight change relative to within-group baseline except for rosiglitazone, which is mean weight change relative to placebo.

†Reduction in hazard (1.0 – hazard ratio); acarbose estimate adjusted for age, sex, and body mass index.

‡Absolute percentage difference (drug – placebo).

Ramipril and Rosiglitazone Medication) trial, more than 5000 overweight patients with IGT (plasma glucose, 140–199 mg/dL) and/or IFG (plasma glucose, 110–125 mg/dL) without cardiovascular disease were randomized to rosiglitazone (titrated to 8 mg daily), ramipril (to 15 mg daily), both, or placebo [24,25]. After a median of 3 years, rosiglitazone reduced the composite outcome of incident diabetes or death by 60% and increased the likelihood of regression to normal fasting glucose and glucose tolerance by 70% to 80% compared with placebo [24]. Ramipril did not significantly reduce the risk of death or diabetes; however, it led to normoglycemia in a small number of patients [25]. The combination of rosiglitazone and ramipril had no apparent benefit.

The effect of rosiglitazone on glucose metabolism demonstrated in the DREAM trial should be viewed cautiously. The median fasting plasma glucose level and median 2-hour postglucose load level at study entry were close to normal glycemic targets. Rosiglitazone was associated with significantly higher prevalence of peripheral edema, a 2.2-kg greater body weight, and, importantly, an increased frequency of heart failure [24]. In addition, a recent meta-analysis of clinical trials involving rosiglitazone and an interim analysis of data from the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) study raised a concern of an increased risk for myocardial infarction and death from cardiovascular disease associated with rosiglitazone use [26,27].

Summary

The **Table** provides an indirect comparison of interventions to prevent type 2 diabetes (ie, lifestyle interventions, metformin, acarbose, and rosiglitazone) [28]. Although rosiglitazone was the most effective for preventing type 2 diabetes, its significant safety concerns bar its use for prevention of a disease that has not yet developed, particularly when there are safer and less costly options available (metformin) [28]. Use of acarbose is limited by poor patient adherence. Metformin was recommended by a panel of experts convened by the American Diabetes Association in patients with IFG and/or IGT, if any of the following features applies: age younger than 60 years, BMI of 35 kg/m^2 or greater, family history of diabetes in first-degree relatives, high triglyceride level, low HDL cholesterol level, hypertension, or hemoglobin A_{1c} greater than 6% [29].

Treatment for Obesity

When lifestyle interventions are not effective in promoting weight loss, anti-obesity medications may be considered. Orlistat [30,31], sibutramine [32,33], and rimonabant [34,35], have been effective in promoting and maintaining weight loss. Additionally, orlistat, when accompanied by lifestyle changes, resulted in a greater reduction in the incidence of type 2 diabetes over 4 years and produced greater weight loss than was observed in a control group in a clinically representative obese population [30]. New pharmacologic agents in development are focused on inhibition of nutrient absorption, enhancement of satiety, and alteration of metabolism or energy balance [36]. Bariatric surgery is an option for patients with a BMI of 40 kg/m^2 or greater without comorbidities or for patients with a BMI of 35 kg/m^2 or greater who have significant comorbidities (eg, hypertension, type 2 diabetes, dyslipidemia, sleep apnea).

Case Conclusion

The endocrinologist informs the patient that, while she does not have diabetes, her blood glucose levels are high and likely to increase to the level of diabetes unless they do something to intervene. The physician recommends that they begin by making a serious effort to change her lifestyle, with the primary goal of a 10% weight loss over the next 6 months achieved by diet and increased physical activity. She emphasizes that even modest weight loss will decrease the patient's risk of developing diabetes. The physician helps the patient identify ways to incorporate 150 minutes of physical activity per week into her daily life. She also refers the patient to a nutritionist to help identify ways to decrease calories, reduce dietary fat, and increase fiber intake.

Over the next 6 months, the patient makes an effort to change her diet and find time for exercise. She loses 8 lb (roughly a 4% decrease) but is unable to achieve her weight loss goal. The endocrinologist discusses the possibility of the patient starting metformin at 850 mg twice daily. She stresses that the patient's young age, obesity, family history of diabetes, and dyslipidemia make her a good candidate for metformin. The patient is unsure and promises to work harder to lose weight.

At her next follow-up visit 3 months later, the patient is proud to report that she has engaged her entire family in a lifestyle "make over." She has lost another 9 lb and has begun walking 40 minutes every morning before work. The endocrinologist congratulates the patient on her achievements and encourages her to keep up the good work. She is returned to the care of her family physician for follow-up, with a plan for periodic visits with the endocrinologist as needed.

SUMMARY

The keys to prevention of type 2 diabetes and its complications are early detection, aggressive glycemic control, regular exercise, and weight loss. Nonpharmacologic and pharmacologic approaches should be used to reach glycemic goals and to help promote weight loss. Escalation of therapy to a multidrug regimen is often needed to prevent the microvascular and macrovascular complications of type 2 diabetes.

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JCOM CME WAYNE STATE UNIVERSITY

CME EVALUATION: Early Intervention to Prevent Type 2 Diabetes

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following statements is TRUE?
   A. Worldwide prevalence of diabetes is expected to triple from 2002 to 2030
   B. 10% of the adult U.S. population has impaired fasting glucose
   C. Risk of death is roughly 3 times higher in people with diabetes compared with people without diabetes
   D. Diabetes is the sixth leading cause of death in the United States
   E. Total economic costs attributed to diabetes is approximately $10 billion in the United States

2. Which of the following oral glucose tolerance test results confirm both impaired fasting glucose and impaired glucose tolerance?
   A. Fasting glucose of 95 mg/dL and glucose at 2 hours of 180 mg/dL
   B. Fasting glucose of 105 mg/dL and glucose at 2 hours of 150 mg/dL
   C. Fasting glucose of 120 mg/dL and glucose at 2 hours of 135 mg/dL
   D. Fasting glucose of 98 mg/dL and glucose at 2 hours of 120 mg/dL
   E. Fasting glucose of 85 mg/dL and glucose at 2 hours of 160 mg/dL

3. Which of the following statements about the Diabetes Prevention Program is TRUE?
   A. At an average follow-up of 2.8 years, intensive lifestyle modifications decreased the incidence of diabetes by 58% and metformin decreased the incidence of diabetes by 50% when compared with placebo
   B. Only patients with both impaired fasting glucose and impaired glucose tolerance were included in the study
   C. The goals for the intensive lifestyle intervention group were 7% weight loss and 150 minutes of physical activity per week
   D. Metformin was more cost-effective than lifestyle modifications
   E. In subgroup analyses, metformin was shown to be most effective in preventing diabetes in obese individuals older than 60 years

4. All of these medications have been evaluated for decreasing the risk of progression to type 2 diabetes EXCEPT:
   A. Glipizide
   B. Ramipril
   C. Acarbose
   D. Metformin
   E. Rosiglitazone

5. Metformin has been recommended by a panel of experts convened by the American Diabetes Association for people with impaired fasting glucose and/or impaired glucose tolerance if they have which of the following features?
   A Age younger than 60 years
   B. BMI ≥ 35 kg/m^2
   C. Family history of diabetes in first-degree relatives
   D. Hypertension
   E. Hypertriglyceridemia
   F. All of the above

EVALUATION FORM: Early Intervention to Prevent Type 2 Diabetes

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