5 The Global Burden of Diabetes

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Keypoints

- Diabetes results in a range of distressing symptoms, altered daily functioning (requiring attentive monitoring and treatments), changed family roles, higher costs, lost productivity and premature mortality, which are felt by households, communities, and national economies.
- Diabetes is the fifth leading cause of death in the world (4 million deaths annually), outnumbering global deaths from HIV/AIDS; 80% of this mortality occurs in low and middle income countries, disproportionately affecting the young and economically active populations.
- Cost appraisal methods require epidemiologic, clinical, and economic data, and utilize different approaches to calculate the direct medical costs (of treatment, diagnosis, monitoring), indirect costs (of lost outputs from disability and premature death) and intangible losses (psychosocial burdens) attributable to diabetes.
- Even though there are large variations in methods of cost appraisal, cost items incorporated and purchasing power, as well as accessibility to and patterns of clinical care resulting in widely varied between-country per capita expenditures, it is clear that the presence of diabetes results in excess consumption of resources worldwide.
- Progressive severity of disease complications, co-morbidities and complexity of therapy all increase the monetary, infrastructural and human resource costs of care.
- Individuals in vulnerable subpopulations are at an elevated risk of developing diabetes and progression toward significantly harmful outcomes, and devote a large proportion of resources toward their therapies and diabetes care; confronting the increased susceptibility and burdens will require addressing the underlying political, socioeconomic and behavioral factors that perpetuate disparities.

Introduction

Diabetes has emerged as a major health problem worldwide, with serious health-related and socioeconomic impacts on individuals and populations alike. Furthermore, the pandemic growth of diabetes is being spurred on by transitioning demographic (e.g. population aging), socioeconomic, migratory, nutritional and lifestyle patterns, and an affiliated proliferation in overweight and obese adults and children [1–2]. The International Diabetes Federation estimates there are 285 million people with diabetes worldwide in 2010 [3], and projects the absolute number will surpass 400 million in the coming twenty years. The overwhelming majority of this escalation will be attributable to growth of type 2 diabetes (T2DM). Rapid socioeconomic transformations seen with globalization, increasing urbanization, industrialization and marketization of developing regions will also result in a parallel growth of diabetes precursors (impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) and ensuing health consequences [4–6].

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Current estimates suggest that two-thirds of those affected by diabetes live in low and middle income countries (LMIC). This challenges traditional paradigms that segregated chronic non-communicable diseases (NCDs) as problems of affluent countries alone. Eight out of the top 10 countries with the highest absolute numbers of people with diabetes are developing or transitioning economy countries [3]. While this burden of greater absolute numbers may be partially explained by larger population size, the rates at which NCDs are increasing in these countries amid transition are much steeper when compared with those in more developed affluent countries [7]; by 2025, the number of diabetes cases will increase by 170% in low and middle income countries, compared to a 41% increase in developed countries [8].

Thus far, the attention on health burdens in the developing world has focused justifiably on the persistence of infectious diseases and nutritional deficiencies; however, these same countries must also contend with 80% of global mortality associated with chronic diseases [9,10]. Projections suggest that this already overwhelming "double burden" will be exacerbated by the growth of NCDs. Altogether, projected increases in diabetes in all corners of the globe will result in corresponding escalation of burdens in the form of serious morbidity, disability, diminished life expectancy, reduced quality of life, loss of human and social capital, as well as individual and national income losses. This chapter describes these burdens in a global context, and systematically introduces data regarding regional patterns and associated themes.

Distribution and trends

Epidemiologic evidence quantifies the impacts and predictors of disease, identifies vulnerable populations and their needs, and facilitates formulation of appropriate disease prevention and control strategies; however, there are still limited representative epidemiologic data originating from a great many LMICs. Moreover, the utility of currently available estimates is hampered by methodological deficiencies (inconsistent diagnostic criteria, poor standardization of methods) and limited coverage (regional sampling with a predominance of urban studies whereas the vast majority of the populations in question are rural inhabitants). Despite this, notable patterns can be discerned and can be described by giving examples from regions where they are particularly noteworthy.

In Africa, there is:
- A general lack of awareness about chronic diseases and their risk factors.
- Limited data originating from a few localized centers in certain regions (western, eastern and southern) of the continent. The latest data (1998–2004) show prevalence rates of 1–3% in rural areas and 6–10% in urban environments [11].
- A growing double burden of communicable diseases and nutritional deficiencies, along with NCDs, especially where there is rapid economic development and globalization. Between-country differences in NCD prevalence likely reflect different stages of socioeconomic and epidemiologic transitions [12].
- A tendency for cultural (perceptions of excess weight and imported processed foods as symbols of status and luxury) and societal (stigmas regarding loss of weight as a sign of HIV infection) factors to influence health-seeking behavior [11,13].
- Variation in risk by ethnicity, with Black Africans showing a greater preponderance toward hypertension, while those of Egyptian and Asian Indian origin demonstrate higher prevalence of diabetes [14].

In Europe, the USA and Canada:
- Available data are derived from population studies, records of insulin and antidiabetic medication sales and/or reimbursement claims. Estimates still suggest 30–50% of people in these high income countries (HIC) have undiagnosed diabetes [4].
- Annual incidence of type 1 diabetes (T1DM) is increasing in Europe (+3.2% per year) and North America (+5.3% per year); the highest reported incidence rate is in Finland (40.9/100,000 per year) [15,16].
- Prevalence of T2DM is highest and growing fastest in vulnerable subgroups such as lower socioeconomic groups and the elderly [4].
- Life expectancy of people with diabetes, although reduced when compared with the general population, is markedly higher than in developing regions of the world. This is largely attributable to differences in access to self blood glucose monitoring and therapies to control glycemia.
- Uptake and costs related to newer and more expensive investigations and therapies are associated with inflated national health expenditures.

In Latin America:
- There is wide variation in prevalence rates (1.2–8%) of diabetes, reflecting the diversity of ethnicities and stage of development between countries.
- The pattern of T1DM incidence seems to correspond to the size of the population of Caucasoid origin.
- Diagnosis of diabetes frequently occurs late in the course of disease. Thus, complications may be present in 30–40% of cases at time of presentation for health care.
- Poor accessibility to health services results in only 30–40% of cases actually receiving therapy [17].

Asia is emerging as the epicenter of the cardiometabolic pandemic, because:
- Populous countries in this region are confronted with diabetes risk being manifest at younger ages and at lower body mass indices compared with populations in other regions.
- Patterns of genetic and/or ethnic propensity; South Asians and peninsular Arabs have markedly elevated metabolic risk [18]; Japanese are reported to have the highest prevalence of genetic polymorphisms [19]. Rural–urban differences in prevalence together suggest both gene–environment interactions and influences of the "thrifty" genotype.
- Estimates suggest a three- to fivefold increase in prevalence of T2DM over the last three decades, and an increasing prevalence of T2DM in children, with major implications for future burden in this region [20,21].
- India is estimated to have 50.8 million people living with diabetes [3], the highest absolute number in any country [22] and projections suggest that one-fifth of all people with T2DM will be living in the Indian subcontinent by 2030 [23].
- The "Asian Indian phenotype" is characterized by a preponderance to deposition of metabolically active visceral adiposity which may explain the greater vulnerability to diabetes in this population [24–26], while Western Pacific Islanders also demonstrate a markedly elevated risk.

Diabetes is renowned as a "silent epidemic" [22]. The slow progression and lack of symptoms in the early stages of disease preclude seeking medical attention and preventative care. As such, reported prevalence reflects an underestimate of the number of cases because it does not account for undiagnosed cases. Population studies estimate that 30–50% of diabetes cases are as yet unrecognized, even in the most advanced countries [4,17]. Also, almost half of all newly diagnosed cases will have already developed diabetes-related complications in the form of nerve, eye, kidney, and/or vascular diseases [23,27,28]. Target organ damage of this nature can be life-threatening and/or seriously disabling [29].

The traditional socioeconomic gradient associated with chronic diseases may itself be transitioning. As the world's urban population size begins to outnumber those living in rural areas, many developing economies face enormous challenges related to the growth of peri-urban slums and squatter settlements, the disparities in provision of basic amenities and lack of adequate sanitation and nourishment. Further challenges include subsequent exposure to contemporary dietary choices, tobacco use and mechanization of transport with consequent growth in the incidence of NCDs. Thus, the paradigm is shifting *globally* towards the inverse relationship found in established market economies where the greatest burdens of NCDs are felt by the least well-off segments of the population [30–35]. In India for example, Ramachandran *et al.* [36] demonstrated that although family history and prevalence of glycemic abnormalities in high-income groups were double those of low-income groups, the reverse was true for smoking, alcohol consumption, prevalence of co-morbid cardiovascular risks and occurrence of complications (macrovascular disease, cataracts, proteinuria and neuropathy). Recent prevalence and trend data show greater disease susceptibility in lower socioeconomic groups in India [37,38], mimicking patterns in wealthier nations [39–42]. As this chapter progresses, it will become evident that the countries with the greatest burdens of disease are also those least equipped to manage the growing epidemics.

Major burdens

The burden of any disease, including diabetes, can be described by its health-related impacts: the morbidity and mortality caused, and the social and economic costs to individuals, families, communities and national economies (Box 5.1). Evaluation of resources utilized or lost, be they human, social, monetary or infrastructural, and placing objective "values" on them may be inherently partial to the perspective taken. The term "value" may be used to describe the measured and/or perceived net worth of resources consumed or lost because of illness and/or infirmity which is the mode used in this chapter. Economists use this term to express the net benefit derived from an investment in health care in proportion to the amount of resources used [43].

Box 5.1 Evaluation of burden

Health-related burdens
- Health seeking and utilization (frequency and costs)
- Disease events and/or ill health
- Morbidity (physical and psychosocial)
- Mortality

Social implications of disease
- Disability
- Alteration of social roles or family structure
- Caregiver or "intangible" burdens

Economic costs of disease
- Direct medical expenditure
- Ancillary expenses of health seeking and care
- Indirect costs (losses in productivity)

Acute and chronic disease complications

The patterns of major health-related burdens of diabetes vary by the type of disease. T2DM accounts for 90–95% of all cases worldwide. Both T1DM and T2DM, the two most common forms, may be associated with acute and chronic metabolic consequences, but the frequency of events varies according to the underlying pathophysiology and level of glycemic control.

Acute fluctuations in serum glucose may rapidly spiral into emergency situations, with potentially fatal repercussions if untreated. Episodes of severe acute hyperglycemia (e.g. diabetic ketoacidosis [DKA] and hyperosmolar hyperglycemic syndrome) or, conversely, severe hypoglycemia, most often require immediate medical management. Longer term follow-up is then intended to promote better blood glucose regulation and avoidance of precipitants of diabetic emergencies (e.g. infection, non-compliance with treatments, missing meals, alcohol abuse). Apart from atypical variants such as ketosis-prone T2DM in African subjects [11], the vast majority of acute complications occur in patients with T1DM, while approximately 10–12% occur in subjects with T2DM. When treated properly, the mortality from acute hyperglycemic episodes such as DKA is extremely low (e.g. DKA mortality in Taiwan, USA and Denmark were estimated to occur in 0.67–4.0% of cases) [44,45]. In contrast, in some African countries, mortality from DKA can be as high as 25–33% [46], although the incidence of these complications from LMIC settings is limited [47]. Individual patient (e.g. age, additional co-morbidities) and resource (e.g. hospital facilities, experience of staff) characteristics may also modify the outcomes. In underresourced settings for example, complex, cumulative and interconnected barriers (poor accessibility, inadequate therapeutic instruments and medication, and insufficient numbers of trained staff) result in poor glycemic control and higher risk of mortality [48]. As such, early life mortality in patients with T1DM in low-resource settings is commonplace. The post-diagnosis life expectancy in some regions of Africa is just 1 year [49].

Apart from glucose dysregulation, both T1DM and T2DM are associated with damaging effects on tissues, with eventual progression to devastating complications. Diabetes increases the risk of macrovascular diseases (cardiovascular diseases [CVD], which comprise coronary heart disease and cerebrovascular disease or "stroke," and peripheral vascular disease [PVD]), microvascular diseases (retinopathy and nephropathy), neuropathies, and the consequences that stem from these (e.g. congestive heart failure, diabetic foot). These complications are associated with considerable morbidity, reduced quality of life, disability, premature mortality and high economic costs.

In addition, T2DM is associated with the "metabolic syndrome," a collection of cardiovascular risk factors (abdominal obesity, hyperinsulinemia, hypertension, dyslipidemia, proinflammatory and procoagulant states). It is believed that these biochemical and inflammatory derangements are intimately linked, possibly by a central mediating factor. In Latin America, it is estimated that 53–69% of people with diabetes have abnormal serum lipid subfractions, and 34–67% have hypertension [17]. As such, these factors increase the likelihood of developing additional risks, and with each added risk, predispose one to an exponentially increasing risk of atherosclerotic vascular disease events and mortality [50].

Moreover, T2DM has a distinctive association with coronary heart disease (CHD). Those with diabetes have a two- to fourfold higher risk of developing CHD than people without diabetes [51]. More significantly, however, the age- and sex-adjusted cardiovascular mortality risk in patients with diabetes is equivalent to that of individuals without diabetes who have had a previous myocardial infarction (MI) [50,52,53]. Precursors common to both T2DM and CVD (insulin resistance, visceral adiposity and excess inflammation) [54–58], and a complex mix of mechanistic processes such as oxidative stress, enhanced atherogenecity of cholesterol particles, abnormal vascular reactivity, augmented hemostatic activation and renal dysfunction, cumulatively confer this elevated risk of CHD [59]. As such, simply controlling glucose has not been found to reduce CVD events and mortality in large randomized controlled trials at least in the short term [60–62]. The implications therefore are that individualized comprehensive multifactorial risk management, involving the treatment of all co-morbidities, has been advocated for people with T2DM [63,64], adding to the burdens placed on patients, providers and health systems.

Diabetes also increases the risk of renal dysfunction. In Africa, it is estimated that within 5–10 years following diagnosis, 32–57% of people with diabetes will have developed microalbuminuria [48,65]. Also, diabetes is the primary cause in approximately 45% of patients with end-stage renal disease (ESRD) requiring dialysis or transplantation in the USA [66,67]. Meanwhile, approximately one in four persons with diabetes have some visual impairment, and 5% of all cases of blindness globally are caused by diabetes [68]. Particularly in the case of retinopathy and nephropathy, duration of disease, age, glycemic control and blood pressure control have all been found to be prominent modifying factors of disease onset, progression and outcomes.

Neuropathies are also common consequences of diabetes. One-third of Sri Lankan people with diabetes surveyed had lower extremity sensory loss putting them at risk of ulceration [69], while a similar proportion of people with diabetes in African countries were found to have either neuropathy or compromised peripheral vascular circulation [70,71]. The combination of neuropathy, increased susceptibility to infection, poor wound healing and poor distal circulation increases the risk of lower extremity amputation 15- to 40-fold [67,72].

The most significant repercussion of the asymptomatic early natural history of the diabetes and low community awareness is that subclinical disease results in progressive tissue injury. Microvascular and macrovascular complications cause morbidity, greater health-seeking and increased mortality risk in all regions of the world [23,27,73].

Health utilization patterns

Health seeking and health utilization behaviors are influenced by a number of individual, provider and system level factors. In the case of diabetes, ill health and morbidity as well as preventative care motives result in incrementally more health service utilization. In Costa Rica, for example, people with diabetes made 55% more medical visits than those without diabetes, and German patients with diabetes averaged 31 yearly consultations with general practitioners (GPs) and/or specialists [74,75]. In Sweden and Italy, approximately half of diabetes-related consultations were at hospital outpatient departments or dedicated diabetes centers, respectively, and the remainder were with GPs [76,77]. In Latin America, diabetes accounts for an estimated 35 million medical visits annually [74].

Various studies have shown that having diabetes doubles one's risk of hospitalization compared to not having diabetes, and this risk is amplified by the development of diabetes-related complications. The presence of poor peripheral circulation increases the risk of hospitalization by 70%, while CVD increases this risk by 310% [67]. The Cost of Diabetes in Europe Type II Study (CODE-2) reported 13% of people with T2DM were hospitalized (with an average stay of 23 days) over the 6-month study follow-up, while Germany's Cost of Diabetes Mellitus (CoDiM) study reported that 28.8% of people with diabetes had at least one hospital admission in 2001 [75]. Although studies from most regions of the world report late-stage macrovascular or microvascular complications as the leading cause of diabetes-related hospitalizations, lower income settings such as Ethiopia confront a greater proportion (almost two-thirds) of admissions in the form of acute episodes of dysglycemia.

Health care infrastructure and financing have strong impacts on health seeking and utilization. In India, estimates suggest that 85–95% of all health care costs are borne by individuals and their families from household income [78–81]. In Latin America, 40–60% of diabetes expenses are derived from out-of-pocket payments. A survey in Jamaica showed that 57% of the sample reported financial difficulties as a result of illness, and of these, half disclosed that they had avoided therapy because of economic constraints [74]. Financial limitations to accessing treatment are not confined to LMICs, as illustrated by 19% of elderly Americans revealing curtailed purchases of diabetes medications as a result of costs [82,83].

When one considers that the average number of medications used by people with diabetes in India is 3.5 [79], the cost implications are substantial. These drugs include antihypertensives, lipid-lowering, antidepressant medications and aspirin in addition to glucose-lowering drugs). The use of oral hypoglycemics increases health expenditure by 40% compared to the general population, while regular insulin use is a further twofold greater expense. As such, data from Germany show that use of insulin with or without oral agents increases total costs 3.1–3.4 times [75,84].

Increased health seeking and utilization in people with diabetes and associated complications result in greater medical costs incurred, compared to the general non-diabetic population.

Disability

Aside from the medical or biologic dysfunction caused by disease, there are implications of ill health for individual and interactive functioning in society. This concept of "disability" is distinctive from simple biomedical models of disease and signifies that psychosocial illness or physical deviations from generally accepted norms of anatomical structure or physiologic function may impair one's ability to perform domestic and occupational activities, and assume societal roles. As a result, diabetes may inhibit one's general utility and ability to integrate fully in society.

Diabetes can lead to disability through a variety of ways. Excluding the medical aspects of diabetes-related complications that directly restrict bodily function, diabetes may be considered a "hidden" disability, whereby the individual concerned is hampered from routine activities, but displays no physical manifestation of this illness. For example, children with diabetes may be unable to participate in all activities their contemporaries are engaged in and may suffer wrongful discrimination. Adults in the workplace may have lower work performance by virtue of any number of symptoms (impaired fine motor skills and concentration, grogginess, urinary frequency) [85] or even decline in cognitive functioning [86–88]. Those requiring insulin may be limited additionally by highly structured activities of daily living (the requirement of meticulous glucose monitoring, insulin administration, timed eating), recurrent hospitalizations, hyperglycemic and hypoglycemic episodes, and by regular preventative or therapeutic medical visits.

Indeed, the physical manifestations of diabetes become more significant with the development of complications. As such, visual impairment, restricted mobility (from shortness of breath, chest pain or even amputation) and general ill health (ranging from increased susceptibility to infection all the way to uremia related to irreversible renal dysfunction) are all considerable impediments to productive work and engagement in socially valuable activity. Cross-sectional studies in the USA have demonstrated that elevated glycated haemoglobin (HbA_{1c}) is associated with a higher likelihood of missing work, greater hours absent [89] and reduced at-work efficiency [85].

Depending on the health status of the individual and severity of disease, disability can be temporary or permanent. There is limited country-specific data on the permanent disability resulting from diabetes, although diabetes is the leading cause of adult-onset blindness, non-traumatic amputations and irreversible kidney failure worldwide [22]. Data from Chile showed that 8% of people with diabetes had some form of permanent disability [74].

Less tangible, but no less severe, are the psychosocial burdens that may accompany diabetes and affect functioning [90,91]. In a health maintenance organization cohort of 1642 people with diabetes, 12% were unemployed, 7% of those employed had missed more than 5 working days in the previous month and 4% of employed subjects reported difficulties with completing work tasks. Of those with any form of work disability inducing absence and/or poor productivity, over half had minor and/or major signs and symptoms of depression [92].

The complexity of disability as a limitation of individual and societal function is in quantifying this shortcoming. There are several methods that have been used which factor in age, education and occupation, but most have at least some imperfection because of the necessity of making judgments about the value of activities. This is especially difficult where there are cultural and ideological dissimilarities between the evaluator and the population being appraised.

Mortality

Ascertaining the global mortality attributable to diabetes is no easy task. Most mortality statistics rely on documented causes of death and do not acknowledge the roles of glucose dysregulation in underlying mortality associated with CVD and renal diseases. Danaei *et al.* [29] have therefore argued that evaluating actual diabetes-related mortality should take into account that diabetes contributes to 21% of CHD and 13% of stroke mortality worldwide. The World Health Organization (WHO) incorporated these sentiments into calculating that diabetes is the fifth leading cause of death worldwide in 2000 [93]. The International Diabetes Federation's most recent *Diabetes Atlas* approximates that diabetes is responsible for 6.8% of total global mortality (4 million deaths) annually [22,94]. In addition, the mortality attributable to diabetes would be even higher if deaths related to IGT were also included. This diabetes precursor independently increases the risk of mortality, and has a prevalence of 15–40% in adults [6].

Altogether, diabetes is associated with premature mortality, shortening life expectancy by approximately 7–15 years [95,96]. In developed countries, CVDs account for an overwhelming 65–75% of deaths in people with diabetes [97,98]. In low-resource settings, infections and acute metabolic emergencies are still the prevailing causes of death in people with diabetes [11,12,65,99]. ESRD also carries inexorably high mortality, mainly because of inaccessibility (physical and financial) of treatment (dialysis and/or transplantation) in most LMICs [11]. As a result, globally, CVD and nephropathy are the most prominent fatal endpoints, and occurrence is analogous to duration of disease in that early life survival and long-standing diabetes increase susceptibility to succumbing from these illnesses [27].

There is regional variation in the global distribution of diabetes-related mortality. Estimates for the percentages of deaths attributable to diabetes by region are shown in Table 5.1. Although the proportion of deaths in LMICs is lower than in more developed countries, the absolute numbers of deaths, by virtue of larger population size, outnumber those in economically developed countries. South Asia is currently reported to have the highest absolute number of diabetes-related deaths annually [100]. Also, there is a noticeably greater proportion of deaths in

Table 5.1 Estimated percentage of deaths attributed to diabetes by age and World Health Organization (WHO) region. All figures are presented as male/female percentages. Adapted from Roglic *et al.* [93].

Region	Age (0–34 years)		Age (35–64 years)		Age (≥65 years)		All ages	
	Male	Female	Male	Female	Male	Female	Male	Female
African Region	0.5	0.8	7.1	7.9	2.7	4.1	2.2	2.5
Region of the Americas	0.4	0.5	11.6	17.8	5.4	7.7	6.0	8.6
Eastern Mediterranean	0.5	0.8	14.8	22.3	6.6	10.0	6.1	8.8
European Region	1.0	0.9	9.5	11.3	5.8	4.4	6.5	5.1
Southeast Asia Region	0.8	0.9	12.7	18.2	5.1	8.2	5.4	6.9
Western Pacific Region	0.2	0.3	6.4	9.2	3.01	5.1	3.4	4.8

younger age groups in LMICs, resulting in higher loss of life years, and affecting the economically active subpopulations in these countries.

It must be mentioned that in Africa, the HIV/AIDS epidemic has already altered patterns of mortality and life expectancy and is projected to modify these further. Irrespective of the fact that sub-Saharan Africa accounts for 72% of HIV-related deaths worldwide [101], projections based on demographic trends alone suggest that the prevalence of diabetes will continue to grow in this region. Widespread use of antiretroviral therapy will also directly (in the form of pancreatic dysfunction associated with therapy) and indirectly (increasing longevity of life) affect diabetes prevalence. The scarcity of data emanating from this continent does not allow a greater comprehension of the relative impacts of these forces versus contemporary sociodemographic and epidemiologic transitions.

Economic and social implications

The prototypical chronic nature of diabetes requires empowered self- and clinician-guided management for the duration between diagnosis and death. Forestalling complications and premature mortality is the central theme underlying glucose control and preventative management. Together, the care and serious consequences of diabetes are burdensome and costly. Quantifying the costs of diabetes from the perspectives of diabetes patients as well as national resource use and losses are critical towards informing appropriate health care planning, resource allocation and response strategies.

Approaches used to estimate economic costs of disease vary, not only by the perspective taken, but also by methodology applied, data sources used, year of estimation, as well as purchasing power and clinical practice patterns in different settings (Table 5.2). Needless to say, between-country comparisons are even more problematic where issues emerge regarding uncertainty of incidence and prevalence estimates, and standardization of measures and criteria. General principles and concepts of estimating cost are described [1,67,102,103].

Table 5.2 Examples of different treatment patterns in high-income countries.

Country	Proportion of diabetes patients receiving treatment			
	Diet and/or exercise (%)	OHA (%)	Insulin (%)	Both OHA and insulin (%)
USA [124]	16	57	14	13
Germany [75]	28	44	16	11
France [84]	–*	80	14.7	5.3

OHA, oral hypoglycemic agents.
* Database query only recognizes medications prescribed for diabetes.

Types of costs

Direct costs (inputs)

These include costs of treatment and care of the disease, broadly encompassing all outpatient consultations, inpatient care, diagnostic investigations, therapeutic procedures, pharmacotherapy, paramedical care (e.g. home nursing, physiotherapy), patient time, transportation and rehabilitation.

Indirect costs (lost output)

These costs represent the present and future value of economic productivity lost by society on account of temporary or permanent disability, excess morbidity and premature mortality from disease; they are typically calculated by estimating foregone income by investigating the cumulative impacts of absenteeism, employment status and income, for both the individual and caregiver(s).

Intangible costs

Costs are associated with the psychosocial impacts (e.g. stress, depression, emotional problems) and altered quality of life from an illness; they may include diminished family role, informal care and foregone income by family members; these costs are typically difficult to estimate because of relative lack of standardized methods.

Cost appraisal methods

Cost-of-illness method

This is the most widely used approach to describe the direct and indirect costs of disease to society and is conducted by exploring costs in a group of selected persons either over a defined finite period (e.g. 1 year) or through the natural progression of the disease.

Human capital approach

This is a method of estimating indirect costs of disease, with an emphasis on foregone earnings and employment; it is criticized as a tool because of the tendency for overestimating future values, accepting wage disparities and disregarding socially valuable activities such as housekeeping and volunteer work.

Friction cost approach

This approach is a more conservative measure of indirect costs that considers lost productivity as finite where restoration of productivity (return to work or replacement of worker) occurs within a timeframe and therefore limits production losses; it does, however, require detailed data.

"Top-down" approach

This calculatates costs from national databases and/or estimates, partitioning costs of different illnesses according to diagnoses; it requires accurate data entry, especially when indirect costs are being investigated but avoids the risk of double counting.

"Bottom-up" approach

This follows the trail of illness-related costs of a defined subpopulation with the illness, over a finite period.

Studies that have examined costs of diabetes vary in their estimates of the excess costs generated through resource consumption. The major drivers of direct health care costs include health service utilization (outpatient or ambulatory care comprising health practitioner consultations as well as inpatient care); medication usage; diagnostic tests; self glucose monitoring and therapeutic medical devices; and therapeutic procedures. In more developed settings, auxiliary services such as paramedical care (dietitians, physiotherapists, occupational therapists and home nursing) and preventative checks (foot care, urine and eye testing) may contribute to costs. The relative contributions of these cost drivers in various regions of the world are shown in Table 5.3. Themes that surface from these studies affirm the high costs of complications and associated hospitalization in developed countries, but also point to higher relative costs of purchasing medications in LMICs. Indeed, the supplemental costs of drugs for co-morbid CVD risk management are also pronounced.

Demographic and clinical characteristics have profound influences on costs. In Germany, compared to the diabetes-free population of the same age, younger people with diabetes (under 40 years of age) had greater incremental costs (4.1 times) than the people in the elderly age group (only 1.5 times higher) [75]. The types of diabetes have different costs. T1DM accounts for 5.7% of people with diabetes in the USA; medical costs of US$10.5 billion (bn) and indirect losses amount to US$4.4 bn, totaling US$14.9 bn. This is comparatively much lower than the US$159.5 bn that cumulatively account for T2DM care and lost productivity, but the cost burden per case is greater for T1DM [104]. It has been postulated that more consultations and faster progression to retinopathy and nephropathy are the main drivers of cost and mortality risk in those with T1DM [27,76]. In T2DM, coexistence of hypertension and dyslipidemia have relatively more significant roles in mediating risk, outcomes and associated costs.

The presence of diabetes-related complications greatly increases both the magnitude and duration of resource consumption. In particular, CVD and nephropathy are associated with the highest health care costs in most regions of the world. In the USA, medical costs increase by a factor of 1.5 when early CVD manifestations develop, and escalate to 3.6 times with the occurrence of a serious CVD event. Similarly, early renal dysfunction is the basis for 65% more costs, and the onset of ESRD signifies a 771% increase in costs [105–107]. Brandle *et al.* estimated that 1-year direct costs of suffering and surviving a major vascular event in the USA totaled US$24 500 for a myocardial infarction, US$26 600 for a stroke and US$37 600 for an amputation [130]. The Diabetes Health Economics Study Group estimated that complications contribute up to 60% of all direct costs, and 80–90% of indirect losses from absenteeism and lost productivity [108]. A rudimentary, but possibly practical finding by Gilmer *et al.* [109] reports that for every 1% (11 mmol/mol) increase in HbA_{1c} over 7% (>53 mmol/mol), there is a corresponding 10% increase in costs.

National perspectives reveal large differences in the health care expenditure in developed and developing country settings. Although the metrics used are different, per capita expenditure on health in Tanzania (US$4) and South Africa (US$158), as well as annual direct costs of diabetes from Argentina (US$330), France (US$675) and Denmark (US$3535) demonstrate sizeable between-country disparities [110]. Industrialized countries are also advantaged in the organization of health care infrastructure, as well as the financing of the system. For example, nationalized insurance and social security schemes in France and Germany cover 83.4% and 86% of these populations, respectively, which ensures high accessibility to care for citizens [75,84].

The imbalance between resource expenditure and needs is further exemplified by estimates that only 20% of global expenditure occurs in the regions where 80% of people with diabetes live [111], demonstrating that Julian Tudor Hart's [112] "inverse care law" is very relevant to global diabetes burden. This states that "the availability of good medical care tends to vary inversely with the need for it in the population served". As a result of inadequate public spending on health in LMICs (e.g. in India, only 2% of the government's annual budget is devoted to health care), sizeable proportions of household income are spent on health care costs. In Africa, 40% of people are said to earn less than US$1 per day (~$300 per annum) [11,12], and in countries such as Sudan, almost two-thirds of family incomes are required to pay for the care of one child with diabetes [113]. In Mozambique, less than one-fifth of all health facilities have the wherewithal to offer blood glucose and urinary ketone measurement [49]. The other end of

Table 5.3 Regional and country estimates of costs of diabetes.

Country	Year	Method	Annual total cost per patient	Annual total costs for country/region	Main drivers of cost	Limitations
Europe						
8 countries (Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, UK) – CODE-2 Study [125]	1999	Cost-of-illness, prevalence-based study, patient and practitioner surveys, n = 7000 T2DM	€2834 (range: €1305–3576)	€29 billion	Hospitalizations (55%); other drugs – mainly cardiovascular (21%); ambulatory care (18%); antidiabetic drug costs (7%)	6-month retrospective design subject to recall bias, extrapolation error that excludes seasonal variation
France [84]	1998–2000	Retrospective patient reimbursement data (national database)	€3680 (1998) – €3914 (2000)	€5.7 bn (2000); €2.4 bn directly on diabetes care	Inpatient care (42%), outpatient care (58%); ambulatory care (18%); antidiabetic drug costs (7%)	Excluded patients with diabetes controlled on lifestyle measures; excluded indirect and intangible costs
Sweden [77]	1994	Cost-of-illness, top-down, prevalence design	n/a	US$766.1 million (43% direct, 57% indirect)	Direct: hospital care (58%), drugs (18%), ambulatory care (13%), devices (11%) Indirect: early retirement (55%), absenteeism (24%), mortality (22%)	Excluded costs of other illnesses related to diabetes; excludes those treated by dietary modification alone
Italy [76]	1998	Cost-of-illness, bottom-up, multicenter, retrospective database query of OPD costs; n = 2260	2 month costs: €136.8 (T1DM) and €123.3 (T2DM)	n/a	T1DM patients (n = 592) had more consultations; T2DM patients (n = 1668) had more diagnostic tests and day-hospital procedures Drug costs: 32–36% (T1DM) and 13–24% (T2DM)	Study limited to 2 months; Excluded costs of hospital care (known to be 30–50%); excluded indirect costs
Germany – CoDiM Study [75]	2001	Cost-of-illness, prevalence-based, retrospective database query; n = 26 971	€10 281; €5262 (direct) and €5019 (indirect)	€30.6 bn (including €14.6 bn directly due to diabetes)	Excess costs related to: inpatient care, medications (insulin, drugs to treat co-morbidities, and complications); increasing age; use of medical devices	Indirect costs not included; data protection requirements preclude validating diagnoses; cross-sectional observation; illness severity varied
Africa						
Sudan [113]	2001	Cost-of-illness, bottom-up approach: parent interviews of 147 children with T1DM	US$283 per child	n/a	Direct costs: insulin (36%), glucose testing, physician visits Indirect costs: poor school performance, 65% of family expenses were used for care of one T1DM child	Subject to recall bias; sample may not be representative of wider population (private clinics); subjects had ≤5 years duration of diabetes

South Asia						
India (South India) [80]	Pre-1998	Cost-of-illness, bottom-up approach: interviews and billing data; private (n = 422) and government-funded (n = 174) clinics	Median Rs.4510 (surgery = Rs.13 880; inpatients = Rs.7505; OPD = Rs.3310)	Estimated Rs.90.2 bn (~US$ 2.2 bn)	Surgical or inpatient care; duration of diabetes	Quality and costs at government-funded institutions are unknown (no fee charged)
Other studies in India: North India [79]; CODI study; others [81,126,127]	Unknown	Cost-of-illness, bottom-up approach: questionnaires and disability assessments; n = 50 at OPD Community-based surveys of diabetes costs (national perspective)	Rs.14 508 (€264); direct (68%), indirect (29%) Rs.19 914; direct (36%), indirect (64%)	n/a	Direct: drug costs (62%), dietary changes (20%), travel costs, investigations Indirect: loss of income, loss of caregiver income (education and income correlates such that higher levels result in greater loss) Direct: hospitalization (35%), monitoring and doctor visits (34%), drug costs (31%)	Small sample size; short follow-up (6 months) with extrapolation; did not evaluate intangible and social burdens Wide variation in annual cost-per-patient estimates (e.g. Rayappa *et al.* [122] Rs.8595 = $191–208; Bjork *et al.* [129] Rs.7189)
Pakistan [129]	2006	Cost-of-illness: questionnaires; human capital approach; n = 345 (age = 20–60) at 6 OPD clinics	PKR 11 580 (= US$197)	Direct costs projection = PKR 71 bn (= US$1.21 bn) annually	Direct: medication (46%), laboratory investigations (32%); age, complications, and duration of disease were drivers of cost	Inclusion restricted to 20–60 year age group; did not include costs of self-monitoring; calculation of lost productivity limited to those employed
Americas						
USA [130]	2000–2001	Cost-of-illness study: surveys, chart reviews, and claims data; n = 1364 T2DM subjects from Michigan HMO	US$1684 (for diet-controlled, no CVD risks or complications) to US$10 500 (obese, insulin-treated, high BP, renal, and vascular disease)	n/a	Multipliers: ESRD with dialysis (×10.53), history or MI (×1.9), insulin treatment (×1.59), PVD (×1.31), CbvD (×1.3), treated BP (×1.24) † Redekop *et al.* showed age, insulin use, micro- and macrovascular complications, and dyslipidemia are cost drivers	Analysis limited to T2DM; not representative of general population of USA; costs excluded out-of-pocket expenses and indirect costs
USA [131	2007	Cost-of-illness, prevalence-based study: Cost of Diabetes Model utilizing national surveys and claims database (16.3 million people in 2006)	US$ 11 774 ($6649 directly for diabetes care)	US$174 bn; $116 bn (direct), $58 bn (indirect costs)	Direct medical costs: complications (50%), diabetes care (23%), general medical costs (27%) Indirect: premature mortality (46%), disability and lost productivity (54%)	Estimates do not include: intangible costs, caregiver opportunity costs and undiagnosed diabetes

Continued on p.78

Table 5.3 *Continued*

Country	Year	Method	Annual total cost per patient	Annual total costs for country/region	Main drivers of cost	Limitations
Latin America and Caribbean [74]	2000	Cost-of-illness, prevalence-based study: cost estimates for groups of countries and human capital approach	US$703 (range: $442–1219)	US$ 65.2 bn; $10.7 bn (direct), $54.5 bn (indirect)	Direct: drug costs (44%), consultations (24%), complications (23% – especially nephropathy) Indirect: disability and productive life years lost (93%), mortality (7%)	General lack of data forced use of estimates in heterogeneous countries Diabetes-related deaths undercounted on death certificates; high indirect cost may reflect poor access to medical care
Mexico [132]	2003–2005	Extracted data for a standard case and natural history; human capital approach; 50% of population are insured, 40% are low-income uninsured	Villareal-Rios *et al.* [134] report US$708–1488 per patient	US$317 m; $140 m (direct), $177 m (indirect) Phillips *et al.* [135]: US$100 m (direct); $330 m (indirect)	Direct: drug costs (39%), complications (32%, especially nephropathy), hospitalizations (12%), consultations (11%) Indirect: permanent disability (94%), mortality (4.5%), temporary disability (1.5%)	Restricted to T2DM and patients attending public institutions; excludes out-of-pocket expenses and the private sector
Canada [135]	1998	Cost-of-illness, prevalence-based, top-down, national database query	n/a	CAN$3.7 bn; 70% (direct), 30% (indirect); CAN$ 4.8–5.2 bn if undiagnosed cases included	Direct: hospital costs (50%), medications (31%), physician care (19%) – medical costs of complications 1.6 times more than diabetes alone Indirect: diabetes (45%), complications (55%)	Reliance on coding of cases subject to error; limited indirect cost evaluations; prevalence estimates and practice patterns vary across provinces; home, nursing care, and glucose testing not included in costs
Australia						
Australia [136]	2000	Cost-of-illness, prevalence-based, bottom-up study; n = 1294 T2DM	n/a	A$636 m	Age, co-morbidities	Changes in practice patterns between recruitment and cost appraisal may bias results; indirect costs or hospitalization for other illnesses not included
Australia – DiabCost Study	2003	Cost-of-illness, bottom-up: T2DM patients; self-reported surveys	A$9625 (if no complications); $15 580 (with complications)	A$3 bn	–	Data were self-reported; costs not associated with DM could not be separated out

A$, Australian dollar; BMI, body mass index; bn, billion; BP, blood pressure; CAN$, Canadian dollar; CbvD, cerebrovascular disease or stroke; DM, diabetes mellitus; €, European Union Euro; ESRD, end-stage renal disease; GP, general practitioner or primary care doctor; HMO, health maintenance organization; m, million; MI, myocardial infarction; OHA, oral hypoglycaemic agent; OPD, outpatient department; PKR, Pakistani rupee; PVD, peripheral vascular disease; QOL, quality of life; Rs., Indian rupee; SES, socioeconomic status; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; US$, US dollar.

the spectrum comprise developed countries such as Germany and the USA, which spend €31.3 billion and US$116 billion annually on direct costs of diabetes, respectively. Of the estimated US$2.2 trillion in health care expenditures in the USA in 2007, one out of every US$7 spent was for diabetes [114]. These expenses are partially related to differences in pricing and prescription, but are also linked to the high costs of new diagnostic and therapeutic options (e.g. while annual cost of treating a patient with maximal daily doses of metformin is US$46, the equivalent costs of using thiazolidinediones are US$710–980) [115].

Additional considerations with regard to national economic impact concern the distribution of diabetes burden *within* populations. In low and middle income countries, diabetes and its complications disproportionately affect the economically productive age range (15–69 years), while in mature market economies, the disease affects the older (≥65 years), disadvantaged and ethnic minority subpopulations. The implications emanating from these trends are that economic development in transitioning countries may be subdued because of loss of unrealized productivity, while direct health costs for the aging and uninsured populations in developed countries will continue to escalate [1].

In LMICs, the lowest income groups bear the greatest burdens, paying a larger proportion of their household incomes towards diabetes care (34% and 27% for the urban and rural poor, respectively, vs 4.8% and 5.0% for the high income urban and rural groups in India, respectively) [116]. Year-on-year increases in this proportion are greater in impoverished groups, and worsen with duration of diabetes, presence of complications, hospitalization, surgical therapy and glycemic control requiring insulin [81,116,117].

Furthermore, LMICs contain large and growing populations of people with pre-diabetes, as well as groups of people unaware that they have an asymptomatic metabolic disorder. Pre-diabetes is independently associated with the development of complications and increased specialist consultations, adding up to at least US$443 in supplementary expenses per person in the USA [118]. For individuals with undiagnosed diabetes, proxy measures of health service utilization suggest that annual costs are approximately US$2864, and may escalate depending on the severity of complications that have developed by the time of recognition and formal diagnosis [119].

Augmented expenditures associated with complications further perpetuate destitution and socioeconomic disadvantage (i.e. opportunity costs of health care expenses are often endured by foregoing children's education). Meanwhile, hardship amplifies vulnerability to disease. The Cost of Diabetes in India (CODI) [43] and Bangalore Urban District (BUD) [120,121] diabetes studies showed a later age at diagnosis of diabetes and occurrence of disabling complications were associated with lack of awareness, and being unemployed and less educated (e.g. a 7-year difference in age of diagnosis was demonstrated between illiterate people and those with college education). Similar observations substantiate a bidirectional link between poor health and poverty (Figure 5.1).

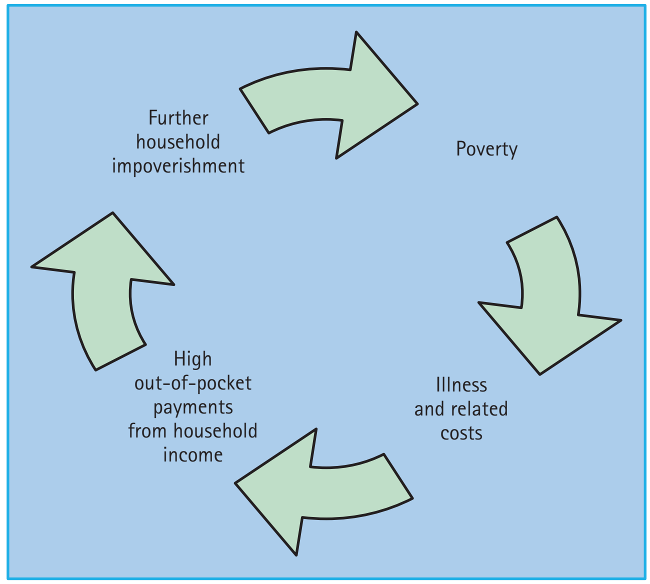

Figure 5.1 Cycle of poverty and ill health. Poverty predisposes one to illness, and costs of illness in a system of fee-for-service care have the potential to impoverish households, further perpetuating poverty.

Broadly speaking, diabetes results in roughly 1.5–5 times greater health care expenditure than the general population, depending on the context and the cost appraisal methodology employed [75,77,80,84,103,114]. In addition, it is important to note that the complex overlaps and interconnections between the underlying pathophysiology of T2DM and associated co-morbidities of the broader metabolic syndrome may alter the scope of costs. As such, depending on the viewpoint and chosen values, resource use attributable to diabetes alone may in fact underestimate the broader range of costs associated with diabetes-related illnesses as a group. Also, undiagnosed diabetes may not be described as a contributor to morbidity, mortality and resource use, suggesting that we may be underestimating the true burden of this disease. This is particularly relevant in regions of the world where there are few or no representative data regarding disease prevalence and causes of death. Finally, the value placed on the opportunity cost of diabetes-related infirmity has not been widely quantified or even qualitatively described.

Changing trends in costs

The global burdens associated with diabetes have been growing rapidly, and are projected to escalate even further in the future. The hypothesized explanations for this trend of increasing burden include, and are not limited to, the rising prevalence of diabetes and pre-diabetes worldwide; aging and longevity accompanied by costly co-morbidities; lowered diagnostic thresholds; more attentive detection of cases; availability of newer, more costly treatment methods on the basis of industry research and development; and changes in clinical management, especially growth in use of self glucose monitoring and medical devices, new therapeutic drugs and increasing demand for paramedical services. While it is evident that these latter reasons are more relevant in HICs, the continued epidemiologic transitions will no doubt affect LMICs too. It is unfortunate that scarcity of resources and inadequate access in these settings will result in greater disability and mortality, perpetuating the obstacles to socioeconomic development.

Gaps and future directions

Diabetes imposes serious health, social and economic burdens worldwide. Quantitative calculations suggest that direct and indirect costs of diabetes worldwide cumulatively total US$376 bn in 2010 [111]. Almost half of all global expenditure occurred in the USA, which is home to only 8% of those affected by diabetes worldwide. Given the disparities in burdens, access and expenditures described previously, more widespread and reliable data are a first step towards greater equity [122]. In addition, studies are needed that include both long-understood and emerging diabetes complications, such as cognitive function, in the models, to create better estimates of diabetes-attributable mortality, morbidity and cost. Assessing burdens using reliable consistent methods will aid our comprehension of the complex mix of programmed, predisposing and modifiable factors associated with diabetes, and lays a foundation for policy development and advocacy for greater global consciousness.

Despite varied estimates of expenditure, the pattern is consistent: people with diabetes experience greater symptoms, morbidity, co-morbidities and mortality than those without diabetes; they have diminished functional capacity and psychosocial illness; and incur greater costs for health care, self-care and losses in earning potential and societal role. While reductions in quality of life are less numerically evident, they are no less distressing. Needless to say, intervening before diabetes onset may hold great benefit in reducing global burdens; however, although there is evidence from large trials demonstrating that prevention can forestall conversion from pre-diabetes to diabetes, widespread translation of these findings is hampered by multiple levels of barriers (political, social, cultural, behavioral and economic factors).

In the future, preparation for the increasing diabetes burden requires progress in wider collection of reliable data (especially assuaging the scarcity from low and middle income countries regarding diabetes-related mortality, complications, disability and costs), and a greater emphasis on cost-effectiveness studies which may inform better resource allocation. On the shoulders of compelling evidence, greater investment and political will are required to overcome low accessibility and awareness, as well as to translate the evidence into practical real-life implementation of proven and effective prevention strategies [123].

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