Diabetes Epidemiology: Guiding Clinical and Public Health Practice

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Epidemiology provides a scientific basis for clinical and public health practice. Indeed, epidemiology can be used to guide how we define, diagnose, and screen for diabetes, to describe the present and future burden of diabetes, and to highlight opportunities for intervention.

What is diabetes?

Diabetes is a group of disorders characterized by high glucose levels that cause unique eye, kidney, and nerve complications and an increased risk for cardiovascular disease. A number of approaches have been used to diagnose diabetes. Some have been based on statistical approaches to defining abnormal or high glucose levels and others on the risk of complications. In populations with a low prevalence of diabetes, glucose levels are normally distributed and diabetes may be defined as glucose levels greater than the mean glucose level plus 2 SDs (Fig. 1*A*). In the 1950s, Stefan Fajans and Jerome Conn studied large groups of healthy lean individuals without family histories of diabetes, administered oral glucose loads, and measured glucose levels at time intervals following the glucose loads. They observed normal distributions of glucose levels 60, 90, and 120 min after the glucose load and defined abnormal glucose tolerance based on this simple approach (1). In populations with a high prevalence of diabetes, there is a bimodal distribution of glucose levels and diabetes may be defined as glucose levels greater than the antimode (Fig. 1*B*). Bimodal glucose distributions were first observed among Pima Indians (2), and analyses based on this finding were subsequently used by the National Diabetes Data Group (3) and the American Diabetes Association Expert Committee (4) to establish the fasting and 2-h post–glucose load glucose criteria for diabetes.

Another approach to diagnosing diabetes looks at the association between glucose level and complications and defines diabetes as glucose levels above the threshold associated with complications (Fig. 1*C*). The problem with this approach is that there appears to be different glycemic thresholds for different complications. When we examined the prevalence of diabetic retinopathy by decile of fasting plasma glucose and 2-h plasma glucose, we found that the fasting plasma glucose threshold associated with retinopathy was between 108 and 130 mg/dl and that the 2-h plasma glucose threshold was between 155 and 215 mg/dl, consistent with current diagnostic criteria for diabetes (5). More recently, however, the Diabetes Prevention Program Research Group reported that diabetic retinopathy was present in 7.6% of patients with impaired glucose tolerance (IGT) and 12.5% of patients within 6 to 12 months of making the transition from IGT to diabetes (6). Similarly, in a large middle-aged work force, microalbuminuria was present in 4.0% of nondiabetic individuals but in 16.1% of subjects with IGT (7). The slope of the relationship between glucose level and degree of albuminuria increased at 2-h plasma glucose levels between 121 and 166 mg/dl (7). We have previously reported that distal symmetrical peripheral polyneuropathy was present in 6.1% of Egyptian subjects with normal glucose tolerance, 10.0% of those with IGT, and 13.6% of those with newly diagnosed diabetes (8). More recently, Singleton et al. (9) looked at glucose levels in patients with "idiopathic" painful sensory neuropathy and found that 30–50% had IGT, suggesting that lesser degrees of hyperglycemia may be associated with diabetic neuropathy. Perhaps most importantly, prospective data from 22 European cohorts and nearly 30,000 patients without a history of diabetes followed for up to 11 years demonstrated that the hazard ratio for cardiovascular mortality begins to increase at 2-h plasma glucose levels between 140 and 200 mg/dl (10).

Thus, if we define diabetes as hyperglycemia associated with adverse health outcomes and if we consider microvascular, neuropathic, and macrovascular complications, then the 2-h glucose threshold to define diabetes should be at the level currently used to define IGT (≥140 mg/dl). Defining diabetes at this level would have the advantage of erasing the somewhat arbitrary distinction between IGT and diabetes and would likely promote earlier lifestyle and pharmacologic interventions for glycemic management, more aggressive management of cardiovascular risk factors, and earlier surveillance for microvascular and neuropathic complications.

How should we diagnose diabetes?

Currently the American Diabetes Association recommends that the oral glucose tolerance test not be used in routine clinical practice (4). Unfortunately, this recommendation illustrates how far diabetologists have strayed from their roots as endocrinologists. Endocrine principles dictate that one should measure the plasma hormone or its principle metabolite and when investigating suspected endocrine underactivity, stimulate hormone pro-

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Abbreviations: DCCT, Diabetes Control and Complications Trial; DPP, Diabetes Prevention Program; IGT, impaired glucose tolerance; TRIAD, Translating Research Into Action for Diabetes; QALY, quality-adjusted life-year.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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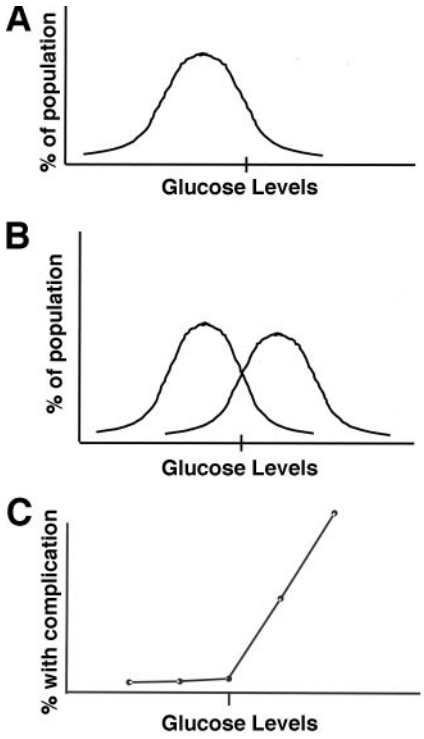

Figure 1—*Approaches to diagnosing diabetes. A: Glucose level greater than the mean + 2 SDs. B: Glucose level more than antimode. C: Glucose level associated with complication.*

duction. Since diabetes is associated with insulin deficiency and hyperglycemia, endocrine principles would suggest that a stimulated or post–glucose load glucose level should distinguish normal from abnormal better than an unstimulated or fasting glucose level. Historically, criteria for the diagnosis of diabetes have relied on post–glucose load glucose levels (Table 1). Indeed, the criteria proposed by Fajans and Conn (1) did not use a fasting glucose criterion but relied on 60-, 90-, and 120-min post–glucose load values and recommended a 120-min cut point of 140 mg/dl. In 1964, the U.S. Public Health Service criteria for the diagnosis of diabetes included a fasting glucose of 125 mg/dl and a 2-h value of 140 mg/dl (11).

Should A1C be used to diagnose diabetes? My answer to this question is no. Even independent of the issues of A1C standardization (12), there are issues related to the sensitivity and accuracy of A1C as a measure of glycemia. When we examined the distributions of fasting plasma glucose, 2-h plasma glucose, and A1C in the Egyptian population and studied the sensitivity of the antimode threshold when specificity was fixed at 99%, fasting plasma glucose was 84% sensitive, 2-h post–glucose load glucose was 90% sensitive, and A1C was only 68% sensitive in diagnosing diabetes (5).

Another problem with A1C is that there is substantial interindividual variation in A1C that is not explained by glycemia. In nondiabetic individuals, A1C varies markedly among individuals but changes little over time in the same individual (13). Less than 30% of the variance in A1C in nondiabetic subjects with normal glucose levels is explained by fasting or post–glucose load glucose levels (14). This unexplained variation in A1C levels in the near-normal range would make it difficult to establish a diagnostic threshold to distinguish normal from abnormal.

This problem is compounded by the fact that A1C may differ systematically by race and ethnicity independent of glucose levels. Saaddine et al. (15) looked at A1C levels in nondiabetic individuals 5–24 years of age studied in the National Health and Nutrition Examination Study (NHANES)-3. Even after adjusting for age, sex, education, BMI, and fasting plasma glucose, hemoglobin A1C levels were higher in Hispanics and blacks than in whites. More recently, we analyzed baseline data from the Diabetes Prevention Program (DPP) and from A Diabetes Outcome Progression Trial (ADOPT). In the DPP, in participants over 25 years of age with impaired glucose tolerance, after adjusting for factors including age, sex, BMI, fasting glucose, postprandial glucose, and glucose area under the curve, A1C was higher in Hispanics and blacks than in whites. In ADOPT, in subjects with recently diagnosed type 2 diabetes treated with diet and exercise alone, A1C levels adjusted for age, sex, and BMI were higher in North American Hispanics and blacks than in North American Caucasians in spite of comparable or even lower fasting and post–glucose load glucose levels among North American Hispanics and blacks (16). Thus, A1C may not be as sensitive as post–glucose load glucose level or even fasting glucose level and may not be valid for diagnosing hyperglycemia among individuals or across racial and ethnic groups.

How should we screen for diabetes?

How does the choice of cut point and frequency of screening affect the performance of screening tests for diabetes? Is the most sensitive screening test always the best? The answer to this question is again, no (17). To date, most studies of screening for diabetes have examined screening at one point in time (18). If one conceptualizes screening as an ongoing process, it dramatically affects the way one approaches screening. We simulated screening with random plasma glucose using cut points of 100, 130, and 160 mg/dl in the U.S. population 45–74 years of age without known diabetes (19). We assumed that positive screening tests were followed by oral glucose tolerance tests

Table 1—*Criteria for abnormal glucose tolerance tests*

	Fajans and Conn (1954) (ref. 1)	USPHS (1964) (ref. 11)	NDDG (1979) (ref. 3)	WHO (1980/1985) (ref. 27)	ADA (1997) (ref. 4)
Glucose dose	1.75 g/kg IBW*	100 g	75 g	75 g	75 g
Fasting	—	125	140	140	126
30 min	—	—	200	—	—
60 min	185	195	200	—	—
90 min	160	—	200	—	—
120 min	140	140	200	200	200
180 min	—	125	—	—	—
Criteria for positive test	All three	At least three	Fasting or 120 min and intermediate	Fasting or 120 min	Fasting or 120 min

ADA, American Diabetes Association; NDDG, National Diabetes Data Group; USPHS, U.S. Public Health Service; WHO, World Health Organization. *IBW = ideal body weight from Metropolitan Life Insurance Tables.

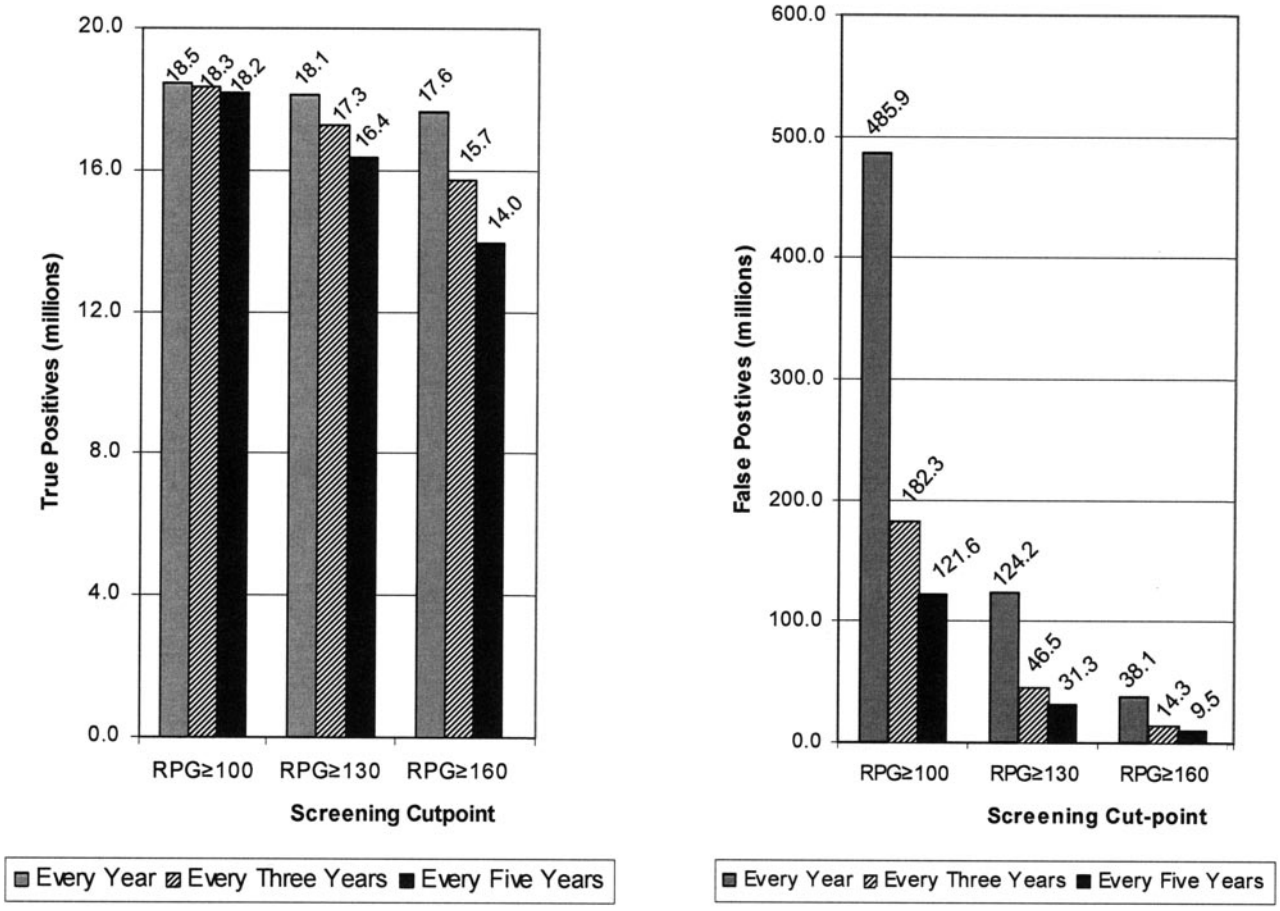

Figure 2—*Cumulative true and false positives. Reprinted with permission from ref. 19.*

and looked at 1-, 3-, and 5-year screening intervals over 15 years. The most sensitive screening test, a random plasma glucose of 100 mg/dl, resulted in very few false-negative tests, ~500,000 after the first screen. Using the least sensitive test, a random plasma glucose of 160 mg/dl, left ~4 million people undetected after the first screen. With repeated screenings, performance improved and false-negative tests decreased with all approaches except with the least sensitive test performed least frequently. Figure 2 shows the cumulative true positive and false-positive test results. The most sensitive test, a fasting plasma glucose of 100 mg/dl applied annually, resulted in the most true positive cases detected, but over the course of 15 years, all approaches except the least sensitive screening test performed least frequently resulted in similar numbers of true positive cases detected (15.7–18.5 million). In contrast, there was a huge difference in the number of false-positive tests. The random plasma glucose of 100 mg/dl performed annually resulted in almost 486 million false-positive tests over 15 years. Use of a test with moderate sensitivity but high specificity such as a random plasma glucose with a cut point of 130 mg/dl every 3 years provided a good yield (17.3 million true positive tests) and substantially reduced the number of false-positive screening tests requiring follow-up (46.5 million false-positive tests over 15 years).

There has also been interest in developing multivariate models to screen for diabetes. These have included equations to predict future risk of diabetes and equations to predict prevalent undiagnosed diabetes. We developed a multivariate model using age, sex, BMI, random plasma glucose, and postprandial time to identify people at increased risk for prevalent undiagnosed diabetes (20). Other investigators using Dutch (21), English (22), Danish (23), and Indian popula-

Table 2—*Models to screen for prevalent diabetes*

Author	Ref.	Population	Variables	Sensitivity (%)	Specificity (%)	AUC (%)
Tabaei	20	Egyptian	Age, sex, BMI, RPG, PP time	65	96	88
Baan	21	Dutch	Age, sex, BMI, BP	78	55	68
Griffin	22	U.K.	Age, sex, BMI, BP, steroids, smoking, FH	77	72	80
Glumer	23	Danish	Age, sex, BMI, BP, physical activity, FH	73	74	80
Ramachandran	24	Indian	Age, BMI, waist circumference, physical activity, FH	77	60	73

AUC, area under the curve; BP, blood pressure; FH, family history of diabetes; PP time, postprandial time; RPG, random plasma glucose.

Table 3—*Strategies to prevent diabetes and its complications, 1980*

Problem	Interventions	% Preventable	Preventable cases/year
Type 2 diabetes	Diet and exercise	50	293,000
Stroke	Blood pressure	85	19,000
Coronary heart disease	Blood pressure, smoking, lipids	45	38,000
Peripheral vascular disease	Blood pressure, smoking	60	24,000
Blindness	Laser	60	3,500
End-stage renal disease	Blood pressure	50	2,000
Amputations	Blood pressure, smoking, glycemia	50	15,000

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tions (24) have developed similar screening models (Table 2). In general, equations that do not include glucose measures have not performed as well as those that have in predicting prevalent undiagnosed diabetes.

What is the present and future burden of diabetes?

Epidemiologic modeling can also be used to define the present and future burden of diabetes. In the early 1980s, we critically reviewed the descriptive epidemiology of type 1 and type 2 diabetes and made projections of the future burden of diabetes (25). We estimated that in the U.S. in 1980 there were ~19,000 new cases of type 1 diabetes and ~19,000 deaths per year. We predicted that the prevalence of type 1 diabetes would remain relatively stable. In contrast, we estimated that there were ~590,000 new cases of type 2 diabetes per year and ~304,000 deaths. Based upon this simple model, we projected that the prevalence of type 2 diabetes would increase by ~6% per year in the U.S. and estimated that by 2000, ~15 million Americans would be diagnosed with diabetes. Centers for Disease Control surveillance data have confirmed these projections (26).

Subsequently, we worked with the World Health Organization to project the number of persons over the age of 20 with diabetes in the world in the years 1995, 2000, and 2025 (27). In these analyses, we defined diabetes using both fasting and 2-h post–glucose load glucose levels, considered both diagnosed and previously undiagnosed diabetes, and generated estimates by applying age- and sex-specific diabetes prevalence rates from more than 100 communities in 38 countries to current and future population projections obtained from the United Nations Population Division. For developed countries, we assumed that diabetes prevalence rates applied nationwide and for developing countries that the rural rate was one-half the urban rate. We further assumed that for countries lacking prevalence estimates, those of the ethnically and socioeconomically most similar countries applied and that age, sex, and urban- and rural-specific diabetes prevalence rates remained constant over time. Based on the conservative assumption that population growth, aging, and urbanization capture present and future trends in diabetes frequency, we projected that the number of adults with diabetes worldwide would increase 122% from 135 million to 300 million. The number of adults with diabetes would increase by 42% in developed countries, from 51 million to 72 million, and 170% in developing countries, from 84 million to 228 million.

Unfortunately, empirical data have again largely confirmed these projections. In a cross-sectional study of diabetes in Egypt performed in the early 1990s, we found that the prevalence of obesity was lower in men living in rural areas and in poor urban areas and higher in men living in higher socioeconomic urban areas. The highest prevalence of obesity was in women living in the lower socioeconomic areas of Cairo. The prevalence of diabetes in adults in Egypt ranged from 5% in rural communities in the Nile delta to 10% in lower socioeconomic areas of Cairo and over 20% in higher socioeconomic areas in Cairo (28). More recently, studies of diabetes in Arab Americans in Dearborn, Michigan, have demonstrated an epidemic of diabetes with diabetes prevalence rates of 16% in women and 20% in men, rates very similar to those seen in persons living in the higher socioeconomic areas of Cairo (29).

What should be done?

Diabetes is an enormous and growing problem fueled by changing population demographics, urbanization, and lifestyle factors. What should be done? In the early 1980s, we examined the descriptive epidemiology of diabetes and highlighted areas where interventions, if systematically applied, could impact health (Table 3) (30). We estimated that diet and exercise could prevent up to 50% of type 2 diabetes or almost 300,000 cases of diabetes per year, with a substantial impact on downstream complications, comorbidities, and cost. The other striking finding from this analysis was that cardiovascular disease was the major cause of morbidity and mortality in diabetes (30). The DPP has established that the incidence of type 2 diabetes can be delayed or prevented by 58% with an intensive lifestyle intervention (31). The efficacy of lifestyle intervention has been confirmed by trials from Finland (32), China (33), and India (34). The Diabetes Control and Complications Trial (DCCT) showed that improved glycemic control reduced the risk of clinically meaningful retinopathy, nephropathy, and neuropathy in type 1 diabetes (35). Perhaps even more exciting are the recent results of the Epidemiology of Diabetes Interventions and Complications (EDIC) study, an epidemiologic follow-up of the DCCT cohort. At the end of the DCCT, intensive therapy patients had an A1C of 7% and standard therapy patients an A1C of 9%. Standard therapy patients were introduced to intensive therapy, and over 5 years of follow-up, the difference in A1C between intensive and conventional therapy patients diminished so that all patients had A1Cs of slightly less than 8%. Among patients with no evidence of diabetic retinopathy or diabetic nephropathy at study end, there was a persistent, beneficial effect of previous intensive therapy on microvascular complications (36–38).

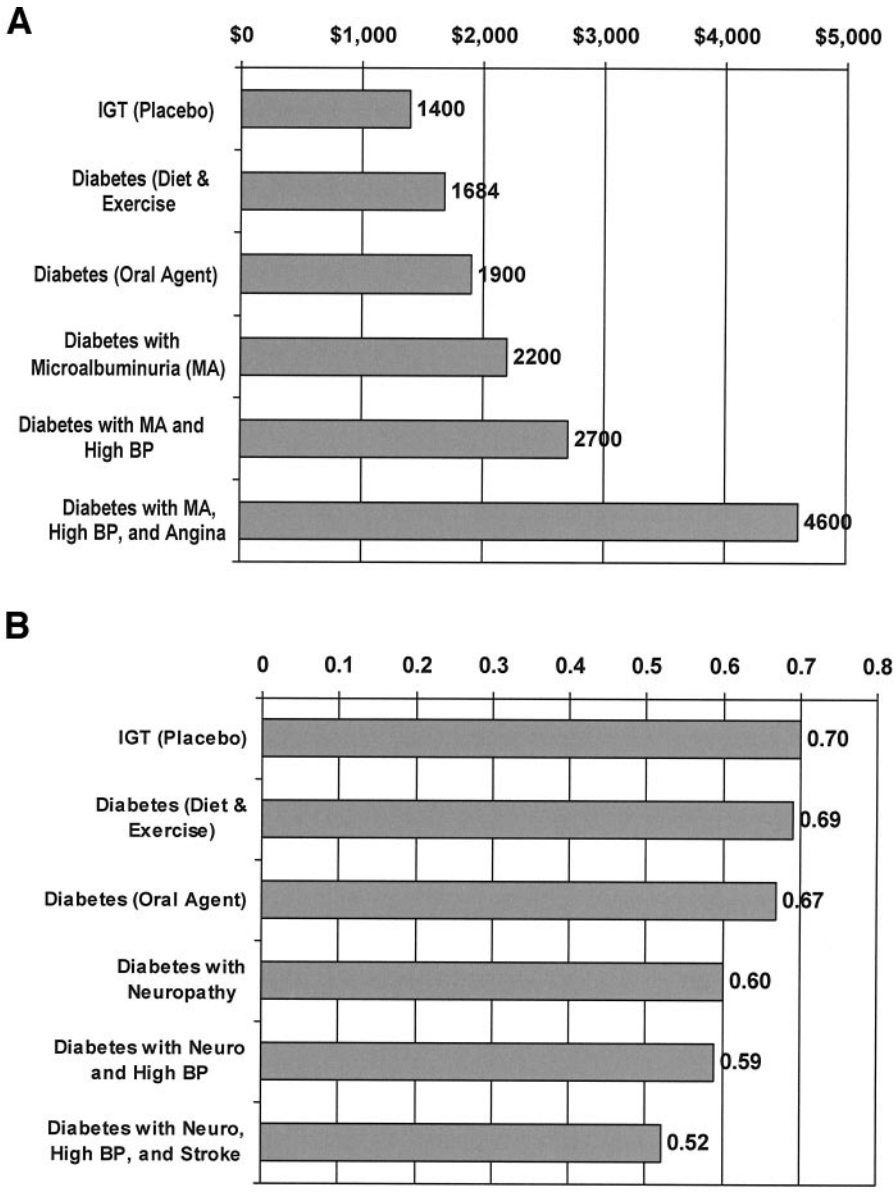

Figure 3—*Annual direct medical costs (*A*) and health utility scores (*B*) in a man progressing from IGT to diabetes with complications. BP, blood pressure.*

The cumulative incidence of nonfatal myocardial infarction, stroke, and death from cardiovascular disease, although not different at the end of the DCCT, was also reduced by 57% at 11 years of follow-up (39). So, clinical trials have demonstrated the feasibility of preventing diabetes and its complications, and epidemiologic follow-up has shown the importance of early aggressive glycemic management.

What is the cost-effectiveness of diabetes prevention?

To address the cost-effectiveness of diabetes prevention, the DPP Research Group performed a prospective economic analysis that adopted a health system perspective and looked at cost per quality-adjusted life-year (QALY) gained over a lifetime (40). Interventions were assessed as they were implemented in the DPP, and sensitivity analyses were performed by age and to assess the interventions as they might be implemented in routine clinical practice (40). Empiric data on costs, quality of life, and health outcomes were prospectively collected in the DPP (41,42). To project costs, quality of life, and health outcomes over the lifetime of an individual, we developed a cost model, a quality of life model, and a type 2 diabetes model. The cost model was developed with information from a large number of patients with type 2 diabetes (43). Demographic and disease state variables were assessed with questionnaires and medical chart review, and costs were assessed with HMO insurance claims. Similarly we developed a diabetes quality of life model (44). Demographic and disease state variables were assessed with a questionnaire, and health utilities were assessed with the same multiattribute utility model used in the DPP.

Figure 3 illustrates the models with the annual direct medical costs and health utility scores for a man progressing from IGT to diabetes with complications. In the DPP, the annual direct medical costs of IGT treatment and other medical care were $1,400 per person per year. The model demonstrated that when the person developed diabetes, complications, or comorbidities, costs increased (Fig. 3*A*). Similarly, in the DPP, the health utility score for a man with IGT treated with placebo was 0.70. The model demonstrated that the health utility score for a man with diabetes treated with diet and exercise was 0.69 and that quality of life decreased with additional treatments, complications, and comorbidities (Fig. 3*B*).

The third part of the simulation was a Markov model that followed the DPP patient cohort from diagnosis of IGT to diabetes to death. IGT transition probabilities were based on the DPP (40). Diabetes, microvascular, and macrovascular transition probabilities were based on the UK Prospective Diabetes Study (UKPDS) and other studies in the literature (40). In this analysis, we assumed a 10-year time interval between DPP onset and UKPDS clinical diagnosis of type 2 diabetes (40). The model tracked costs, QALYs, disease progression, five complications, and survival.

Compared with the placebo intervention, the metformin and lifestyle interventions both delayed the time to development of diabetes and reduced the cumulative incidence of diabetes (Fig. 4). The metformin intervention increased the time to which half of the people developed diabetes by 3.4 years relative to the placebo intervention, and the lifestyle intervention increased the time by 11.1 years. Metformin reduced the cumulative incidence of diabetes by 8% (from 83 to 75%) and the lifestyle intervention by 20% (from 83 to 63%). Not surprisingly, the interventions increased cost but, by delaying or preventing the development of diabetes, reduced the cumulative incidence of complications and comorbidities and increased length of life. Over a life-

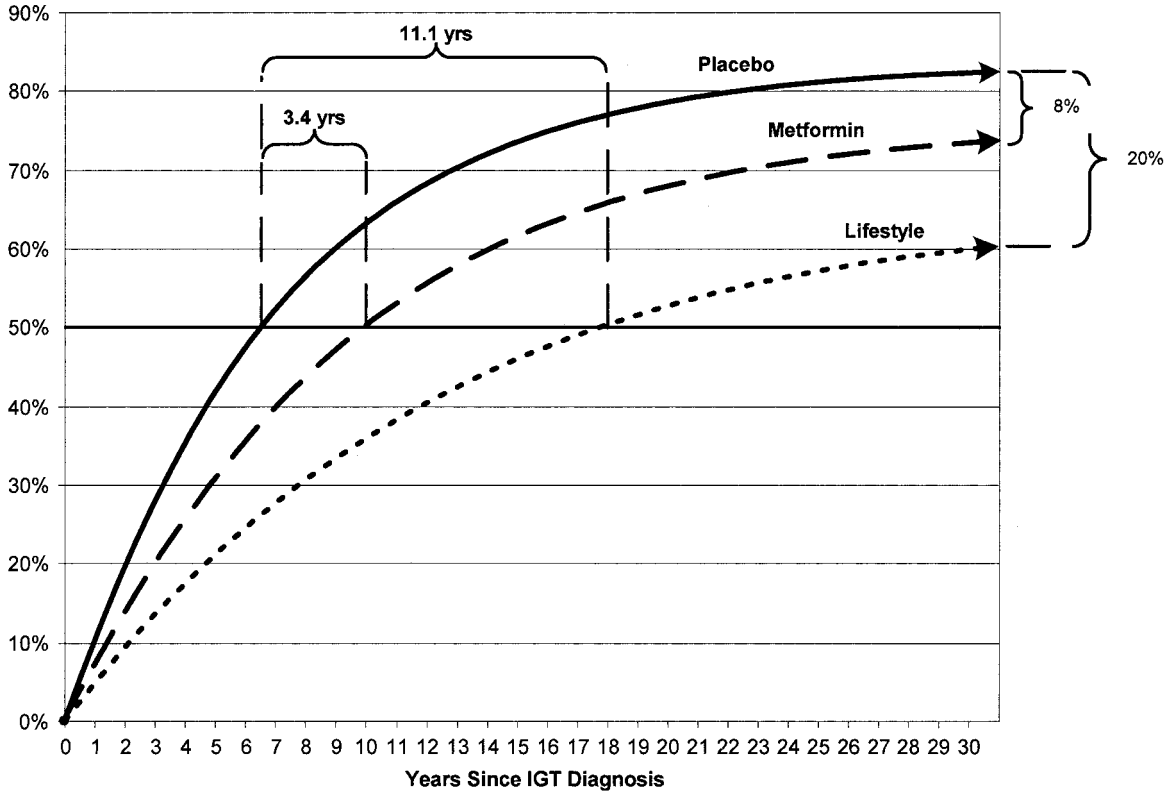

Figure 4—*Cumulative incidence of diabetes. Reprinted with permission from ref. 40.*

time, the metformin intervention was the most expensive, the lifestyle intervention intermediate, and the placebo intervention the least expensive. Compared with the placebo intervention, the lifestyle intervention cost about $635 more over a lifetime and the metformin intervention almost $4,000 more over a lifetime. Because they developed the fewest complications and lived the longest, individuals in the lifestyle intervention group experienced the most QALYs. Those receiving metformin experienced fewer QALYs, and those in the placebo group experienced the fewest QALYs. Compared with the placebo group, individuals in the lifestyle intervention gained about 0.57 QALYs and those receiving metformin 0.13 QALYs. The cost per QALY for the lifestyle intervention was about $1,000 and that for metformin about $31,000.

Other investigators have examined the cost-effectiveness of lifestyle intervention for diabetes prevention. Caro et al. (45) used data from the Finnish Diabetes Prevention Study and the DPP to simulate diabetes prevention and Palmer et al. (46) looked at diabetes prevention from a number of European perspectives. They, like us, found lifestyle intervention to be very cost-effective for diabetes prevention. In contrast, Eddy et al. (47) used the Archimedes model and found lifestyle intervention not to be cost-effective for diabetes prevention. Their published report shows a cost per QALY gained of almost $63,000 for lifestyle intervention and ~$36,000 for the metformin intervention.

It is unclear why the two simulations provided similar estimates of the cost-effectiveness of the metformin intervention with such dissimilar estimates for the cost-effectiveness of the lifestyle intervention, but at least two factors may explain this difference. One difference relates to assumptions regarding intervention costs. In our simulations, we assumed that the lifestyle intervention stopped at the onset of diabetes. In contrast, Eddy et al. assumed that the lifestyle intervention continued for the duration of the simulation. Costs are greater if people with diabetes continue to receive the lifestyle intervention and there is no impact on diabetes prevention; thus, the apparent cost-effectiveness is reduced. The second issue relates to the progression of diabetes and its complications. The DPP simulations and the Archimedes simulations projected a similar cumulative incidence of diabetes in patients receiving the lifestyle intervention (63 vs. 61%, respectively). In contrast, the cumulative incidence of complications was much higher in the DPP simulation than in the Archimedes simulation (for example, 39% cumulative incidence of myocardial infarction vs. 10%), and mortality was extremely low in the Archimedes simulation (11% mortality at 30 years follow-up, mean attained age 81 years). If diabetes is not associated with complications or adverse health outcomes, there is no benefit to preventing diabetes. From a single payer perspective, we still believe that intensive lifestyle intervention for diabetes represents a good value for money and should become clinical and public health practice in the U.S.

What can be done?

We now have treatments to prevent diabetes and its complications. How can they be translated into routine clinical practice to reduce the burden of diabetes? Again, epidemiology can provide answers. Translating Research Into Action for Diabetes (TRIAD) is a Centers for Disease Control– and National Institutes of Health–funded prospective observational study looking at diabetes care in managed care (48). TRIAD has focused on how

health plan and provider group structure and organization affect the processes and outcomes of diabetes care. TRIAD has demonstrated that for-profit and not-for-profit health plans seem to have comparable processes of care (49), groups that compensate physicians by salary and reward quality and patient satisfaction have better processes of care (50), and plans that have high cost-sharing in terms of co-payments and out-of-pocket costs have lower levels of preventive care (51). Referral management does not appear to be associated with worse processes of care (52) and intensity of disease management, including use of registries, physician reminders, and profiling, and care management is associated with better processes of care but may not be associated with better intermediate outcomes (53).

As a part of TRIAD, we have also had the opportunity to implement a population-based intervention for diabetes. In April 2004, the University of Michigan announced a major initiative to promote the health and well-being of the University community by removing financial barriers to proven-effective, evidence-based interventions. Initially, this has included waiving or reducing co-payments for antidiabetic, antihypertensive, antidepressant, and lipid-lowering medications and for diabetic eye exams for University of Michigan employees and their dependents with diabetes with the hope of improving processes of care, outcomes of care, health-related quality of life, and productivity. Over the next couple of years, we'll be working to evaluate this program.

If translated into practice, such health system interventions may reduce the burden of diabetes and its complications.

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