The Economic Costs of Diabetes

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Joel Rodriguez-Saldana

Paradigms of Medical Care

- "We must do everything, no matter the cost."
- "We must do everything at the lowest possible cost."
- "We must add value to resources."

Introduction

The Value of Health Care. Achieving high value for patients must become the main goal of health care delivery, with value defined as the health outcomes achieved per dollar spent [1, 2]. For a medical condition like diabetes, no single outcome captures the results of care [1]. Outcomes in health care are multidimensional and interactive. Clinicians traditionally are concerned with the clinical outcomes of treatment (Bootman et al. 1996); many of them conceive that economic resources are nonlimited or at least should be and that patients' views and opinions are secondary to their wisdom and expertise. During the last three decades, health care payers and administrators have focused on the economic outcomes of health care decisions, and patients are becoming increasingly knowledgeable and involved in health care (Bootman et al. 1996). They want to know how their quality of life will be affected or about the satisfaction of other patients with the proposed treatment. Clinical, economic, and patient outcomes are closely linked. The true value of health care interventions and programs can only be assessed if all three dimensions of outcomes are measured and considered (Bootman et al. 1996). When aligned and measured, the three outcomes represent health politics [3].

The intrinsic desire to improve patients' perspectives contrasts with the reality of translating the results of evidence-based medicine to all patients and their involved costs. Diabetes costs include the costs of disease at several levels: from individuals to the family, health providers, payers, institutions and society, and the clinical, economic, and patient outcomes obtained by glucose and metabolic control on the natural history of disease. Above all, the patient's vision prevails, as does their longing to receive timely medical care to satisfy their needs for physical and emotional support.

Economics in Health Care: The Basics

Economics is about getting better value from the deployment of scarce resources [4]. Since the 1960s, economists have turned their attention to health services and have considered the economic aspects of different alternatives in the financing, planning, and management of health care [4]. Costs are important in economics, but not more than benefits. Cost is a measure of sacrifice in that since resources are finite, deploying them means a lack of availability for other purposes [4]. Clinicians are usually not aware of the economic resources they consume and the cost of those resources [4]. Health economics is about opportunity cost and benefits because keeping costs down means maximizing the benefits and efficiency of health care [4]. From this perspective, the view that health services (diabetes care in this case) should be about meeting total needs results in confused thinking and romanticism in health care planning [5]. There are not and never will be enough resources to cover all the costs of diabetes care [6]. If this notion of scarcity of resources is accepted, the logic of comparing the costs and benefits of an intervention is more appealing [6]. Resources devoted to an intervention mean less resources available to another. From this perspective, costs should be addressed in terms of benefits sacrificed for the best alternative use of resources: opportunity costs [6]. In some cases, a cost analysis can provide useful information

J. Rodriguez-Saldana (✉)
Multidisciplinary Diabetes Center Mexico, Mexico City, Mexico

J. Rodriguez-Saldana (ed.), *The Diabetes Textbook*, https://doi.org/10.1007/978-3-031-25519-9_3

but does not consider the relative effectiveness of treatment alternatives, and a cost-benefit approach should be advocated, weighing the benefits and costs of different patterns of care [5]. In other cases, when scarce resources should be devoted to one intervention rather than another, a cost-benefit analysis should be undertaken [6]. One final issue of health economics is ethical: clinical practice requires resources for diagnosis, monitoring, and treatment. The inevitability of considering cost can be perceived for resources over which clinicians have control, but it is not easy when several categories (sources of resources) are not available [7]. Allocation of scarce resources is an everlasting problem despite any utopian dreams of unlimited care for everyone and a variety of efforts and proposals assuming that that dream will become a reality [8]. This issue involves moral questions about justice and equity and implications for quality of life [8, 9]. To summarize, Drummond et al. proposed a series of basic notions of health economics for clinicians wishing to acquire a grasp in the field, including [10]: (1) human wants are unlimited but resources are finite, (2) economics is about benefits, but it is also about costs, (3) health care delivery is only one way of improving the health of the population, (4) choices in health care should always involve value, and (5) reducing inequality always comes with a price [10].

Economic analysis has become an integral component of health programs all over the world. In 2021, the World Health Organization (WHO) reported that global spending on health more than doubled in real terms over the last two decades, reaching 8.5 trillion USD in 2019, or 9.8% of the global gross domestic product [11]. In the same report, the WHO describes the inequalities in the distribution of economic resources: high-income countries account for 80%, of which 70% comes from the government, while low-income countries are highly dependent on out-of-pocket spending (44%), and external aid (29%) [11]. Most concerning is the fact that the share of health in government spending increased in upper-middle and high-income countries, stagnated in lower-middle-income countries, and declined in low-income countries [11]. Out-of-pocket spending is a financial burden for people with diabetes, even in developed countries [12, 13], and is largely unaccounted for in studies about diabetes costs. The high frequency of comorbidities will increase the financial burden of people with diabetes and discourage the continued use of medications that prevent disease progression [14].

To summarize, economic analysis of costs is essential for the following reasons:

1. They are limited and finite, even in developed countries.
2. In countries like the United States, health expenditures have surpassed inflation rates without accompanying reductions in the burden from the leading causes of morbidity and mortality.
3. The competing demands of other programs influencing health (education, employment, nutrition).
4. Persistent deficiencies in the use of economic resources and waste despite scarcity. Increasing resources does not necessarily result in improvements in the quality of health care; it may also reduce it.

Interestingly, developed countries pioneered the design of methods to estimate the costs of disease, measure the results of interventions, and devise strategies to contain the ascending costs of health care.

Economic Analysis and Financial Analysis. Economic analysis consists of the estimate of the net value (the direct and indirect costs) of diseases, whereas financial analysis refers to the comparison of alternative resources, or the "opportunity cost." From the medical and patients' perspectives (when not out-of-pocket), costs would be irrelevant. In the "real world" of limited resources, administrators or payers have to decide. To make these decisions, it is essential to have information about the consequences (outcomes) of different interventions, in terms of not only clinical but also economic effectiveness.

Costs. Medical care involves three types of costs: (1) direct medical costs: directly attributed to the disease and its management, involving screening, prevention, diagnosis, and treatment and including medical visits, medications, and hospital admissions; (2) direct nonmedical costs; (3) indirect morbidity and mortality costs to patients, their families, and society; and (4) intangible costs, short-term and long-term consequences of disease for patients, their families, and society (years of life lost, loss of opportunity for spouses and children [15].

Types of Economic Analysis

Economic evaluation is about costs and consequences (Drummond et al. 2015). It provides a framework to make the best use of clinical evidence through an organized approach to the available alternatives on health, health care costs, and other valuable effects. Economic and clinical evaluations are not alternative approaches; they are essential components to achieving the desired outcomes (Drummond et al. 2015). The evaluation of new or existing health care interventions involves five steps: (1) efficacy: the capacity to achieve its stated goals in optimal circumstances, (2) effectiveness: the demonstration that an intervention does more good than harm, (3) efficiency or cost-effectiveness: the combined assessment of the effectiveness of the health care

intervention and the economic resources required to deliver the intervention, (4) availability: matching the supply of services to the persons who require them, (5) distribution: examination of who gains and who loses by choosing to allocate resources to an intervention instead of another [16].

Efficiency Measures

Three methods are used to assess the economic consequences of interventions: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis:

Cost-benefit analysis is defined as all of the costs required to achieve a benefit (a clinical outcome) [15, 17]. A main challenge in cost-benefit analysis is the ability to account for all the costs and benefits in monetary units.

Cost-effectiveness analysis is defined as a series of analytical and mathematical procedures that support selecting an intervention [15, 17]. It can be measured in monetary units or clinical outcomes. The main challenge consists of establishing the magnitude of the clinical benefit.

Cost-utility analysis is defined as the total cost to achieve a unit of quantity or quality of life. Measurement units are quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) [15, 17]. The rationale for using QALYs is that it allows for comparisons of different therapies regardless of health problems or diseases [9].

The Study of the Costs of Diabetes. Every disease involves three types of costs: direct costs, resources used for prevention, screening, diagnosis, and treatment; indirect costs from loss of productivity, absenteeism, early retirement, disability, and early death; and intangible costs from the effect of disease on the quality of life of people. The study of the financial costs of diabetes has covered two complementary fields: (1) cost of illness studies, which initially focused on comparisons of direct costs between people with diabetes and without diabetes and which increasingly include outcomes and (2) comparative analysis of interventions. Costs of illness studies are descriptive, cross-sectional, or longitudinal, relate all costs to a specific disease, and involve two approaches: top-down, or burden of disease, and bottom-up, or person-based. Top-down studies include the direct costs of illness (inpatient, outpatient, nursing home) between people with and without diabetes and have particularly focused on the progressive and lifetime costs of complications and comorbidities. Bottom-up studies involve societal costs and quality-of-life measures. Cross-sectional studies have confirmed the impact of direct diabetes costs on a country's gross domestic product and per capita and the large proportional impact of diabetes on health systems, while incidence-based studies have shown the incremental medical care costs of diabetes before and after diagnosis, showing that the rise in medical spending associated with diabetes begins well in advance of the diagnosis of diabetes, accelerates as diagnosis approaches, immediately after diagnosis, and steeply increases for patients with complications. The study of the financial consequences of diabetes is a recent topic that started with cost-of-illness studies and moved forward to include cost-effectiveness analyses of individual interventions, economic analyses of randomized controlled trials, and systematic reviews. The first studies about the cost of illness were carried out in Sweden, the United Kingdom, and the United States in the 1980s. The initial studies about the cost of diabetes complications started to appear in the 1990s along with evidence about the benefits of metabolic control on the risk of microvascular and macrovascular complications. In the last two decades, the number and scope of studies about diabetes have escalated to include cost-of-disease and cost-effectiveness studies. Table 3.1 depicts a chronological summary of studies about the costs of disease in diabetes, starting with the classical report by Jönsson in Sweden. Beyond depicting the direct and indirect costs of diabetes, over the years, cost of illness studies have been enriched by the inclusion of other relevant variables in the outcomes, like comorbidities, avoidable hospital admissions, and patient outcomes:

The Economic Burden at the Global Level. Measuring the global costs of diabetes confirmed the magnitude of the problem and revealed persistent limitations in objective measurement [66–68]. In 2015, a systematic review by Seuring et al. reported large variations in methods and cost estimates and the absence of control groups in most studies, resulting in large differences in direct and indirect costs. In their review, direct costs ranged from $242 USD on out-of-pocket expenditures in Mexico to $11,917 USD for direct costs in the United States. Indirect costs show similar variations: from $45 USD in Pakistan to $16,914 USD in the Bahamas [66]. Interestingly, and in stark contrast with high-income countries, a substantial part of the cost burden comes out-of-pocket. Regression analysis revealed that direct costs are positively associated with the gross domestic product of each country and that the United States has particularly high costs [66]. In 2017, Bommer et al. published the results of the first global cost-of-illness study building on the methods of the IDF Diabetes Atlas, in which the estimated cost of diabetes in 2015 amounted to $1.31 trillion USD, or 1.8% of the world gross domestic product (GDP) [67]. In their report, indirect costs represented 34.7% of the total, due to labor-force dropout (48.5%), absenteeism (3.9%), presenteeism (2.1%), and death [67]. Morbidity-associated factors dominate in high-income countries, whereas premature mortality

Table 3.1 Studies about the costs of diabetes

Year and country	Author and reference	Type of study	Results
1983 Sweden	Jönsson [18]	Inpatient statistics from 19 county councils in 1977	Total economic costs in 1978: 1300 million SEK
			Institutional care: 2/3; noninstitutional care: 1/3 of direct costs
			Direct costs: 43% of the total
			Indirect costs: 57%, dominated by permanent disability: 60%
			Higher share of direct costs for diabetes than for cancer, cardiovascular or musculoskeletal diseases
			Total number of bed days: 656,000
			Hospital discharges: 25,700
			A slow decrease in admissions for acute care since 1970, an increasing number of bed days in long-term care
			Years lost from retirement: 8000
			Total loss of production caused by early retirement: 438 million SEK
			Direct costs from management: 313 million SEK
			Direct/indirect costs from complications: 1004 million SEK
			Total loss of production caused by premature death: 176 million SEK
1989, UK	Gerard et al. [19]	Cost of illness study, including: (1) direct costs, (2) indirect costs, (3) welfare effects from disability or distress	Total direct costs: £238.9
		Estimation as the sum of inpatient, outpatient and primary care costs	Total indirect costs: £343.0 million
1989, USA	Huse et al. [20]	Estimations based on the prevalence of diabetes, microvascular and macrovascular complications and mortality in people with type 2 diabetes	Total costs in 1986: 19.8 billion USD
			Direct costs: 11.6 billion USD
			Indirect costs including disability and premature death: 19.8 billion USD
1991, France	Triomphe [21]	National estimation extrapolated from a sample of 109 patients with type 1 and type 2 diabetes	Average medical costs: type 1, 12,178 FFr; type 2, 6908 FFr
			Distribution of costs:
			Type 1 Diabetes
			Hospitalizations: 33.9%
			Laboratory tests: 4.9%
			Medical visits: 5.5%
			Medications: 44.7%
			Other: 11.0%
			Type 2 Diabetes
			Hospitalizations: 40.1%
			Laboratory tests: 5.7%
			Medical visits: 8.1%
			Medications: 34.3%
			Other: 11.8%
			Hospital admissions: 144,936; percent of the total: 2.2%
			Hospital costs of diabetes in 1987: 195,500 billion FFr; percent of the total: FFr: 1.7%

1991, USA	Jacobs et al. [22]	Cost of illness study	Hospital admissions in excess of those occurring in the general population in 1987: 786,903; 2.0% of the total
		Data from the National Hospital Discharge Survey to estimate the cost of hospitalizations from chronic complications	Total cost of inpatient care: $5091 million
			Cardiovascular complications: 74%
			Renal disease: 10%
			Neuropathy: 3.6%
			Ophthalmic disease: 1.5%
1992, USA	Rubin et al. [23]	Cost of illness study	Hospital admissions from acute complications: 372,000
		Data from the National Medical Expenditure Survey 1987	Emergency visits: 647,000
			Hospital admissions from chronic complications: 731,000
			Medical visits: 15.700 million
			Visits to dietitians: one million
			Glucose monitors: 9.4 million
			Prescriptions of antidiabetics and insulin: 41 million
			Direct costs: 45.2 billion USD
			Economic expenditures per capita
			People with diabetes: $9493.00 USD
			People without diabetes: 2604.00 USD
			Percentage of expenditures devoted to the management of complications: 50% of the total
			Percentage of the total health expenditure devoted to diabetes: 15%
1996 Finland	Kangas et al. [24]	Cost of Illness study	Total health expenditure per patient:
		30,266 questionnaires receiving medications through pharmacies in Finland in 1989	With diabetes: $3941 USD
			Without diabetes: $1326 USD
			Total costs represent 5.8% of the total health expenditure, were three times higher than the average health costs for people without diabetes, and were distributed as follows:
			Inpatient care: 81%, 13% of all available hospital beds in the country
			Medications: 9%
			By comparison, the cost of ambulatory care and resources for self-care is lower, amounting to 8% and 2%, respectively
1998, Sweden	Henriksson and Jönsson [25]	Cost of illness study	Economic burden of diabetes in Sweden in 1994: 5746 million SEK
			Direct costs: 2455 million SEK, 43% of the total
			Indirect costs: 3291 million SEK
1998, USA	American Diabetes Association [26]	Cost of illness study	Total medical expenditures in the United States in 1997: $77.7 billion USD, $10,071 USD per capita
		National Health Care Survey Data	Direct costs: $44.1 billion
			Acute care costs: $7.7 billion
			Chronic complications: $11.8 billion USD
			Excess prevalence of general medical conditions: $24.6 billion USD
			Proportional costs: Inpatient care: 62%
			Outpatient care: 25%
			Nursing home care: 13%
			Indirect costs: $54.1 billion USD; from premature mortality: $17.0 billion USD, from disability: $37.1 billion USD

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
1998, USA	O'Brien et al. [27]	Cost of disease study	Direct medical and indirect expenditures attributable to diabetes in 1997: $98 billion USD
		Data from multiple sources to estimate direct medical costs on managing type 2 diabetes chronic complications and hypoglycemia	Hospital costs: 62%
			Ambulatory costs: 25%
			Nursing home care: 13%
			Average event costs:
			Acute myocardial infarction: $27,630 USD
			Cerebrovascular events: $40,616 USD
			End-stage renal disease: $63,659 USD
			Blindness: $3486 USD
			First low extremity amputation: $26,894 USD
			Second low extremity amputation: $27,132 USD
			Hypoglycemia: $188 USD
			Indirect medical costs increased from $46.6 billion in 1992 to $54.0 billion in 1997 due to an increase in the number of people with disabilities from diabetes
			With a prevalence of 3.0%, total expenditures for diabetes comprised 8% of health care expenditures in 1997, a more than fourfold difference compared with people without diabetes
1999, USA	Brown et al. [28]	Analysis of clinical data from 11,768 patients with type 2 diabetes to assess the progressive costs of complications	Per-person costs increased from baseline:
			Variable from primary to specialized care
			By more than 50%, from $1087 USD to $2033 USD over 9 years after initiation of a cardiovascular drug
			By 360% after a major cardiovascular event
			By 65% with abnormal renal function
			By 195% with advanced renal disease
			By 771% with end-stage renal disease
			Greatest cost savings would be achieved by preventing major cardiovascular events and progression to stage 3 renal disease
2000, Sweden	Henriksson et al. [29]	Cross-sectional, cost of disease study	Total annual direct costs in Sweden in 1998: 7 billion SEK, 6% of the total health care expenditures, more than four times higher than a previous national estimate
		Estimate the direct costs of type 2 diabetes and the influence of complications	Annual per patient cost: 25,000 SEK, 42% from hospitalizations
			Hospitalization costs: 2.7 billion SEK
			Hospitalization cost per patient: 10,599 SEK
			Ambulatory costs: 2.161 billion SEK
			Ambulatory costs per patient: 7719 SEK
			Medication costs: 1.8 billion SEK
			Medication costs per patient: 6665 SEK
			Costs in patients with macro and microvascular complications:
			Hospitalization: 29,555 SEK
			Ambulatory care: 11,053
			Medications: 9520 SEK
			Average costs for patients without complications: 24,983 SEK
			Average costs for patients with complications: 50,128 SEK
			Difference: 25,145 SEK
			Higher costs with longer duration of disease, from 20,977 SEK with less than 5 years to 22,059 SEK between 5 and 10 years

2000, USA	Nichols GA et al. [30]	Cost of disease study	An economic burden from impending diabetes is apparent for at least 8 years before diagnosis, beginning with outpatient and pharmacy services ranging from $156 to $245 USD/year
		Review of electronic records of a large health maintenance organization to describe and analyze medical care costs 8 years before the diagnosis of type 2 diabetes	The single class of drugs with the highest incremental costs were antihypertensives
			Incremental costs averaged $1205 USD per type 2 diabetes patient per year, including $1913 USD each year for the 3 years preceding diagnosis
2001, Sweden	Norlund et al. [31]	Cost of disease study	Physical dependence increased from 1.3% in people younger than 65 years to 14.6% in those aged 80 years or older
		1677 people with diabetes from the catchment area of Southern Sweden, 2.4% of the total population	Leading diabetes complications included:
		Interview and physical examination to establish physical dependence and comorbidities	Retinopathy, proliferative: 32.9%
		Health depreciation as a capital asset as a result of illness and death	Foot problems: 31.3%
			Ischemic heart disease: 22.1%
			Congestive heart failure: 14.5%
			Cerebrovascular disease: 11.3%
			Foot ulcers: 8.4%
			Total direct and indirect costs per person with diabetes in SEK: 61,738 Total direct costs: 36,173
			Distribution:
			Home-help hours: 11,315
			Inpatient days: 11,294
			Retirement home: 4795
			Nursing home: 3085
			Nurse visits: 1984
			If no monetary value was assigned to home help by relatives, the total average cost would be reduced by 10%
			Total indirect costs: 25,565
			Distribution:
			Early retirement: 19,610
			Sick days: 5955
			Incremental use of resources in 1 year by people with diabetes was 1.2 more medical visits and 5.3 more nurse visits
			Compared with people without diabetes, the incremental losses in production amounted to 9.4 sick days
			Frequency of early retirement: 14.2% higher
			When diabetes-related complications are included, the cost of disease is 2–3 higher
			The incremental costs are more than double for the population
			Diabetes generates high costs to society

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Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2003, USA	American Diabetes Association [32]	Cost of illness study	Total medical expenditures in the United States in 2002: $132 billion USD
		Based on an estimate of 12.1 million people in the United States in 2002 diagnosed with diabetes, an increase of 1.8 million (1.7%) from year 1997 estimates	Health care expenditures: $92 billion
			$13,243 USD per capita
			Direct costs: $91.8 billion, 52% for people ≥65 years
			Hospital inpatient care: $40,337 billion USD, 31% of the total
			Nursing home care: $13,878 billion USD, 11%
			Outpatient care: $20,130 billion USD, 13%
			Proportional costs: Inpatient care: 31.0%
			Emergency visits: 2%
			Outpatient care: 15.0%
			Nursing home care: 11.0%
			Indirect costs: $39.8 billion USD
			Lost productivity from disability: $7.5 billion USD
			Premature mortality: from diabetes: 21.5 billion USD
			The estimates are conservative and probably underestimate the true costs of diabetes
2004, Mexico	Arredondo and Zúñiga [33]	Cost evaluation method based on instrumentation and consensus techniques	Comparing the economic impact in 2003 vs. 2005, a 26% increase in financial requirements was observed
			Total costs: $317,631.206 USD
			Direct costs: $140,410.816
			Indirect costs: $177,220,390
2010, Mexico	Rodríguez Bolaños et al. [34]	Cost of illness study	Total direct costs: $452,064,988 USD, 3.1% of operating expenses
		Review of medical charts from 497 patients from a social security institution treated at secondary and tertiary medical care units from 2002 to 2004	Annual average cost per patient: $3193.75
			Cost per patient without complications: $740.34
			Cost per patient with complications: $3550.17 USD
			It is essential to identify possible savings, redistribute economic resources, and improve medical care at the early stages of the disease
2011, UK	Simmons and Wenzel [35]	Cross-sectional, retrospective 12-month audit in a single teaching hospital to assess mortality, bed day per year and diabetes attributable hospitalization cost	4864 diabetes hospital admissions, 12.9% of the total
			Bed occupancy: 13.9%
			Risk of death among people with diabetes: 18.1% higher
			Mean bed days:
			Men with diabetes: 10.9 vs. 6.3 in men without diabetes
			Women without diabetes: 11.4 vs. 5.9 in women without diabetes
			Mean costs
			People with diabetes: £5835
			People without diabetes: £3706
			Diabetes attributable hospitalization cost: 46.5%, an HbA1c >10% was associated with excess hospitalization
			Approaches known to reduce hospitalization through the improvement of primary diabetes care are urgently required

2011, USA	Nichols, Vupputuri, Lau [36]	Cost of diabetes study to estimate the direct medical costs of patients with type 2 diabetes and hypertension by the level of proteinuria to evaluate differences between patients with and without nephropathy progression	Patients with normoalbuminuria who progressed to microalbuminuria experienced an annualized change in baseline costs that was $396 USD higher than those who maintained normal albuminuria ($902 vs. $506)
			Among patients with microalbuminuria, progression was significantly associated with a $747 USD difference in annualized change in outpatient costs compared with no progression ($1056 vs. $309)
			Among patients who progressed, costs were 37% higher following progression from normoalbuminuria to microalbuminuria ($10,188 vs. $7424), and 41% higher following progression from microalbuminuria to macroalbuminuria ($12,371 vs. $8753)
			Progression of diabetic nephropathy is strongly associated with higher subsequent medical care costs in hypertensive patients with diabetes
			Preventing progression from normo- to microalbuminuria and micro- to macroalbuminuria may reduce the economic burden of diabetic nephropathy
2013, USA	Zhuo, Zhang, Hoerger [37]	Cost of disease study	Lifetime direct costs of treating type 2 diabetes and complications according to the age of diagnosis in men:
		Type 2 diabetes simulation model to simulate disease progression and direct medical costs among a cohort of newly diagnosed type 2 diabetes patients based on the 2009–2010 National Health and Nutritional Survey	25–44 years: $124,700 USD
			45–54 years: 106,200 USD
			55–64 years: $84,000 USD
			≥65 years: 54,700 USD
			Lifetime direct costs of treating type 2 diabetes and complications according to age of diagnosis in women:
			25–44 years: $130,800 USD
			45–54 years: 110,400 USD
			55–64 years: $85,500 USD
			≥65 years: 56,600 USD
			Effective interventions that prevent or delay type 2 diabetes and diabetic complications might result in substantial long-term savings in health care costs
2014, Spain	Arrieta et al. [38]	Cost of illness study from a descriptive, cross-sectional analysis of a sample of 3268 patients with type 2 diabetes	From an estimated population of 390,944 people with diabetes, 172,406 will experience macrovascular complications and 212,283 will experience microvascular complications during their lifetimes
			The mean cost of complications per patient is estimated at EU 4121.54, 66% from macrovascular complications
			Total costs from diabetes complications: EU1.611 billion, EU1.065 billion from macrovascular complications, 545 million from microvascular complications
			The economic impact of diabetes complications will increase with higher diabetes prevalence

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Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2015, USA	Ozieh et al. [39]	Cost of illness study from 2053 adults with diabetes registered in the 2011 Medical Expenditure Panel Survey	Percentage of patients with self-reported chronic kidney disease (CKD): 9.7%
			By comparison of a $9689.49 USD expenditure in people without CKD, the unadjusted medical expenditures from CKD amounted to $20,726 USD
			Adjusted mean expenditures were $8473 USD higher
			Estimated unadjusted total expenditures for CKD: more than $43 billion USD in 2011
			CKD is a significant contributor to the financial burden for people with diabetes, minorities, and the uninsured experience barriers in accessing care
2016, Iran	Davari et al. [40]	Cost of illness study	Mean total costs
		Retrospective observational study	Public fees:
		Analysis of medical records of 2898 people with Type 2 diabetes from a tertiary care center to estimate 1-month direct costs	Laboratory tests: $20.4 USD
			Medications: $65.9 USD
			Medical visits: $17.9 USD
			Private fees:
			Laboratory tests: $52.4 USD
			Medications: $67.8 USD
			Medical visits: $35.6 USD
			Outpatient direct costs for diabetes increased 14.6 times over 10 years
			Medications are the main component
			Estimated national direct costs of diabetes: $810 million USD
2016, Denmark	Sortso et al. [41]	Cost of disease study	Total health care costs: EUR 1.64 billion
		To investigate the relationship between costs, with and without complications in a National Diabetes Register	Cost per person-year: EUR 5509
			On average, a person with diabetes without complications consumes twice as many health care resources as a person without diabetes
			With complications, a person with diabetes consumes three times the health care resources with higher gradients among younger patients, men than women, and for secondary care
			From no complications to minor or major complications, increased health care costs ranged from EUR 1782 to EUR 7534
			Productivity loss amounted to EUR 1.77 billion
			Patients with diabetes received on average a lower income than people without diabetes
			Additional costs were estimated to be EUR 761 million
			Total costs of diabetes in 2011: EUR 6.67 billion
			Diabetes costs increase with increased complications, providing an economic rationale for secondary prevention
2016, Mexico	Lugo-Palacios, Cairns [42]	To estimate the financial and health burden of diabetic ambulatory care sensitive hospitalizations (ACSHs) from public general hospitals at a national level, 2001–2011	Over one decade, 195,778 ACSHs were identified, accounting for one-fifth of total ACSHs for any cause
			Total ACSHs due to diabetic complications increased >130% over 10 years
			The estimated financial costs due to diabetes complications increased 125%
			Diabetic foot hospitalizations showed an increasing trend, growing by 160% and surpassing renal failure
			Estimated DALYs increased by 112%; renal failure had the highest health burden
			Despite promotion and prevention efforts to improve the control of diabetes across the health system, the financial and health burden of ACSHs associated with diabetes complications increased dramatically
			Given the WHO cost-effectiveness criterion, it would have been cost-effective to spend $1.146 billion USD on primary care interventions to avoid the DALYs associated with diabetes complications

2016, Mexico	Lugo-Palacios, Cairns, Masetto [43]	To estimate the financial and health burden of diabetic ambulatory care sensitive hospitalizations (ACSHs) in a large social security institution 2007–2014	Over 7 years, 322,977 ACSHs were identified, of which kidney failure and diabetic foot represented 78%
			Diabetes complications increased 10.3% over this period
			Multiple admission for the same complications occur in 15% of patients
			Diabetes costs increased by 8.4% in 7 years, with kidney failure as the most important cause, accounting for 43% of costs
			Estimated DALYs decreased by 13.6%, representing more than 50% of the estimated total
			Timely and effective primary care could reduce the burden of preventable hospitalizations
			Resources used to treat avoidable hospitalizations could be used to fund more and better primary care
2017, Israel	Porath, Fund, Maor [44]	Cost of illness study in a large health maintenance organization	Median annual cost in cost units (CU): 4420
		Retrospective analysis, 1 year duration	Differences between costs for people with diabetes and people without diabetes accounted for 85% of people 35–44 years old and 24% of people 75–84 years old
			Medical costs increased similarly for patients with controlled and poorly controlled diabetes and with comorbidities
			Costs were significantly impacted by kidney disease
			Leading factors affecting costs were HbA1c level, male gender, chronic diseases, diabetes complications, disease duration, and stage of renal failure
			Early treatment of diabetes and its complications is cost-effective
2017, Hong Kong	Jiao et al. [45]	Cost of disease study to estimate medical costs associated with diabetes complications from the Hospital Authority Clinical Management System through modelling	Expected baseline cost of a 65-year-old person without complications: $1521 USD
			Stroke and foot ulcers had the highest incremental costs
2017, Germany	Jacobs et al. [46]	Cost of illness study based on a random sample of all German people with statutory health insurance	Per capita costs for people with type 2 diabetes: EUR 4957 in 2009, EUR 5146 in 2010
			People with diabetes had 1.7-fold higher health expenses than people without diabetes, with the largest expenses in medications and inpatient treatment
			Medical care for people with diabetes accounts to 10% for total health insurance expenses
2017, USA	American Diabetes Association [47]	Cost of illness study from national surveys, Medicare standard analytical files and claims databases for the commercially insured population	Total estimated direct costs of diabetes in 2017: $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity, accounting for one in four health care dollars
			Average medical expenditures per year: $16,750 USD
			Medical expenditures for people with diabetes are 2.3 times higher than expenditures for people without diabetes
			Indirect costs include increased absenteeism ($3.3 billion USD), reduced productivity at work ($26.3 billion USD), reduced productivity for people outside the labor force ($2.3 billion USD), inability to work because of disease-related disability ($37.5 billion USD), and loss of productivity due to premature death ($19.9 billion USD)
			After adjusting for inflation, the economic costs of diabetes increased 26% from 2012 due to the increased prevalence of diabetes and the increased cost per person with diabetes
2018, USA	Squires et al. [48]	Cost of illness study	Diabetes costs increased from $37 billion USD in 1996 to $101 billion in 2013
		Estimates extracted from a health metrics database from 1996 to 2013	In 2013, the greatest amount of health care spending occurred on medications (57.6%), followed by ambulatory care (23.5%)
		Disease burden was extracted from the Global Burden of Disease 2016 Study	Between 1996 and 2013, pharmaceutical spending increased by 327%, especially by 144% increased pharmaceutical spending between 1996 and 2013

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2018, USA	Shresta et al. [49]	Cost of illness study using data from three national 2013–2014 databases to estimate direct costs and a human capital approach to estimate indirect costs	The estimated median state economic costs were $5.9 billion USD, ranging from $694 billion to $55.5 billion in total
			The estimated cost per person with diabetes was $18,248, ranging from $15,418 to $30,915 per person with diabetes
			The estimated direct medical costs ranged from $2.8 billion to $8.5 billion, and indirect costs ranged from $3.0 billion to $9.6 billion
			Indirect costs were larger than costs from mortality
			Economic costs for diabetes vary extensively across U.S. states, and are not associated with the size of the population
2018, Germany	Kähm et al. [50]	Cost of disease to estimate costs associated with diabetes complications using statutory health insurance data from 316,220 patients with type 2 diabetes in 2013–2015	Base case estimated total costs for the example of a 60- to 69-year-old man: diabetic foot EUR1293, amputation EUR14,284, retinopathy EUR671, blindness EUR2933, nephropathy EUR3353, end-stage renal disease EUR22,691, fatal stroke EUR11,176, nonfatal myocardial infarction/cardiac arrest EUR8035 EUR, nonfatal ischemic heart disease EUR6548, fatal ischemic heart disease EUR20,942, chronic heart failure EUR3912, angina pectoris 2965, retinopathy EUR6130
2018, Ireland	O'Neill et al. [51]	Cost of illness study from a nationally representative sample of 8107 adults aged ≥50 years	Incremental cost from diabetes: EUR 88,894,421
			Compared with people without diabetes, diabetes was associated with 1.49 additional visits to general practitioners annually, with an 87% increase in outpatient visits, a 52% increase in hospital admissions, and a 33% increase in accident and emergency department attendances
			Diabetes is associated with substantial health services use and costs; costing of hospital admissions was EUR60,002,421, accounting for more than two-thirds of the cost burden
			Areas for potential cost savings include a shift in routine management to primary care and improved access to effective ancillary services such as foot care and dietetic interventions
			These findings outline the urgent need to invest in the prevention and management of diabetes
2018, France	Charbonnel et al. [52]	Cost of disease study from a random sample of 600,000 patients registered in a national health insurance database	Extrapolating the results to the whole population with type 2 diabetes in France, the total estimated direct costs amounted to EUR8.5 billion in 2013, corresponding to 5% of all health care expenditure. Per patient medical expenditures were EUR6506 for patients with type 2 diabetes as compared with EUR3668 in the control group
		Cost analysis from a sample of 25,987 patients with type 2 diabetes matched with a control group of 76,406 individuals without diabetes	Cost difference between the two groups was EUR2838 per patient per year, mainly due to hospitalizations (33.2% of the total costs), medications (23.7%) and nursing care (10.9%)
			Total per capita annual costs were lowest for patients receiving metformin monotherapy (EUR4153) and highest for those receiving insulin (EUR12890)
			These results highlight the importance of public health programs aimed at reducing the incidence of type 2 diabetes, preventing diabetic complications through better glycemic control, reducing clinical inertia and improving patient adherence, and developing less costly integrated care programs

2018, USA	Lin, Pope, Zhou [53]	Retrospective observational study on 138,466 privately insured adults newly diagnosed with type 2 diabetes who were classified into five comorbidity groups: (1) concordant only, (2) discordant only, (3) both concordant and discordant, (4) any dominant, (5) none, to investigate the influence of type of comorbidity on health care utilization and costs	Comorbidities were significantly associated with higher health care costs and the magnitude of the association varied with comorbidity type
			Type of comorbidities and costs:
			Discordant only conditions: 27%, $9173 USD
			Dominant conditions and costs: 25%, $38,168 USD
			Concordant and discordant conditions: 24%, $20,401 USD
			Concordant conditions only: 7%, $9000 USD
			No comorbidities: 21%, 3365 USD
			53% of the total costs were attributable to 25% of patients with comorbidities
			Dominant comorbidities and concordant plus discordant comorbidities substantially increase diabetes costs
			Diabetes management must explicitly address comorbidities to address distinctly different health needs and utilization patterns
2018, Mexico	Salas-Zapata et al. [54]	Cost of illness study to estimate the direct costs related to hospitalizations for diabetes and its complications in a social security institution from 2008 to 2013	Hospital discharges during the period of study: 411,302
			Direct costs: $1.563 USD billion, 77.26% for type 2 diabetes, 22.74% for type 1 diabetes
			Magnitude of costs according to complications:
			Renal failure and peripheral arterial disease account for 46% of hospital admissions
			Hospital admissions show an increasing trend in men and in the 15–44 age group, with decreasing amounts in people ≥65 years
			Diabetes management should be multidisciplinary; health institutions should devise strategies supporting diabetes prevention and control
			Costs from hospitalizations could be reduced by delivering optimal primary care
			Essential costs to be addressed include indirect and out-of-pocket costs
2019, USA	Shresta et al. [55]	Cost of illness study to examine changes in diabetes-related preventable hospitalization costs and to determine the contribution of each underlying factor to these changes	During 2003–2014, the estimated total cost of diabetes-related preventable hospitalizations increased annually by 92.9 million USD (1.6%)
		Data from the Nationwide Inpatient Sample for adults to estimate trends in costs in US dollars in total and by condition, including short-term complications, uncontrolled diabetes and lower extremity amputations	Of this 1.6% increase, 75% was due to the increase in the number of hospitalizations
			The cost of short-term complications, lower extremity amputations, and long-term complications increased annually by 4.2, 1.9, and 1.5%, respectively, while the cost of uncontrolled diabetes declined annually by 2.6%
			Total costs associated with preventable hospitalizations increased despite substantial improvements in preventable hospitalizations and reduced lengths of stay, which were offset by increasing costs per day and increases in the size of the diabetes population
2019, USA	Dall et al. [56]	Cost of illness study to estimate the economic burden of undiagnosed diabetes, prediabetes, and gestational diabetes (GDM) in 2017, including state-level estimates from three databases of 5.8 million, 2.8 million and 7.1 million records from 2013 to 2015, in addition of data from the U.S. Census Bureau, the Centers for Disease Control and Prevention and Centers for Medicare & Medicaid Services	Direct costs associated with diabetes, undiagnosed diabetes, prediabetes, and gestational diabetes in 2017: $404 USD billion
			Distribution
			Diagnosed diabetes: $327.2 billion
			Undiagnosed diabetes: $31.7 billion
			Prediabetes: $43.4 billion
			Annual burden per case
			Diagnosed diabetes: $13,240 USD
			Gestational diabetes: $5800 USD
			Undiagnosed diabetes: $4250 USD
			Prediabetes: $500 USD
			The economic burden of diabetes for each US citizen in 2017: $1240 USD
			It is urgent to adopt more comprehensive approaches and better prevention and treatment strategies

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2020, USA	Crossen et al. [57]	Retrospective analysis of type 1 medical costs 2012–2016 from a comprehensive database of 9445 individuals aged ≥18 years and ≥13 months of continuous enrollment	Mean annual cost increased 35%, from $11,178 USD in 2012 to $17,060, mainly because of a 48% increase in the cost of insulin and a 48% increase in the cost of diabetes technology
			The study indicates that the cost of type 1 diabetes care is driven by mounting insulin prices (9.6% per year) and diabetes technology (also 9.6% per year)
			It is possible that short-term costs will be offset by future savings!
2020, Taiwan	Chen et al. [58]	Cost of illness study from 802,429 adults with newly diagnosed type 2 diabetes identified during 1999–2010 and followed until death or December 2013	Annual health care costs for a male or a female diagnosed with type 2 diabetes <50 years, without comorbidities, antidiabetic treatments, or complications: $281 and $298 USD
			Depression was the costliest comorbidity, increasing costs by 64% and 82%, respectively
			Antidiabetics increased costs by 72–126%
			Costs for retinopathy: 36%
			Costs for heart failure: 49%
			Costs for stroke: 202%
			Costs for the five leading costly nonfatal complications increased by 201–599% for end-stage renal disease, 37–376% for stroke, and 13–279% for limb amputation
			Fatal complications increased costs by 1784–2001% and 1285–1584% for cardiovascular or other causes
			The economic burden of vascular complications and death is compelling over time and the impact of depression cannot be ignored
2020, Netherlands	Janssen et al. [59]	Cost of illness study from 2915 individuals who were classified normal glucose tolerance, prediabetes or diabetes based on fasting and 2-h glucose levels, through resource-use and a quality of life questionnaires	Diabetes costs per individual with diabetes: EUR3006
			Health care costs for individuals without diabetes: EUR1377
			People with diabetes had 2.2 times higher societal costs than people with normal glucose tolerance and lower quality of life
			Total costs were 1.6 higher for people with type 2 diabetes and one complication, and 4.8 higher for people with two or more complications
			Higher age, being female, and having two or more diabetes complications resulted in higher costs and lower quality of life
2020, Scotland	McMeekin et al. [60]	To compare costs for three groups of people with type 2 diabetes: (1) at high risk of cardiovascular disease, (2) without cardiovascular disease, (3) with established cardiovascular disease, and for those with established cardiovascular disease, to compare costs incurred by people with type 2 diabetes with an incident cardiovascular disease, with people who remained incident-free over 3 years from a national diabetes registry	Mean annual costs for people at low cardiovascular risk and without established cardiovascular disease: £2500
			For people at high risk: £3300
			For people with established cardiovascular disease:
			£6900
			Costs for people without an incident cardiovascular event: £2100
			Costs of an incident cardiovascular event: £16,700
			Cumulative costs: £4200 and £21,500, respectively
			Cumulative costs by year 3: £5900 and £25,000
			Cardiovascular disease places a significant financial burden on people with diabetes and the global economy
			The results of the study emphasize the financial consequences of cardiovascular disease prevention strategies

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2020, Sweden	Hellgren et al. [61]	Cost of disease study about the economic and clinical burden associated with poor glycemic control, from a national registry of 77,932 people with type 2 diabetes	People with poor glycemic control
			HbA1c ≥7.0%:19,477 (24.9%)
			HbA1c ≥7.5%: 11,753 (15.08%)
			Even short delays in achieving glycemic control have substantial impact on costs and small effects on life expectancy and quality of life
			Benefits were more pronounced over longer-term horizons and versus longer delays in achieving glycemic control
			For people with HbA1c ≥7.0% and ≥7.5% immediate glycemic control was associated with population-level cost savings of SEK 39 and 38, 50 and 77, and 113 and 107 million, respectively, at 3 and 10 years and lifetime, compared with a 1-year delay in achieving control
			Immediate glycemic control was also associated with improvements in population-level life expectancy of 136 and 118, 467 and 470, and 1305 and 928 years, respectively, in the periods
			Population-level life expectancy also increased to 117 and 129, 915 and 858, and 2590 and 2257 years, respectively
			The economic burden of poor glycemic control in individuals with type 2 diabetes is substantial but could be considered reduced by early and effective treatment to achieve and maintain targets
2021, USA	Khan et al. [62]	Cost of illness study of 17,207 subjects without diabetes 5 years before and diagnosed in 2014 from a commercial claims database	Newly diagnosed patients spent $8941 USD more than control subjects over 5 years, approximately $4828 in the year of diagnosis
			The difference gradually widens over time and is greatest in the year of diagnosis
			The compound annual growth rate is 9% higher
			The rise in medical spending associated with diabetes begins in advance of the diagnosis and supports the need to encourage physicians to implement timely identification and prevention efforts to reduce the economic burden of the disease
2021, Germany	König et al. [63]	Cost of illness study of 325 individuals with diabetes and 4490 people without diabetes from a national health survey for adults	Total excess costs: EUR 927 of which EUR 719 were attributable to direct and EUR 209 to indirect excess costs
			Medication costs were 88% higher and had the largest share in excess direct costs
			Direct excess costs:
			For 4–10 years of diabetes duration: EUR 203
			For diabetes complications: EUR 1405
			Indirect excess costs:
			For >10 years duration: EUR 544
			For high education: EUR 995
			Holistic care approaches like disease management programs might be beneficial for people with type 2 diabetes
2021, Canada	Choi et al. [64]	Cost of illness study from a retrospective cohort study of 41,934 patients with diabetes admitted to seven general internal medicine beds between 2010 and 2015	Compared with patients without diabetes, hospital admissions were more frequent and costly for:
			Soft tissue and bone infections (CAN $8794 vs. CAN $5845)
			Urinary tract infections (CAN $5442 vs. CAN $4427)
			Stroke (CAN $8270 vs. CAN $6992)
			Electrolyte disorders (CAN $4422 vs. CAN $3679)
			Nearly one-third of hospital admissions are related to diabetes
			A preventive strategy focused on reducing hospital admissions secondary to soft infectious complications, stroke, and electrolyte disorders would be cost-saving

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2022, Ireland	Sharma et al. [65]	Cost of illness study from secondary data sources	Total diabetes costs: EUR129 million in 2018
			Direct costs: EUR81.5 million, 63% of the total
			Indirect costs: EUR47.5 million, 37% of the total
			Costs per capita
			Direct costs: EUR3994
			Indirect costs: EUR2326
			Potential for cost-effective improvements in type 1 diabetes practices that may reduce the health and economic burden

accounts for most of the indirect costs in middle-income and low-income countries [68]. Substantial regional variations were observed in the economic costs of diabetes: North America had the largest absolute burden, sub-Saharan Africa had the lowest costs, and South Asia was in the middle. High-income countries contribute the most of the economic burden of which 36.5% are indirect costs, and low-income countries bear the lowest burden with an average of 0.7% of GDP [68]. Last but not least, in 2020, the International Diabetes Federation updated its report about global direct diabetes expenditures based on prevalence estimates, United Nations population estimates, World Health Organization health expenditure per capita, and ratios of health expenditure for people with diabetes and without diabetes [68]. The global cost of diabetes for 2019 in adults aged 20–79 years was estimated at 760 billion USD, with 68.7% of the spending on people aged 50–79 years, and is expected to grow to $825 billion USD by 2030 and $845 billion USD by 2045 [68]. Like in previous reports, wide variations in expenditures were observed. The United States has the largest expenditure estimated at $294.6 billion, followed by China and Brazil with USD $109.0 billion and USD $52.3 billion, respectively, and afterwards by Germany (43.8), Japan (23.5), Mexico (17.0), France (16.9), the United Kingdom (14.1), Canada (12.3), and the Russian Federation (10.6) [68]. The main drivers of higher direct costs are poor glycemic control, medications, ambulatory care, hospitalizations, diabetic foot ulcers, cardiovascular disease, end-stage kidney disease, and individual characteristics, including the number of medical visits and the number of comorbidities. In the United States, for example, diabetes costs reached $404 billion USD in 2017. People with diabetes have medical expenditures 2.3 times higher than people without diabetes, accounting for one in four health care dollars. Accurate and comprehensive information on the global economic burden of diabetes will assist clinicians and policy makers in making informed decisions, obtaining resources for activities to prevent or slow its progression, and evaluating the benefits of these interventions [68]. Cost-of-illness studies have been very useful to confirm the increasing economic burden of diabetes at a health-system, national and global level, but do not provide an indication of the value obtained for the money spent [69]. Strategies to analyze the effectiveness of interventions are needed.

Cost-effectiveness of Interventions. Except for politicians and clinicians, it is universally recognized that the economic resources available to meet the demands for health care are limited [70]. Measuring effectiveness in clinical practice should be outcome-oriented, with length and quality of life as the ultimate objectives [70]. Economic analyses are used to describe the costs of health care programs and to ensure that value is obtained for the money spent [71]. The economic analysis of interventions in diabetes started in the 1990s and evolved from economic models to compare the costs and benefits of medications in delaying the progression of advanced complications [72], cost-effectiveness analysis of controlled clinical trials like the Diabetes Control and Complications Trail (DCCT) [73, 74], the United Kingdom Prospective Diabetes Study (UKPDS) [75–81], the Steno-2 Study [82], and comparisons of health care use and costs between real and simulated cohorts of patients with good glycemic control and patients without improvement [83–90].

The evidence collected from clinical trials about intensive therapy has been shown to reduce the risk and advance of diabetes complications [74]. Economic analysis and models have been used to evaluate the cost-effectiveness of intensive therapy for people with type 1 and type 2 diabetes [73–90]. An economic analysis of the DCCT estimated the costs of therapy to be two to three times higher than those of conventional therapy [74]. The results of a Monte Carlo simulation model showed that intensive therapy could reduce 41% the risk of blindness, from 34 to 20%, the risk of end-stage renal disease by 71%, from 24 to 7%, and 43% the risk of amputations, from 7 to 4% [73]. The final analysis compared additional costs from intensive management with savings resulting from preventing or delaying chronic complications: $2000.00 USD per patient with blindness per year, $31,000.00 USD per patient with amputation per year, $45,000.00 USD per patient with end-stage renal disease per year. According to the DCCT, intensive therapy for type 1 diabetes delays 15.5 years in the occurrence of chronic complications and would extend 5.1 years the life expectancy of these patients [73]. Implementing intensive rather than conventional therapy for all the people with type 1 diabetes in the United States would result in a gain of 920,000 years of sight, 691,000 years free from end-stage renal disease, 678,000 years free from lower extremity amputation, and 611,000 years of life at an additional cost of 4.0 billion USD over the lifetime [73]. These were the estimated costs to deliver intensive diabetes care in 1996. The question is if they are affordable in 2022 with the increasing prevalence of type 2 diabetes and the escalating costs of treatment for type 1 diabetes (see below)?

Economic analysis was not initially included in the study design of the UKPDS. However, data were collected throughout the study and were supplemented by cross-sectional surveys of non-patient health care use and quality of life [75]. The evaluations of tight versus less tight blood pressure control [76, 77], intensive versus less conventional blood glucose control [78, 79], and metformin [80] showed that each intervention was highly cost-effective and that all could be provided at modest total costs. Estimation of the cost of all

consultations, visits, hospital admissions, and procedures showed that diabetes complications are associated with substantial immediate and long-term health care costs, not only in the year in which an event occurs but also in permanently raising the average level of inpatient and outpatient costs in subsequent years [81]. In the Steno-2 study, an intensified multifactorial approach was compared with a routine multifactorial intervention for 7.8 years in high-risk individuals with type 2 diabetes and microalbuminuria [82]. At the end of follow-up, individuals randomized to intensified therapy survived for a median of 7.9 years longer, and incident cardiovascular disease was delayed by 8.1 years with a relative risk reduction of 45% and an absolute risk reduction of 20% [82]. The risk of nephropathy, retinopathy, and heart failure was significantly reduced in the intensified therapy group [82]. Information on direct health care costs was retrieved from health registries, and the costs in two groups of 80 patients each were compared. No statistically significant differences were found in total direct costs between the two groups during a 21-year follow-up period. In the intensified therapy group, yearly expenses for prescription drugs were higher than in the conventional therapy group, while in contrast, yearly expenses for primary care and hospital admissions were lower in the intensified therapy group. The difference was driven by the increased costs for admissions related to cardiovascular disease [82]. After 8 years, the yearly costs per individual increased steeply in the conventional treatment group but remained unchanged in the intensified treatment group, albeit after 15 years, the yearly costs in the conventional treatment group started to increase [82]. The results of the study reflect that cardiovascular disease and mortality are delayed by about 8 years in the intensified therapy group, which increases life expectancy by 7.9 years and postpones the occurrence of cardiovascular disease by 8.1 years [82].

Simultaneous reports about the benefits of improving glycemic and overall diabetes control confirmed that they were cost-saving and cost-effective. A historical cohort study conducted in 1992–1997 in a health maintenance organization from the United States showed that mean total costs were $685 to $950 USD less each year in the improved cohort for 1994–1997 [83]. Cost savings in the improved cohort were statistically significant among patients with higher baseline HbA1c levels, and beginning in the year following improvement, the use of services was consistently lower in the improved cohort [83]. In England and Wales, a summary of characteristics of patients with type 2 diabetes from the National Diabetes Audit was used to assess the impact of achieving treatment targets for HbA1c, total cholesterol, and blood pressure on clinical outcomes and health care costs across general practitioner practices [84]. Using the UKPDS Outcomes to estimate long-term health outcomes and health care costs, achieving HbA1c, cholesterol, and blood pressure targets led to a lower incidence of diabetes-related complications, in addition to 0.4–0.6 QALYs and 0.6 years of life gained over a lifetime for each additional target met [84]. The projected health care cost savings arising from fewer diabetes complications as the result of achieving one, two, or three targets compared to none were £859, £940, and £1037 over a patient's lifetime. Interestingly, a typical patient in the lowest-performing decile was projected to gain between 201 and 231 years of life if all patients achieved all three targets [84].

The cost-effectiveness analysis of a hypothetical cohort of people with type 2 diabetes showed that the incremental cost-effectiveness ratio for intensive glycemic control was $41,384 USD per QALY; for intensified blood pressure control, the cost-effectiveness ratio was −$1959 USD per QALY; and the cost-effectiveness ratio for reduction of serum cholesterol level was $51,889 per QALY and increasing with age [85]. Individualized control is cost-saving, primarily due to lower medication costs and decreased life expectancy due to an increase in complications, but also produces more QALYs due to fewer episodes of hypoglycemia and medications [86].

The Evidence about Cost-Effectiveness in Diabetes Management. Starting in 2000, 2010, and 2020, three systematic reviews in which diabetes interventions were stratified confirmed their positive impact in the following categories: (1) clearly cost-saving, including preconception care, intensive hypertension control with ACE inhibitors or angiotensin receptor blockers to prevent end-stage renal disease, comprehensive foot care and patient education to prevent and treat foot ulcers, telemedicine for diabetic retinopathy screening compared with office screening; (2) clearly cost-effective interventions included intensive lifestyle interventions to prevent type 2 diabetes, universal opportunistic screening in high-risk populations, intensive glycemic control (targeting HbA1c <7%) as implemented in the UKPDS study, multicomponent interventions involving behavior change/education and pharmacological therapy for hyperglycemia, hypertension, dyslipidemia, microalbuminuria, nephropathy/retinopathy, secondary prevention of cardiovascular disease with aspirin, early detection of complications and bariatric surgery for individuals with type 2 diabetes, statin therapy for secondary cardiovascular prevention, diabetes self-management education and support, counseling and treatment for smoking cessation, screening every 3 years for type 2 diabetes, integrated, patient-centered care, self-monitoring of blood glucose three times per day among people using insulin, intensive glycemic management for type 2 diabetes, collaborative care for depression [87–89]. The last frontier in cost-effectiveness analysis is the estimation of the health utility impact of diabetes complications [90]. Neuwahi et al. combined the Health Utilities Mark 3

data on 15,252 patients with type 2 diabetes from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Look AHEAD (Action for Health in Diabetes) trials, classified complications and estimated utility decrements [90]. The largest, statistically significant health utility decrements reported were for stroke, amputation, congestive heart failure, dialysis, reduced glomerular filtration rate, angina, and myocardial infarction [90]. Health utility estimates can be used to improve population-based models and to inform policy makers about the benefits, costs, and cost-effectiveness of type 2 screening, prevention, and treatment programs [90].

The Economic Burden of the Disease on Persons with Diabetes and Their Families

The opening statement of the classic article by Ed Wagner's group about chronic disease is probably one of the few "permanent paradigms" in medicine, and an inescapable truth: "in chronic illness, day-to-day responsibilities (including costs) fall most heavily on patients and their families" [91]. The indirect and intangible costs of diabetes are underestimated, their burden increases over the years, and comorbidities impose additional charges. The costs of chronic care, for cardiovascular diseases and cancer, are becoming a serious burden for patients [92]. Diabetes is not an exception, and patients are increasingly suffering signs of financial strain as out-of-pocket costs ascend [92]. The burden of financial hardship from medical bills among individuals with chronic disease results in financial distress, food insecurity, and cost-related medication nonadherence [93], but it is largely unaccounted for in the analysis of diabetes costs. Berkowitz et al. published the results of a cross-sectional analysis of data from 9696 individuals with a variety of chronic diseases including diabetes, in which 23.4% reported cost-related medication underuse, 18.8% reported food insecurity, and 11.0% reported both [94]. The high overall prevalence of food insecurity and cost-related medication underuse highlights one of the main barriers to successful diabetes management [94], but these realities are vetoed in academic forums, where the advantages of new and costly medications are championed regardless of their costs. The ugly reality has to be recognized and addressed: national spending on glucose-lowering medications among adults with diabetes increased 240% by $40.6 billion from 2005–2007 to 2015–2017 in the United States of which insulin and noninsulin medications contributed $26.6 billion (169%) and $12.0 billion, respectively [95]. For insulin, the increase was mainly associated with higher expenditures from analogs (156%); for noninsulin medications, the increase was the result of higher costs of new medications (88%), while the cost of older medications decreased by 34% [95]. Most importantly, the increase in insulin spending came from higher costs per user (out-of-pocket costs) [95]. Having to use multiple insulin doses, the status of people with type 1 diabetes is more alarming [57]. A retrospective analysis of direct costs for children and adolescents with type 1 diabetes showed that mean annual costs increased from $11,178 USD in 2012 to $17,060 USD in 2016, driven primarily by the increase in the costs of insulin, from $3285 USD to $6255 USD, and technology, from $1747 USD to $4581 USD [57]. The authors of this study conclude that the short-term burden of costs could be offset by future savings and that cost-effective analyses should be undertaken to support optimal care [57]. The bottom line is that within 5 years, the direct costs for children and adolescents with diabetes increased by 34.5%, or 7% per year, by comparison with the average annual inflation rate of 1.96% [57]. As already mentioned, the costs of insulin were mainly responsible, increasing by 52.5% in 5 years, or 10% per year!

Considering the acute and long-term health risks of poor glycemic control, it is vital that people with type 1 (and type 2) diabetes have uninterrupted access to insulin (and antidiabetics), yet millions of people with diabetes around the world still struggle to procure medications [96]. Patients are clearly aware of and conceptualize the experience of being without insulin as a "life or death" emergency and have described multiple insulin access barriers including unaffordable health care, institutional unresponsiveness, and personal life transitions [96]. In the face of these adversities, patients resort to several strategies, including omitting medications, asking for lower-priced medications, or self-treatment [97, 98]. Unable to consistently rely on the health care system to facilitate insulin access, patients turn to non-traditional and dangerous alternatives [96]. The negative consequences of these actions have been confirmed but are inexorably linked to the preeminence of social determinants of health in the continuity of diabetes management over a lifetime. The situation is even worse in many low- and middle-income countries which are unable to provide "comprehensive diabetes care" established by international guidelines, and consequently, diabetes care is delivered at a minimal level [99]. To address this reality, Gregory et al. developed a 30-year type 1 care model that looked at the onset of complications, mortality, financial costs, and quality-of-life measures associated with achieving HbA1c levels for "minimal" and "intermediate" care in six countries with varying income levels and geographic locations (Mali, Tanzania, Pakistan, Bolivia, Sri Lanka, and Azerbaijan) [99]. Minimal care was defined as receiving human insulin once or twice per day, two syringes per week, routine clinical care and hospital admissions, and no screening for complications [99]. Intermediate care consisted of a basal bolus regimen for human insulin delivery, 2–3 capillary blood glucose testing per day, point-of-care HbA1c test-

ing, screening for complications, diabetes education, and 24-h emergency call services [99]. The expected outcome for minimal care was an HbA1c range of 12–14% and from 8.0 to 9.5% for intermediate care [99]. According to their model, the cumulative 30-year incidence of complications was much lower for "intermediate" care than "minimal care" [99]. For many people with diabetes all over the world, even intermediate diabetes care is inaccessible or unaffordable.

Conclusions Achieving glucose, cholesterol, and blood pressure targets in patients with diabetes leads to substantial gains in clinical outcomes, a lower incidence of diabetes complications, and quality-adjusted life years (QALYs). Randomized clinical trials significantly increase direct costs but substantially reduce the risk and cost of complications and increase the time free of complications. Underlying factors driving the rising costs of diabetes include deficiencies in health systems, changing demographics associated with increased life expectancy and aging, and the persistence of the status quo. Simmons and Wenzel accurately claimed that in many cases, diabetes inpatients are a case of lose, lose, lose [35]. Health systems unable or unwilling to reinforce multidisciplinary outpatient management can only expect to see increases in the financial and health burden of preventable hospitalizations [36]. To make matters worse, many patients with diabetes struggle to pay medical bills or to pay them at all. To reduce the out-of-pocket costs of prescription drugs, patients resort to several strategies including self-treatment, avoiding taking medications, or asking doctors to prescribe lower-priced medications with negative consequences for their health. Clinical trials have shown that diabetes interventions are cost-saving or cost-effective; achieving these results in the real world is a great challenge. Albeit limited in scope, the study of diabetes costs confirms the increasing impact of the disease on people with diabetes, their families, national health systems, and societies, and represents a call for action to respond in a comprehensive manner to all phases in the natural history of the disease at the prevention level (primary and secondary), at the health care level, and stress the importance of improvements in disease management. The crisis of diabetes costs is worsening; the time to act is now [100].

Multiple-Choice Questions

1. Value of health care is defined as:
   (a) Health care at the highest cost
   (b) Health outcomes appreciated by pharmaceutical companies
   (c) Health outcomes appreciated by physicians
   (d) **Health outcomes achieved per dollar spent**
   (e) Health outcomes achieved per dollar saved
2. The true value of health care can be assessed:
   (a) Only if clinical outcomes are considered
   (b) Only if economic outcomes are considered
   (c) Only if patients' outcomes are considered
   (d) None of the above
   (e) **All of the above**
3. Health economics is about
   (a) Getting better value from the deployment of endless resources
   (b) **Getting better value from the deployment of scarce resources**
   (c) Learning about the use of economic resources
   (d) Saving resources at all cost
   (e) The use of resources to obtain the most advanced technology and medications
4. Opportunity costs are defined
   (a) **As benefits sacrificed for the best alternative**
   (b) As benefits obtained for the most expensive alternative
   (c) As benefits obtained for the most clinically effective alternative
   (d) As risks avoided for the best alternative
   (e) As risks avoided for the future scarcity of an intervention
5. By comparison with people without diabetes, direct health care costs in people with diabetes
   (a) Are equal
   (b) Are lower
   (c) Are one time higher
   (d) **Are two to three times higher**
   (e) Are ten times higher
6. Out-of-pocket spending:
   (a) Is higher in developed countries
   (b) Is the same all over the world
   (c) Is lower in low-income countries
   (d) **Is higher in low-income countries**
   (e) Is irrelevant
7. Indirect medical costs include:
   (a) Medical visits, medications, hospital admissions
   (b) **Patients and family expenditures**
   (c) Years of life lost, loss of opportunity for spouses and children
8. Direct medical costs include:
   (a) **Medical visits, medications, hospital admissions**
   (b) Patients and family expenditures
   (c) Years of life lost, loss of opportunity for spouses and children
9. Intangible medical costs include:
   (a) Medical visits, medications, hospital admissions
   (b) Patients and family expenditures
   (c) **Years of life lost, loss of opportunity for spouses and children**

10. Cost-effectiveness analysis is defined as:
    (a) All the costs required to achieve a clinical outcome
    (b) **Analytical and mathematical procedures supporting an intervention**
    (c) Total costs to achieve a unit of life saved
    (d) Total costs to achieve a unit of quality of life
    (e) The cost to achieve a medical outcome as appraised by clinicians

Glossary[1]

Cost The value of resources engaged in a service.

Cost-benefit analysis An analysis to consider the economic and social costs of medical care and the benefits of reduced loss of net earnings for preventing death or disability. A method for comparing the value of the outcome of all resources consumed (costs) by an intervention against the value (benefits) of the outcome.

Cost-effectiveness analysis A method designed to assess the comparative impact of expenditures on different health interventions. Identifying, measuring, and comparing the significant costs and consequences of alternative interventions to determine the degree to obtain the desired objectives or outcomes.

Cost-effectiveness ratio A comparison between alternatives, the difference in cost divided by the difference in effectiveness.

Cost-utility analysis Economic evaluation in which the outcomes of alternative interventions are expressed in single "utility-based" units of measurement. The most appropriate approach when quality of life is an important outcome.

Direct costs Diagnosis and treatment costs borne by the health system, the community, and patient families.

Health economics Monetary or humanistic trade-offs between wants, needs, and the scarcity of resources to fulfill these wants.

Incremental costs Difference between marginal costs of alternative interventions.

Indirect costs Lost productivity caused by disease to the individual, the family, the society, or the employer.

Intangible costs Costs of pain, grief, suffering, loss of leisure time, years of life lost.

Outcomes The results and value of medical interventions. Multidimensional and dependent on three perspectives: clinical, economic, patients'. The true value of health care interventions can only be assessed if all three dimensions of outcomes are measured and considered.

Pharmacoeconomic research Identification, measurement, and comparison of costs (resources consumed) and consequences (clinical, economic, humanistic) of pharmaceutical products and services.

Pharmacoeconomics Description and analysis of the costs of drug therapy to health care systems and society.

Quality-adjusted life years Adjustment measure that reduces life expectancy, reflecting the existence of chronic conditions causing impairment, disability, and/or handicap as assessed from health surveys, hospital discharge data, or others.

Total costs All costs incurred in producing a set of services.

[1]Modified from [101–103].

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