

## In Brief

Diabetes has a major impact on both affected individuals and society in general, with a total cost in excess of \$132 billion annually not to mention the associated increased morbidity and lost quality-of-life years. This article discusses some of the major studies that have attempted to quantitate the cost of diabetes and reviews the pathophysiology and disease sequelae commonly found in older people with diabetes.

# Emerging Epidemic: Diabetes in Older Adults: Demography, Economic Impact, and Pathophysiology

Steven R. Gambert, MD, and Sally Pinkstaff, MD, PhD

Although diabetes has been a known medical problem for > 2 millennia, it still presents a challenge and will most certainly continue to be a focus of medical care for many decades to come as our population continues to age and live longer than ever before. People who are identified early in life with diabetes are living to a more advanced age as modern treatments and earlier recognition of this potentially devastating disease continue to improve outcomes. The major increase occurring in the number of older people is, however, the main reason for concern for this and all other age-prevalent illnesses.

At the turn of the 20th century, diabetes was a popular theory as to why we age, with all individuals thought to be affected to varying degrees. The basic pathophysiology of diabetes was thought responsible for age-related change, and it was believed that individuals with diabetes exhibited an acceleration of a process that would affect everyone later in life. It was not until several decades later that this theory was discredited and diabetes received its proper recognition as a disease state, albeit one more common with increasing age.

Nevertheless, diabetes, even in those who have been successful in tightly controlling their blood glucose levels, has the potential for accelerating the aging process if one defines

aging as “a loss of reserve capacity.” Physiological changes may occur at a faster rate than in nondiabetic individuals, and, when coupled with other changes that have been associated with increasing age, this increases the potential for an earlier decline in functional capacity. This may lead to a reduced ability to remain independent in both basic and instrumental activities of daily living. For those less fortunate who have not been able to tightly control their blood glucose levels, the adverse outcome is perhaps more dramatic, with both microvascular and macrovascular disease occurring at an earlier age than one would expect, if at all, and major impacts noted on health and quality of life.

### Demographic Imperative

Diabetes is a major problem that will most certainly grow in magnitude as our population continues to age. It has been estimated that there are ~ 20 million individuals in the United States with diabetes, including 5 million adults who remain undiagnosed. In other words, almost 8% of the population > 20 years of age meet current criteria for having a diagnosis of diabetes. Diabetes is an age-prevalent disease, with increased chances of having this illness diagnosed as one ages. Half of the currently affected individuals are > 60 years of age, with the highest prevalence found in those

> 80 years of age, a number expected to reach 40 million by 2050. We will continue to see the number of people with diabetes rise during the next several decades, with one-third of all Americans likely to develop diabetes sometime within their lifetime.

Diabetes is the sixth leading cause of death listed on U.S. death certificates, contributing to ~ 225,000 deaths annually. The risk for death among individuals with diabetes is approximately twice that of people without diabetes of similar age. In fact, when one considers the combined burdens of diabetes and its complications, individuals diagnosed at age 60 have an estimated reduction in life expectancy and number of quality-of-life years of 7.3 and 11.1 years, respectively, for men, and 9.5 and 13.8 years, respectively, for women.<sup>1</sup>

Older people clearly are at increased risk of failing to receive proper counseling, diet, and, for some, potentially life saving medication. Personal preferences regarding interest in complying with guidelines and recommendations may play a role, although many elderly have coexisting illnesses that may interfere with their care and also place them at greater risk of unwanted side effects.

Approximately 1.3 million new cases of diabetes are diagnosed each year in the United States, with type 1 diabetes accounting for 5–10% of cases and type 2 diabetes accounting for 90–95%. Total costs attributable to diabetes have been estimated as high as \$132 billion annually, with indirect medical costs, including disability, lost work days, and premature mortality, major factors in this financial burden. Additionally, there is the harder-to-quantitate factor of lost quality of life. Older adults with diabetes frequently have multiple comorbidities and functional impairments and are a heterogeneous population.<sup>2,3</sup>

Just why are we facing this epidemic? In 1900, 4% of the population was > 65 years of age. This number has steadily grown and is currently estimated at 13%. The segment of people > 80 years of age is increasing at the fastest rate. Furthermore, whereas the majority of those > 65 are now between the ages of 65 and 75 years, there will be a shift in demography over the next few decades such that the majority of the geriatric population will be ≥ 75 years of age.

This is a major concern to health economists because an increasing per-

centage of lifetime health care costs are accounted for during the later stages of life. As our population lives longer and medical advances continue to develop, individuals will have a greater chance of developing diseases that occur more commonly during later life; many individuals will also live with chronic illnesses such as diabetes for many more years than might be possible at present.

Putting it another way, census officials have predicted that the number of people ≥ 65 years of age will double within the next 25 years. By 2030, approximately one-fifth of all Americans, or 70 million individuals, will be older than 65 years of age.

It is hard to predict the exact impact that this demographic change will have because medical advances and socioeconomic improvements have helped to reduce disability, with more people remaining functional for longer periods of time. In 1982, national statistics reported that 26% of people > 65 years of age required assistance to meet their activities of daily living and thus were categorized as “disabled.” This number dropped by one-fifth to 20% by 1999. At present, according to the U.S. Census Bureau, ~ 20% of people > 65 years of age have some chronic disability, with 8% having significant cognitive impairment and 30% having difficulty with mobility. These numbers are lower at the lower limit of this age group and increase with increasing age. For example, cognitive impairment has been reported to be present in 20% of individuals > 80 years of age, similar to the percentage noted for diabetes.

Arthritis and heart disease are the most common chronic conditions affecting older people, with ~ 19% of people > 75 years of age and 12% of those between the ages of 65 and 74 being restricted in their daily activities because of arthritis or some other musculoskeletal condition. Diseases affecting the cardiovascular system significantly affect ~ 11% of people aged 65–74 years and 17% of those > 75 years of age.<sup>4</sup> Clearly, individuals of more advanced age, particularly those > 80 years of age, are more frail and on average have more advanced normal age-related changes and age-prevalent illnesses and are more likely to have an atypical or nonspecific presentation of illness.

It is in this context that we must understand the consequences of hav-

ing the additional diagnosis of diabetes. Diabetes may accelerate the otherwise normal rate of aging on a wide variety of physiological processes and result in disease states that might not otherwise be present.

It has been well recognized that people with diabetes are in the hospital more frequently than nondiabetic age-matched individuals and stay longer in the hospital for a given admission, a similar trend noted in the elderly population in general. Elderly people who have diabetes are at double jeopardy and have a much higher rate of health care utilization. When caring for older people with diabetes, careful consideration must be given to normal age-related physiological changes, coexisting age-prevalent illnesses, and “geriatric syndromes” that may not only affect a prescribed treatment regimen, but also increase the likelihood for drug interactions, side effects, and adverse outcomes. Patients’ ability to comply with a specific treatment may also be effected by diseases that occur more commonly during later life and thus increase the complexity of care.

### Pathophysiology of Diabetes in Older Adults

More than 90% of older adults have type 2 diabetes characterized by insulin resistance with relative insulin deficiency.<sup>5</sup> What makes the elderly population with diabetes more distinctive are the complex age-associated changes in fuel regulation that interact with genetic, behavioral, and environmental influences and contribute to the development of diabetes.<sup>6</sup> This section will focus on the age-related changes leading to type 2 diabetes.

Type 1 diabetes, characterized by insulin deficiency, does occur in the elderly, but the diagnosis is often delayed and the true incidence is unknown because ~ 50% of patients with type 2 diabetes will eventually require insulin. Clinical indicators of type 1 diabetes in older patients include ketonuria at diagnosis, a history of autoimmune endocrine disease, and low body weight.<sup>7</sup> Measuring islet cell and GAD antibodies has not proven useful in the elderly because their presence rises with age and does not reliably predict the rapid development of insulin deficiency.<sup>8</sup> Regardless of age or type of diabetes, progressive hyperglycemia mandates insulin treatment.

The decline in glucose tolerance as part of human aging has been well established.<sup>6,9</sup> Fasting plasma glucose levels increase by 1–2 mg/dl per decade after age 30, and postprandial glucose levels increase by ~15 mg/dl per decade.<sup>10–12</sup> Despite these age-related changes in glucose concentrations, there is no age adjustment for the diagnosis of diabetes because the risk for diabetes-related complications results from hyperglycemia over time and not age.<sup>13</sup>

Given the biological and medical heterogeneity among older adults, it is not surprising that the extent and rate of deterioration in glucose tolerance is variable, leading to insignificant changes in some individuals and frank hyperglycemia and diabetes in others. Clearly, chronological age per se is a poor predictor of an individual's physiological senescence or risk for age-related diseases, including diabetes. The two most important age-associated disturbances in carbohydrate metabolism are reduced insulin sensitivity in muscle, liver, and fat and impairment in insulin secretion from pancreatic  $\beta$ -cells.<sup>6</sup>

**Increased insulin resistance.** The rise in insulin resistance with aging is associated with increased visceral adiposity<sup>14</sup> and is evidenced by elevated fasting insulin levels<sup>15</sup> and a 50% reduction in insulin sensitivity as measured by a model of glucose kinetics.<sup>16</sup> At least part of the insulin resistance in skeletal muscle is explained by a decrease in the muscle content of the glucose carrier protein GLUT4.<sup>17</sup>

Although changes in total body fat, fat distribution, and physical fitness predictably occur with aging and can influence insulin resistance, their influence did not fully explain the decline in glucose tolerance in a group of healthy older men (aged 60–92 years), supporting the concept of age as an independent determinant in the loss of insulin sensitivity.<sup>18</sup> Even without weight gain, body composition changes in older people and is characterized by reduced lean body mass, increased visceral adiposity, and increased intramuscular fat.<sup>19</sup> By the mid-60s, lean body mass decreases 19% in men and 12% in women, despite an average weight gain of 25% in men and 18% in women.<sup>12</sup> As fat distribution changes with greater visceral fat and less subcutaneous fat, insulin resistance increases coincident with an increased risk for type 2 dia-

betes. In a study by Kanaya et al.,<sup>14</sup> visceral adiposity was more closely associated with insulin resistance and diabetes in older women (average age 73 years) than was BMI or any other measure of regional fat distribution. Fat accumulation in muscle and liver cells has been observed in healthy older adults, possibly the result of decreased mitochondrial function, an abnormality seen with aging. Regardless of whether visceral fat deposition is part of normal aging, it is one of the major pathogenic mechanisms driving insulin resistance.<sup>20</sup>

Lifestyle factors that contribute to the age-associated decrease in insulin sensitivity include dietary changes, with higher intakes of saturated fats and simple sugars, and reduced physical activity, with less skeletal muscle mass and reduced strength.<sup>6</sup> Exercise regimens that incorporate aerobic and resistance training can be particularly beneficial in attenuating age-related changes in body composition and can delay or prevent progression to diabetes.<sup>21</sup>

Other factors that may contribute to the age-related decline in glucose tolerance include alterations in the secretion of adipose tissue-derived hormones, such as adiponectin and leptin. Leptin levels fall with age, with greater reductions in women than in men.<sup>22</sup> Because leptin decreases appetite, its decline may contribute to the increased adiposity and body composition changes seen in the elderly. Adiponectin, a protein with anti-inflammatory properties, has been shown to reduce insulin resistance. Higher levels in elderly patients are associated with a lower risk of diabetes, an observation explained in part by the strong relationship between visceral adiposity and the presence of diabetes.<sup>14</sup> The contribution of adipocytokines to the development of insulin resistance with aging remains to be determined.

**Impaired insulin secretion.** The second and equally important pathogenic mechanism related to the decline in glucose tolerance with age is dysfunction of  $\beta$ -cells with alteration in insulin secretion.<sup>9</sup> In response to rising glucose levels, insulin is normally secreted in two phases, initially as a brisk first-phase release of insulin (0–10 minutes), followed by a second, more prolonged, phase (10–120 minutes), which continues as long as necessary to maintain euglycemia. Even

before the development of impaired glucose tolerance and after correcting for the age-associated loss of insulin sensitivity, studies have reported a 50% reduction in  $\beta$ -cell secretory capacity in older patients.<sup>9,16</sup>

Aging is also characterized by a reduced frequency and amplitude of the normal periodic insulin pulses with disruption in the orderliness of insulin release.<sup>23,24</sup> Loss of normal pulsatility is important because these pulses inhibit hepatic glucose output. In a small study comparing healthy middle-aged and elderly adults, first-phase insulin values were similar, whereas second-phase insulin levels were significantly lower in the older group.<sup>25</sup> Once fasting glucose levels reach 115–120 mg/dl, first-phase insulin secretion is lost. By the time impaired glucose tolerance develops with 2-hour postchallenge glucose levels equaling 141–199 mg/dl,  $\beta$ -cell function is already reduced by 60–70%.<sup>5</sup>

Although the mechanisms responsible for  $\beta$ -cell senescence are poorly understood, disturbances in the physiology of the gut-derived incretins have been suggested. Incretins are two gastrointestinal hormones, gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which enhance the secretion of insulin to a greater degree after the oral administration of glucose compared with the amount of insulin secreted when a similar level of hyperglycemia is achieved with intravenous glucose. In elderly patients without diabetes, release of GLP-1 is greater after an oral glucose load but does not result in the expected rise in insulin levels, suggesting  $\beta$ -cell resistance. Once diabetes develops, GLP-1 secretion is reduced, and  $\beta$ -cells are resistant to the effects of GIP.<sup>26</sup>

To assess the pathogenic effects of relative GLP-1 deficiency in type 2 diabetes, studies using GLP-1 or its analog have demonstrated improved insulin secretion with restoration of first-phase insulin in middle-aged adults after a short-term intravenous infusion and in elderly adults after 6 weeks of continuous subcutaneous administration.<sup>27,28</sup> Second-phase insulin release was also significantly enhanced in both groups. The *in vitro* effects of GLP-1 on human  $\beta$ -cell islets have included enhanced cell growth, proliferation of  $\beta$ -cell mass, and inhibition of  $\beta$ -cell apoptosis.<sup>29</sup> Whether these findings will translate

into preserved  $\beta$ -cell function in the elderly awaits further research.

Other pathogenic factors implicated in the age-associated decline in  $\beta$ -cell function include the rise in free fatty acids with age and the accumulation of fat within the  $\beta$ -cell. Reduced  $\beta$ -cell mass and amylin deposits may also contribute, but a full discussion of their influence is beyond the scope of this article.<sup>5,6</sup>

**Other pathogenic factors.** Family history and genetics strongly contribute to the development of diabetes in older individuals, especially those who are sedentary and gain weight with age. In elderly identical twins discordant for type 2 diabetes, the unaffected twins were less obese but still exhibited defects in insulin release and reduced glucose disposal rates.<sup>30</sup> Other factors predisposing to diabetes in the elderly include coexisting illnesses and medications that alter insulin sensitivity, insulin secretion, or both.

**Progression to type 2 diabetes.** The changes in carbohydrate metabolism that occur with aging are similar to the abnormalities observed in type 2 diabetes, although to a lesser degree. Typically, changes in glucose tolerance begin with changes in body composition, rising insulin resistance, and initially compensatory increases in insulin secretion. Because the senescent  $\beta$ -cell is maladaptive in its secretory capacity, especially in genetically susceptible individuals, insulin secretion becomes inadequate, leading to glucose intolerance and diabetes.

It should be emphasized that abnormal glucose tolerance does not develop without a significant  $\beta$ -cell defect. Because increasing visceral adiposity with age is strongly linked with insulin resistance and the development of diabetes, its presence serves to overwhelm the aging  $\beta$ -cell. The roles of incretins and adipocytokines in this process remain to be elucidated.

In summary, the development of type 2 diabetes in older adults represents the progressive worsening of multiple age-related metabolic disturbances plus at least a 50% contribution from environmental, genetic, and behavioral factors. Currently, methods to attenuate the adverse effects of aging and reduce progression to diabetes include physical activity, resistance exercise, and dietary intakes high in fiber and complex carbohydrates and low in saturated fat.<sup>5,6</sup>

### Normal Age-Related Changes, Diabetes, and Impact on Health Status

All elderly people, regardless of whether they have diabetes, have normal age-related changes that have the potential to reduce physiological reserve capacity. This places older people, especially those > 80 years of age, at greater risk of medication side effects, particularly hypoglycemia and hypotension. Counterregulatory mechanisms may be delayed or absent, resulting in prolonged adverse effects with, all too often, undesirable outcomes. A full discussion regarding normal age-related changes is beyond the scope of this article.

Diseases may accelerate the otherwise normal age-related processes, further reducing functional capacity and physiological reserve. Diabetes affects most organ systems and cells in the body, and its ability to compromise physiological function must not be underestimated. Clearly, attention to proper blood glucose control can go a long way to slow or even prevent end-organ and cellular changes that may make age-related changes more significant and problematic than would otherwise be the case if age was the only factor influencing physiological parameters. Disease-specific complications can greatly impair function and, when coupled with other age-related changes, greatly affect elderly patients' ability to independently conduct basic and instrumental activities of daily living and interfere with self-care and disease management.

Amputations occur many times more frequently in individuals with diabetes. Lower-extremity amputation rates increase with age such that 12 of 10,000 diabetic patients < 44 years of age, 45 of 10,000 diabetic patients aged 45–64 years, and 100 of 10,000 diabetic patients  $\geq$  65 years of age are affected.<sup>31</sup> Elderly individuals have been reported to delay treatment as well as underreport major medical conditions, making care even more difficult for older people with diabetes.

Clearly, the complications of diabetes are responsible for a major component of the total cost. Peripheral vascular disease, neuropathy, and social factors are important precursors of diabetic foot ulceration and amputation. In 50% of cases of diabetic foot problems, vascular disease and neuropathy will both be present.

Hospital admissions for peripheral vascular disease and neuropathy account for approximately one-fifth of total bed days associated with diabetes. Although lower economic status has been reported to increase the rate of foot problems, regular visits for diabetic foot problems to a team consisting of a physician, diabetes specialist nurse, podiatrist, and orthotist appear to reduce risk.<sup>32</sup>

Diabetic eye disease is also of particular concern because of its additive effect on age-related changes in eye health. Although diabetes is the most common cause of blindness overall, age-related macular degeneration is the most common cause of blindness in the elderly. Elderly people with diabetes are at an even higher risk of blindness because these two conditions together are responsible for the majority of blindness in older people. All elderly people with diabetes should see an ophthalmologist regularly and maintain glucose control as well as possible, although even then some of the above changes may occur.

Diabetes and hypertension are responsible for the majority of dialysis cases, most of which involve elderly individuals. Diabetic glomerulopathy accounts for 25–35% of people entering end-stage renal disease (ESRD) programs, at a cost of > \$1 billion annually. Histological changes from diabetic nephropathy are present within 5 years of diagnosis; overt nephropathy usually occurs after 15–25 years of diabetes.

Studies have demonstrated significant financial benefit from screening for microalbuminuria, especially in those with type 1 diabetes. One study reported that reducing the urinary albumin excretion rate from 20 to 18% annually would result in a net savings by reducing the number of people with end-stage renal failure requiring dialysis. It was also postulated that if antihypertensive treatment in diabetic patients could reduce the progression of the urinary albumin excretion rate by as little as 33%, median life expectancy for these patients would increase by 4 years. A reduction of 60% would increase life expectancy by 14 years. There would also be a reduction in the need for dialysis and transplantation by 20 and 60%, respectively.<sup>33</sup> Renal impairment is a major problem in elderly people with diabetes. Decreased creatinine clearance (< 60 ml/min per 1.73 m<sup>2</sup>) has been observed in 77% of the U.S.

elderly population with type 2 diabetes, with serum creatinine levels increased in 43%.<sup>34</sup>

Diabetes increases the cost of care for those with ESRD. The number of hospital days for patients with diabetes receiving dialysis was noted to be 37% higher than for ESRD patients without diabetes. Patients with diabetes averaged 45% more days in the hospital posttransplantation compared with those without diabetes. Respective annual per capita costs for all patients with ESRD because of diabetes compared with patients with ESRD without diabetes was noted to be 1.5 times greater for hemodialysis, 1.6 times greater for peritoneal dialysis, and 1.3 times greater for kidney transplantation.<sup>35</sup>

Other frequently encountered genitourinary problems include urinary tract infections, pyelonephritis, and renal carbuncles. Older people more frequently present with urinary incontinence. Although there are many reasons for urinary incontinence in older people, any one of which may be the cause in older people with diabetes, older diabetic patients more frequently will have urinary incontinence because of a coexisting urinary tract infection that leads to hyperirritability of the detrusor muscle; an atonic bladder resulting from autonomic neuropathy that leads to "overflow" incontinence and urinary retention; or osmotic diuresis resulting from glycosuria. A thorough workup to ascertain the cause of the urinary incontinence is necessary, and clinicians must remember that many elderly patients will have several reasons for the same presenting clinical problem; treating only one of them may not provide a solution. Urinary incontinence in itself is another major cost, both to the people affected and to society.

Regarding neuropathy, the highest hospitalization rate among people with diabetes in one study occurred in the 45- to 54-year age group (6.74 per 1,000); the highest rate for nondiabetic control subjects (1.8 per 1,000) was in those aged > 75 years.<sup>36</sup> Patients with diabetes aged > 45 years were 46 times more likely to be hospitalized because of neuropathy as those without this disease. That study also reported that people with diabetes were 21.8 times as likely to be admitted for skin ulcers/gangrene, 15 times as likely for peripheral vascular disease, 10 times as likely for congestive heart failure, and almost 10 times

as likely for atherosclerosis. Cerebrovascular accidents and heart disease were noted to be 6–10 times more common in diabetic patients. The authors concluded that late complications of diabetes resulted in ~ 7 million hospital days costing in excess of \$5 billion dollars annually.

### Impact of Obesity on Diabetes

Adding to the future epidemic of diabetes is the major problem of obesity in the United States, with particular concern regarding the growing number of overweight children. Wolf and Colditz<sup>37</sup> estimated that the direct cost of obesity-associated disease in 1990 alone was \$46 billion, with an additional \$23 billion spent on indirect costs. That year, the cost of type 2 diabetes attributable to obesity was reported to be \$12.7 billion, \$8.85 billion in direct costs and \$3.89 billion for indirect costs associated with lost productivity and excess mortality. It was estimated that 52.6 million work days were lost per year because of obesity-related disease, approximately one-fourth of these days being in those individuals who had coexisting diabetes. Fifteen years later, these numbers have grown considerably and will most certainly affect the cost of diabetes for decades to come.

Obesity as a precipitating factor for the development of type 2 diabetes must not be forgotten. Studies have demonstrated that weight control can delay if not prevent the onset of hyperglycemia and is a proven cost-effective treatment and preventive measure. One study examined the prescription cost savings associated with a weight reduction program in obese patients with type 2 diabetes. At 1 year, the average monthly costs for insulin and oral hypoglycemic agents decreased to 59 and 88% of their pre-diet values, respectively.<sup>38</sup>

It is important to avoid excessive weight loss in older people because the reduction in weight may result in a significant loss of muscle mass and a decline in functional ability. A supervised exercise program may help maintain lean body mass and improve outcome while facilitating weight loss.

### General Considerations

In one study, people with diabetes were reported to be 3.3 times more likely to be diagnosed with ischemic heart disease, 3.1 times more likely with peripheral vascular disease, 2.8 times more likely with hypertension,

and 2.3 times more likely with cerebrovascular disease.<sup>39</sup> They are also 4 times more likely to be hospitalized annually, with macrovascular disease accounting for 87.4% of bed days used for diabetic complications. The risks of acute myocardial infarction and chronic ischemic heart disease were 8.3 and 7.2 times as great, respectively, for people with diabetes compared with age-matched control subjects. Cardiovascular complications accounted for 74% of hospitalization costs for the late complications of diabetes.

The American Diabetes Association (ADA) reported 2.3 million hospital discharges in the United States in 1997 attributable to the care of people with diabetes, or 2.87 per 1,000 people with diabetes. Sixty-two percent of the direct costs of this illness was spent on inpatient care. The remainder of direct costs were attributable to outpatient services and home health care (24.7%), nursing home care (12.5%), and hospice care (0.5%). One-third of the indirect costs were attributable to premature mortality, and two-thirds were spent on disability. People with diabetes had an annual medical expense of \$10,071 per capita versus \$2,669 per capita for those without diabetes.<sup>40</sup>

An interesting study examined the effect of the introduction of reimbursement based on Diagnosis Related Group (DRG) classifications for people with diabetes.<sup>41</sup> The authors compared outcomes for patients with type 2 diabetes who were hospitalized for regulation of glycemia before and after implementation of this process. Post-DRG patients had significantly fewer laboratory tests while in the hospital, were less likely to have an education session with a registered nurse and dietitian, and had fewer rehabilitation consultations. Hospital stay was significantly shorter in the post-DRG group. Although plasma glucose concentrations at the time of discharge were similar in the two comparative groups, individuals in the post-DRG period had significantly more visits to the primary care provider and statistically higher random plasma glucose concentrations after hospital discharge. This may potentially affect cost because of higher rates of complications in those who have less tight blood glucose control.

Huse et al.<sup>42</sup> reported on the cost of type 2 diabetes in 1986; 59% of

diabetes-related health care expenditures were found to be directly attributable to diabetes or its complications, and 41% percent were related to an excess prevalence of related conditions, mostly circulatory disorders. Per case, annual health care expenditures attributed to type 2 diabetes ranged from \$1,274 among men < 65 years of age to \$3,078 among women ≥ 65. They also noted that there were 144,000 premature deaths attributable to diabetes, or 6.8% of all U.S. mortality during that year; this was estimated to be a loss of 1,445,000 years of life. Of the 144,000 deaths, cardiovascular disease was the cause in 124,000.<sup>42</sup>

### Direct and Indirect Financial Concerns

Because most of the costs of diabetes result from its chronic complications, programs designed to increase the early diagnosis and treatment of diabetes are suggested as ways of reducing both direct and indirect costs. Using data from several government surveys, the National Health Interview Survey, National Hospital Discharge Survey, National Nursing Home Survey, and National Ambulatory Medical Care Survey, it was reported that direct costs accounted for 47% of the total expense, with indirect costs estimated at 53%.<sup>43</sup> Indirect costs include short-term morbidity, long-term disability, and premature mortality.

Diabetes must be recognized early and dealt with effectively if we are to maximize quality as well as quantity of life, both of which are costs that need to be considered. Hospitalization of people with diabetes accounts for > 80% of direct diabetes-related costs. Another study reported annual inpatient costs per patient with diabetes at \$7,150, compared with \$1,220 for people without diabetes. The corresponding averages for annual outpatient costs were \$1,225 and \$330, respectively.<sup>44</sup>

A study evaluated expenses incurred for hospital stays, nursing home stays, physician visits, laboratory tests, prescriptions, supplies, and self-monitoring tests, using estimates of use (inpatient, outpatient, and nursing home) attributable to diabetes to estimate the economic impact of this disease on older people. Only data from individuals > 65 years of age were evaluated, and only type 2 diabetes was considered. The authors attributed 400,000 admissions and 3.9

million hospital days to diabetes or its complications in the study period. Increased length of hospital stay for patients with diabetes who were admitted for other non-diabetes-related conditions added another 1.5 million patient days. Hospitalization plus inpatient physician visits yielded \$4.1 billion, or 79.7% of all expenditures. Nursing home costs totaled \$306 million (5.9%), and \$742 million (14.4%) resulted from outpatient care including office and nonoffice physician visits, laboratory tests, and prescriptions. On a per-person basis, expenses averaged \$4,265, ~ 50% higher than for age-matched individuals without diabetes.<sup>45</sup>

Another study reported health care costs based on the 1987 National Medical Expenditure Survey extrapolating data to 1992 based on U.S. Census demographic data corrected for inflation. Based on an estimated prevalence of 31.1 cases of diabetes per 1,000 people, it was estimated that 7.7 million people had confirmed diabetes in the United States at that time. This number likely underestimated those with diabetes, given the higher prevalence of diabetes in the elderly and the greater percentage of older people during this time period. That said, the authors concluded that \$105.2 billion (14.6%) of the U.S. total for health care expenditures was being spent on the health care of individuals with diabetes. Inpatient care for people with diabetes was more than six times that of those without this disease, and the cost of office visits was approximately twice as high. Medication and durable medical equipment was more than five times higher, home health care six times higher, and emergency room care one and a half times higher. Differences in health care costs were highly significant for all age groups studied and for the group when considered as a whole.<sup>46</sup>

Data from the 1991 National Hospital Discharge Survey reported that middle-aged people with diabetes were 60% more likely to be hospitalized for general medical conditions than people without diabetes. The greatest relative risks were for peritonitis/intestinal abscess, respiratory failure, liver disease, and male genital disorders. Among the elderly, there was no significant difference between the groups in overall risk of hospitalization for general medical conditions, but those with diabetes had elevated

risks for liver disease, septicemia, and diseases of pulmonary circulation, among others. People with diabetes were hospitalized for longer periods of time in both age groups, and health care costs were also higher for those with diabetes.<sup>47</sup>

Caruthers<sup>48</sup> evaluated per capita medical costs for diabetes-related problems and found them to be three and a half times higher for people with diabetes than for those without diabetes. These differences were statistically significant at all ages studied but were greatest for people aged 45–54 years. The total cost for diabetic patients was estimated in this report to be \$112 billion annually.

Damsgaard<sup>49</sup> reported in the *Danish Medical Bulletin* that elderly people with diabetes scored higher on a scale measuring subjective health symptoms and had a greater frequency of objective findings. This led to a greater number of visits to primary care providers, especially for those who required insulin to manage their blood glucose.

### Role of Intensive Therapy

The U.K. Prospective Diabetes Study and the Diabetes Control and Complications Trial (DCCT) demonstrated that tight control of blood glucose is capable of reducing many of the complications of diabetes by as much as an estimated 50%. The annual cost of intensive therapy with multiple daily insulin injections is ~ \$4,000 per year or 2.4 times the cost of conventional therapy. Most of the difference in cost is attributable to differences in the frequency of outpatient visits and self-monitoring of blood glucose. The annual cost of intensive therapy with continuous subcutaneous insulin infusion was even higher at \$5,880. This additional cost resulted entirely from the cost of the pump and pump-related supplies. Costs associated with the major side effects of intensive therapy, such as excessive weight gain and severe hypoglycemia, were three times the cost of treating the side effects of conventional therapy, but as a percentage of the total cost, there was little difference noted.<sup>50</sup>

Costs associated with intensive therapy in the DCCT in academic settings likely underestimate the true cost in community health settings where hypoglycemia might occur more frequently. Nevertheless, the cost of treatment, even if an order of

magnitude higher than reported, is less than the cost of treating diabetes-related complications. Many hospitals that have adopted intensive programs for diabetic patients have reported major savings, with reductions in length of hospital stay of 1–1.92 days compared with patients on less stringent protocols.<sup>51</sup>

### Summary

Diabetes is a major problem that will continue to stress our health care finances for decades to come. It has been estimated that the number of individuals diagnosed with diabetes in the United States will increase by as much as 165% during the next 50 years. The greatest growth in numbers will be among those  $\geq 75$  years of age (336%) and among African Americans (275%).

Diabetes ranks as one of the top two causes of blindness, renal failure, and lower-limb amputation. It is one of the leading causes of death, with 80% of people with diabetes dying of cardiovascular disease. The World Health Organization has estimated that the number of people with diabetes globally will rise from its current estimate of 151 million to 221 million by 2010 and to 300 million by 2025.<sup>52</sup> This increase is expected to occur in almost all countries throughout the world, with the largest increase predicted to occur in developing countries, especially those in Asia. By 2050, it has been estimated that there will be an additional 18 million people with diagnosed diabetes in the United States alone. This will result largely from the demographic changes occurring, with increases in the number of elderly and high-risk minority populations.

Although 27% of this increase will be explained by population growth, 36% will result from changes in age prevalence as individuals with lifelong diabetes live for longer periods of time, and the aging of America continues to bring a greater number of people diagnosed with diabetes during later life. A rise in the number of children with type 2 diabetes has also been noted. This is thought to result from sedentary lifestyles and the epidemic of obesity that is occurring in children and young adults. Foods rich in calories and saturated fats have become all too common as dietary choices of our nation's youth.

The cost of diabetes, its prevention, and its treatment will significantly

affect the budgets of countries throughout the world for decades to come. We need a concerted effort to aggressively tackle the problem of diabetes. Socioeconomic factors play a major role in nutrition and health care and must be addressed on both an individual and societal level if we are to be successful in preventing this potentially devastating and costly disease.

All may not be so grim, however. During the past 2 decades, data from the National Health and Nutrition Examination Survey and the Behavioral Risk Factor Surveillance System have shown that the proportion of people with diabetes who have poor glycemic control (e.g., hemoglobin A<sub>1c</sub> [A1C] levels  $> 9\%$ ) has declined by 3.9%, and the proportion of people with diabetes who have fair or good lipid control significantly increased by 21.9%. The proportion of people with A1C levels of 6–8% has increased from 34.2 to 47.0%. The use of appropriate health care screening by people with diabetes has also increased, with annual lipid testing up by 8.3%, dilated eye examinations up by 4.5%, and foot examinations up by 3.8%. Use of annual influenza vaccines and aspirin use by people with diabetes have increased by 10.7 and 13.1%, respectively.<sup>53</sup>

Future strategies for prevention will most certainly be developed and may include treatment with gene therapy as well as the use of certain pharmaceutical agents, such as ACE inhibitors.<sup>54</sup> Aging is a lifelong process, and attention to proper prevention and care is essential at all ages. The ADA most recently has estimated the total health care costs in the United States for diabetes at \$132 billion, \$91.8 billion of which is spent on direct costs, and \$39.8 billion is spent on indirect costs. Early recognition and treatment can make a major difference in this cost while also improving outcome, reducing morbidity, and improving the quality and quantity of life for many millions of people.

### References

- <sup>1</sup>Narayan KM, Boyle JP, Thompson J: Lifetime risk for diabetes mellitus in the United States. *JAMA* 290:1884–1890, 2003
- <sup>2</sup>Mary SC, Fried LP, Volpato S, Williamson J, Brancati FL, Blaum CS: Patterns of disability related to diabetes mellitus in older women. *J Gerontol A Biol Sci Med Sci* 59:148–153, 2004
- <sup>3</sup>Blaum CS, Ofstedal MB, Lana KM, Wray LA: Functional status and health outcomes in older

americans with diabetes mellitus. *J Am Geriatr Soc* 51:745–753, 2003

<sup>4</sup>Bureau of Census Report [article online]. Available from [www.census.gov/prod/2006pubs/p23-209.pdf](http://www.census.gov/prod/2006pubs/p23-209.pdf)

<sup>5</sup>DeFronzo RA: Pathogenesis of type 2 diabetes mellitus. *Med Clin North Am* 88:787–835, 2004

<sup>6</sup>Meneilly GS: Pathophysiology of diabetes in the elderly. In *Diabetes in Old Age*. 2nd ed. Sinclair AJ, Finucane P, Eds. Chichester, U.K., John Wiley & Sons, 2001, p. 155–164

<sup>7</sup>Sturrock NDC, Page SR, Clarke P, Tattersall RB: Insulin dependent diabetes in nonagenarians. *BMJ* 310:1117–1118, 1995

<sup>8</sup>Meneilly GS, Tildesley H, Elliott T, Palmer JP, Juneja R: Significance of GAD positivity in elderly patients with diabetes. *Diabet Med* 17:247–251, 2000

<sup>9</sup>Chen M, Bergman RN, Pacini G, Porte D: Pathogenesis of age-related glucose intolerance in man: insulin resistance and decreased beta-cell function. *J Clin Endocrinol Metab* 60:13–20, 1985

<sup>10</sup>Reaven GM, Reaven EP: Effects of age on various aspects of glucose and insulin metabolism. *Mol Cell Biochem* 31:37–47, 1980

<sup>11</sup>Samos LF, Roos BA: Diabetes mellitus in older persons. *Med Clin North Am* 82:791–803, 1998

<sup>12</sup>Hornick TR, Kowal J: Clinical epidemiology of endocrine disorders in the elderly. *Endo Metab Clin North Am* 26:145–163, 1997

<sup>13</sup>American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 29 (Suppl. 1):S43–S48, 2006

<sup>14</sup>Kanaya AM, Harris T, Goodpaster BH, Tyllavsky F, Cummings SR: Adipocytokines attenuate the association between visceral adiposity and diabetes in older adults. *Diabetes Care* 27:1375–1380, 2004

<sup>15</sup>Gumbiner B, Polonsky KS, Beltz WF, Wallace P, Brechtel G, Fink RI: Effects of aging on insulin secretion. *Diabetes* 38:1549–1556, 1989

<sup>16</sup>Roder ME, Schwartz RS, Prigeon RL, Kahn SE: Reduced pancreatic B cell compensation to the insulin resistance of aging: impact on proinsulin and insulin levels. *J Clin Endocrinol Metab* 85:2275–2280, 2000

<sup>17</sup>Houmar J, Weidner MD, Dolan PL: Skeletal muscle GLUT4 protein concentration and aging in humans. *Diabetes* 44:555–560, 1995

<sup>18</sup>Shimokata H, Muller DC, Fleg JL, Sorkin J, Ziemba AW, Andres R: Age as independent determinant of glucose tolerance. *Diabetes* 40:44–51, 1991

<sup>19</sup>Obisesan TO, Aliyu MH, Bond V, Adams RG, Akomolafe A, Rotimi CN: Ethnic and age-related fat free mass loss in older Americans: the Third National Health and Nutrition Examination Survey (NHANES III). *BMC Public Health* 5:41–49, 2005

<sup>20</sup>Petersen KF, Shulman GI: Etiology of insulin resistance. *Am J Med* 119:10S–16S, 2006

<sup>21</sup>Singh MA: Exercise to prevent and treat functional disability. *Clin Geriatr Med* 18:431–462, 2002

- <sup>22</sup>Isidori AM, Strollo F, More M, Caprio M, Aversa A, Moretti C, Frajese G, Riondino G, Fabbri A: Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights. *J Clin Endocrinol Metab* 85:1954–1962, 2000
- <sup>23</sup>Meneilly GS, Ryan AS, Veldhuis JD, Elahi D: Increased disorderliness of basal insulin release, attenuated insulin secretory burst mass, and reduced ultradian rhythm of insulin secretion in older individuals. *J Clin Endocrinol Metab* 82:4088–4093, 1997
- <sup>24</sup>Meneilly GS, Veldhuis JD, Elahi D: Disruption of the pulsatile and entropic modes of insulin release during an unvarying glucose stimulus in elderly individuals. *J Clin Endocrinol Metab* 84:1938–1943, 1999
- <sup>25</sup>Meneilly GS, Elliott T: Metabolic alterations in middle-aged and elderly obese patients with type 2 diabetes. *Diabetes Care* 22:112–118, 1999
- <sup>26</sup>Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, Holst JJ: Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab* 86:3717–3723, 2001
- <sup>27</sup>Fehse F, Trautmann M, Holst JJ, Halseth AE, Nanayakkara N, Nielsen LL, Fineman MS, Kim DD, Nauck MA: Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 90:5991–5997, 2005
- <sup>28</sup>Meneilly GS, Greig N, Tildesley H, Habener JF, Egan JM, Elahi D: Effects of 3 months of continuous subcutaneous administration of glucagon-like peptide 1 in elderly patients with type 2 diabetes. *Diabetes Care* 26:2835–2841, 2003
- <sup>29</sup>Farilla L, Bulotta A, Hirshberg B, Li Calzi S, Khoury N, Noshmeh H, Bertolotto C, Di Mario U, Harlan DM, Perfetti R: Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology* 144:5149–5158, 2003
- <sup>30</sup>Vaag A, Henriksen JE, Madsbad S, Holm N, Beck-Nielsen H: Insulin secretion, insulin action, and hepatic glucose production in identical twins discordant for non-insulin-dependent diabetes mellitus. *J Clin Invest* 95:690–698, 1995
- <sup>31</sup>Podolsky S: Diabetic complications: the diabetic foot. In *Diabetes Mellitus in the Elderly*. Gambert SR, Ed. New York, Raven Press, 1990, p. 87–103
- <sup>32</sup>Ward JD: The cost of diabetic foot problems. *Pharmacoeconomics* 8 (Suppl. 1):55–57, 1995
- <sup>33</sup>Borch-Johnsen K: The economics of screening for microalbuminuria in patients with insulin-dependent diabetes mellitus. *Pharmacoeconomics* 5:357–360, 1994
- <sup>34</sup>Varas-Lorenzo C, Rueda de Castro AM, Maguire A, Miret M, Blance C: Cardiovascular co-morbidity in the U.S. elderly population with renal and glucose metabolism impairment: the Third National Health and Nutrition Examination Survey. *Pharmacoepidemiol Drug Saf* 11:S53–S57, 2002
- <sup>35</sup>Narins BE, Narins RG: Clinical features and health-care costs of diabetic nephropathy. *Diabetes Care* 11:833–839, 1988
- <sup>36</sup>Jacobs J, Sena M, Fox N: The cost of hospitalization for the late complications of diabetes in the United States. *Diabet Med* 8 (Symposium):S23S29, 1991
- <sup>37</sup>Wolf AM, Colditz GA: The cost of obesity: the U.S. perspective. *Pharmacoeconomics* 5 (Suppl. 1):34–37, 1994
- <sup>38</sup>Collings, RW, Anderson, JW: Medication cost savings associated with weight loss for obese non-insulin dependent diabetic men and women. *Prevent Med* 24:369–374, 1995
- <sup>39</sup>MacLeod KM, Tooke JE: Direct and indirect costs of cardiovascular and cerebrovascular complications of type II diabetes. *Pharmacoeconomics* 8 (Suppl. 1):46–51, 1995
- <sup>40</sup>American Diabetes Association: Economic consequences of diabetes mellitus in the U.S. in 1997. *Diabetes Care* 21:296–309, 1998
- <sup>41</sup>Weinberger M, Ault KA, Vinicor F: Prospective reimbursement and diabetes mellitus: impact upon glycemic control and utilization of health services. *Med Care* 26:77–83, 1988
- <sup>42</sup>Huse D, Oster G, Kilen A, Lacey M, Colditz G: The economic costs of non-insulin-dependent diabetes mellitus. *JAMA* 262:2708–2713, 1989
- <sup>43</sup>Bransome ED: Financing the care of diabetes mellitus in the U.S.: background, problems, and challenges. *Diabetes Care* 15 (Suppl. 1):1–5, 1992
- <sup>44</sup>Finder SF, Smith MD, McGhan WF: Digging out savings in diabetes care: costing out care. *Bus Health* 12:69–70, 72, 1996
- <sup>45</sup>Weinberger M, Cowper PA, Kirkman MS, Vinicor F: Economic impact of diabetes mellitus in the elderly. *Clin Geriatr Med* 6:959–970, 1990
- <sup>46</sup>Rubin RJ, Altman WM, Mendelson DN: Health care expenditures for people with diabetes mellitus. *J Clin Endocrinol Metab* 78:809A–809F, 1994
- <sup>47</sup>Ray NF, Thamer M, Taylor T, Fehrenback SN, Ratner R: Hospitalization and expenditures for the treatment of general medical conditions among the U.S. diabetic population in 1991. *J Clin Endocrinol Metab* 81:3671–3679, 1996
- <sup>48</sup>Caruthers C: Tallying the cost of diabetes. *Bus Health* 14:SR8–SR13, 1996
- <sup>49</sup>Damsgaard EM: Why do elderly diabetics burden the health care system more than non-diabetics? *Danish Med Bull* 36:89–92, 1989
- <sup>50</sup>The DCCT Research Group: Resource utilization and costs of care in the Diabetes Control and Complications Trial. *Diabetes Care* 18:1468–1478, 1995
- <sup>51</sup>Conklin MS: Hospitals adopt intensive programs for diabetic patients to avoid high inpatient costs. *Health Care Strateg Manage* 12:11–13, 1994
- <sup>52</sup>Zimmet P: Diabetes epidemiology as a trigger to diabetes research. *Diabetologia* 42:499–518, 1999
- <sup>53</sup>Saadine JB, Cadwell B, Gregg EW, Engelgau MM, Vinicor R, Imperatore G, Narayan KM: Improvements in diabetes process of care and intermediate outcomes: United States, 1988–2002. *Ann Intern Med* 144:465–474, 2006
- <sup>54</sup>Thornley-Brown D, Wang X, Wright JT, Randall OS, Miller ER, Lash JP, Gassman J, Contreras G, Appel LJ, Agodoa LY, Check D: Differing effects of antihypertensive drugs on the incidence of diabetes mellitus among patients with hypertensive kidney disease. *Arch Intern Med* 166:799–805, 2006

Steven R. Gambert, MD, is a professor of medicine at Johns Hopkins University School of Medicine and chairman of the Department of Medicine at Sinai Hospital of Baltimore, Md. Sally Pinkstaff, MD, PhD, is an assistant professor of medicine at Johns Hopkins University School of Medicine and director of Diabetes Programs at Sinai Hospital of Baltimore.