Chapter 3
Impact of Diabetes Complications

Diabetes complications are generally divided into **acute complications**, including diabetic ketoacidosis (DKA), hyperglycaemic hyperosmolar state (HHS) and hypoglycemia; and **chronic complications**, including macrovascular and microvascular complications.

Diabetic ketoacidosis is the initial clinical manifestation in many cases of type 1 diabetes. According to the recent IDF estimates, there were 128,900 newly diagnosed cases of type 1 diabetes in 2019 globally [1]. The increase in incidence of type 1 diabetes results in higher number of cases of DKA.

Initial clinical presentation as DKA is found in 25% of cases with type 1 diabetes in developed countries, such as the UK, France, Poland, and the US [1–5]. The high incidence of this life-threatening diabetes complication urged launch of campaigns for increasing public awareness of type 1 diabetes, and earlier diagnosis among children and adolescents [1, 6].

Situation in countries with limited resources is worse as new onset type 1 diabetes is often misdiagnosed, resulting in higher incidence of DKA as initial presentation [1]. It has been reported that 75% of all endocrine pediatric emergencies in developing countries are children with type 1 diabetes and DKA [7].

Diabetic ketoacidosis is a major cause of mortality in children with type 1 diabetes in developing countries. Unfortunately, there are striking differences between developed and developing countries in terms of DKA related mortality. Rates of mortality caused by DKA in developing countries are in the range of 6–24% compared to 0.15–0.31% in developed countries (Fig. 3.1) [7–9]. It is alarming that the relative risk of DKA related mortality in developing countries is up to 40–80 times higher than in developed countries.

Hyperglycaemic hyperosmolar state (HHS) in developing countries was associated with newly diagnosed type 2 diabetes and poor glycaemic control due to non-adherence to prescribed diabetes medications [10]. There are limited data on hypoglycemia in developing countries; however, it is reported to be associated with significantly increased risk of mortality [11].
Chronic diabetes complications are generally divided into **macrovascular** and **microvascular**. Macrovascular complications include coronary artery disease, congestive heart failure, cerebrovascular disease and peripheral vascular disease. Many people with diabetes suffer from silent myocardial ischemia and sudden cardiac death [12]. Microvascular complications include retinopathy, nephropathy and neuropathy.

Additionally, diabetes has been reported as a major risk factor for increased morbidity and mortality in those infected in the recent pandemic of COVID-19. The increased morbidity and mortality have been particularly relevant for the people with diabetes complications. One of the possible explanations for the worse outcomes of COVID-19 in people with diabetes could be the effects of hyperglycemia on the suppression of the immune system, as those with inadequate glycaemic control have increased risk for any infection. It is due to the hyperglycemia and diabetes complications that people with diabetes have been categorized as very high risk for the COVID-19 related morbidity and mortality. On the other hand, contracting COVID-19 by people with diabetes increases their risk of developing acute diabetes complications.

It has recently been reported that people with diabetes and COVID-19 were more likely to suffer from severe pneumonia, excessive inflammation responses and hypercoagulable state, compared with those who had COVID-19 but not diabetes [13]. Another recent study found that while diabetes does not increase the likelihood of being infected with COVID-19, those with diabetes may experience worse outcomes from the disease, including death [14]. Based on the data from 12 studies about the prevalence of diabetes among adults with COVID-19, findings were in
line with the association between diabetes and excess mortality from any acute and chronic condition, including infections [14].

**Cardiovascular diseases** are the main cause of mortality worldwide, exceeding all the other causes. It is estimated that approximately 18 million people have died from CVDs in 2016, representing one third of the total mortality worldwide. The largest share of cardiovascular deaths (85%) is due to coronary artery and cerebrovascular disease [15].

It was mentioned that approximately 4.2 million adults aged 20–79 years have died due to diabetes and its complications in 2019, representing 11.3% of the global mortality from all causes in this age group [1]. Sadly, almost half of the diabetes related mortality was in people under the age of 60 years [1].

Cardiovascular diseases are the leading cause of morbidity and mortality in people with diabetes. Development of CVDs in people with insulin resistance, the main underlying disorder in type 2 diabetes, is a progressive and long-term process, characterized by endothelial dysfunction and vascular inflammation leading to formation of atherosclerotic plaques. It is estimated that 80% of people with type 2 diabetes would die from cardiovascular events [1, 16, 17].

People with diabetes have two to four times higher risk of developing CVD compared to non-diabetes population. The relative risk is higher in people with diabetes of younger age and in women [1, 17, 18]. Diabetes related mortality is higher in women than in men (2.3 million vs 1.9 million, respectively), and this excess risk can be mainly attributed to the higher risk of cardiovascular mortality in women with diabetes [1, 19]. Increased risk for CVD begins in the pre-diabetic range as the current cut-off values for diagnosis of diabetes are defined according to the increased risk for microvascular complications, such as retinopathy.

Most common form of CVD in people with diabetes, as in the general population, is coronary artery disease [20]. Recent study estimated the prevalence of CVD in people with type 2 diabetes at 32.2%, and majority of those were diagnosed with coronary artery disease (21.2%) (Fig. 3.2) [20].

**Fig. 3.2** Prevalence of CVD and coronary artery disease in people with type 2 diabetes, data adapted from [20]
The incidence of CVD and the associated mortality has declined in developed countries in the recent decades. The efforts of many developed countries to reduce the major cardiovascular risk factors, such as dyslipidemia, hypertension and smoking, resulted in a progressive reduction of cardiovascular morbidity and mortality in these countries [1, 15]. It is only obesity and the associated diabetes that manifest a trend of continued growth, and if such trends are not reversed, they have the potential to overcome the positive effects of the reduction of other major cardiovascular risk factors [1, 15].

However, those trends of reduced CVD morbidity and mortality have not been replicated in developing countries [1, 15]. The burden of CVDs is enormous in developing countries as 75% of all cardiovascular deaths occur in those countries [15]. People with diabetes in developing countries have a higher prevalence of CVD compared to developed countries [1, 20]. Possible explanations could be the higher prevalence of the major risk factors, such as smoking, uncontrolled hypertension and uncontrolled dyslipidemia. Psychosocial stress and lower levels of physical activity also play a role in the development of CVD.

The management of CVDs in developing countries is complex since they often lack fully functioning healthcare systems able to timely diagnose and treat those affected at an early stage. Furthermore, people from developing countries are lacking modern treatment options, including medications and technology, which is the reason the cardiovascular mortality rates are higher in middle- and low-income countries [20, 21]. Epidemiological studies including people of South Asian origin have shown a 2–3 times higher risk of developing CVD compared to Caucasians [20, 21].

Taking into consideration the magnitude of the problem, CVDs exert a huge burden not only on the healthcare systems, but on the whole societies and economies, especially of developing countries. People with diabetes related CVD in developing countries are covering many of the healthcare expenditures ‘out of pocket’, which might be a challenge for the timely and adequate management. Latest diabetes treatments for reduction of cardiovascular outcomes in people with diabetes and established CVD, such as GLP-1RA and SGLT2i, remain available only for a minor part of diabetes population in developing countries, or are not available at all due to their cost.

Cardiovascular diseases are the most prevalent cause of morbidity and mortality in the Republic of North Macedonia [22]. It is estimated that almost two thirds of all cases of morbidity in the country are due to CVD [22]. The country has recently been categorized as a very high risk European country for cardiovascular mortality [22, 23]. High diabetes prevalence and strong association between diabetes and CVD, further contribute to the complexity of diabetes burden on the socioeconomic prospects of the country.

Dedicated National Program on CVDs has been introduced in the country strengthening the public healthcare resources, such as opening of novel centers for interventional cardiology aiming to have one center per 200,000 inhabitants, introduction of neonatal cardiac surgery, opening of adult University Clinic of Cardiac Surgery, as previously all cardiac surgery interventions were performed in the
private clinics. In addition, a lot has been invested in the education of physicians and nurses in the areas of cardiology and cardiac surgery, and the introduction of novel methods was strongly encouraged.

Since most of the cardiovascular risk factors are modifiable, and CVDs are the major cause of morbidity and mortality in developing countries, there is a huge opportunity to curb the increasing trends of CVD prevalence in a setting with limited resources. Preventive activities should include control of hypertension, dyslipidemia and hyperglycemia, increasing physical activity, reduction of obesity, termination of smoking, and management of psychosocial stress.

Diabetic retinopathy is a microvascular complication considered to be the leading cause of blindness in the population of working age globally [1]. Blindness caused by diabetic retinopathy has devastating consequences, not only for the person with diabetes, but for the whole society. If diagnosed early, diabetic retinopathy in many cases could be treated to prevent further worsening and development of blindness. In addition to diabetic retinopathy, macular edema, cataracts and glaucoma are also more prevalent in people with diabetes [1].

It is reported that almost one third of all people with diabetes have some form of diabetic retinopathy, and one third of them have the most severe, vision threatening form of diabetic retinopathy [1]. Diabetic retinopathy has been associated with inadequate glycaemic control, duration of diabetes, and with some major cardiovascular factors, such as hypertension and smoking [1].

Healthcare systems in developing countries that do not include routine screening for diabetic retinopathy have to face the burden of people with diabetes developing proliferative retinopathy or diabetic maculopathy, and ultimately blindness, taking a huge toll on the limited resources. The burden of diabetic retinopathy in developing countries is highest, and the readiness of healthcare systems to manage it is lowest.

Diabetic retinopathy has been strongly associated with type 1 diabetes [1]. In people with type 2 diabetes, the prevalence of diabetic retinopathy is higher in developing countries [1]. It is reported that the annual incidence of diabetic retinopathy ranges from 2.2% to 12.7%, and annual progression to sight threatening diabetic retinopathy ranges from 3.4% to 12.3% [24].

Evidence from the developed healthcare systems confirm that systematic screening for diabetic retinopathy results in reduction of incidence of visual impairment and blindness [25, 26]. Innovative approaches are required for the management of diabetes retinopathy in healthcare systems with limited resources and minimal infrastructure. Lack of qualified and competent resources in developing countries could often be substituted by the use of modern technology, especially with the recent introduction of diabetic retinopathy cameras with integrated artificial intelligence [27]. Those technologies could facilitate detection of cases where early treatment is needed to prevent further deterioration. They could also enable remote analysis of captured images by qualified and competent healthcare providers [27].

According to the WHO World Report on Vision, 146 million people had diabetic retinopathy, and 45 million had vision threatening diabetic retinopathy in 2019 [28].
By 2040, it is anticipated that 70 million people will have vision threatening diabetic retinopathy (Fig. 3.3) [28].

The WHO recognizes diabetic retinopathy as one of the five most common causes of moderate and severe visual impairment and blindness that is preventable and treatable. Although the target set by WHO was to reduce prevalence of avoidable visual impairment by 25% by 2019, this target has not been achieved in the developing countries [28].

**Diabetic nephropathy**, a form of Chronic Kidney Disease (CKD), is a microvascular diabetes complication and a leading cause for end stage renal disease. It is estimated that 38% of people with type 2 diabetes will develop CKD, and half of them will develop moderate to severe CKD (Fig. 3.4) [29, 30].

**Fig. 3.3** Number of people with vision threatening diabetic retinopathy, data adapted from [28]

**Fig. 3.4** Prevalence of CKD in people with type 2 diabetes, data adapted from [29, 30]
Globally, 80% of all cases of end stage renal disease requiring dialysis are caused by diabetes, hypertension or combination of both [1]. The prevalence of end stage renal disease in diabetes population is ten times higher compared to non-diabetes population [1]. There has been a continuous rise in CKD, mainly associated with the rising prevalence of type 2 diabetes. End stage renal disease and dialysis is another huge challenge for the healthcare systems, especially in developing countries [1].

In order to reduce the burden of diabetic nephropathy, early diagnosis and treatment of CKD is mandatory. Routine screening for albuminuria, Urinary Albumin Creatinine Ratio (UACR), and calculation of estimated Glomerular Filtration Rate (eGFR) is a simple and cost-effective strategy to identify those at risk, and initiate a timely treatment, even in a setting with limited resources [31]. There is a strong association between CKD and other macrovascular and microvascular complications. Major cardiovascular risk factors play significant role in the development and progression of CKD.

Financial burden of diabetic nephropathy is enormous, even in the healthcare systems of developed countries. In the US, it is estimated that mean annual healthcare costs were almost 50% higher among people with diabetic nephropathy compared to people with diabetes without nephropathy [1, 32]. People with diabetes undergoing dialysis have 300% higher annual healthcare costs compared to people with type 2 diabetes without complications, and those with end stage renal disease and kidney transplantation have 500% higher costs [1, 32].

People with diabetes and peripheral vascular disease (PVD) have an increased risk of diabetic foot amputation, coronary artery disease, cerebrovascular disease, and increased risk of mortality [1, 33, 34]. Routine screening of PVD is mandatory as approximately half of the people with diabetes and PVD are asymptomatic, and one third have atypical symptoms [1, 35–37].

Diabetic neuropathy is very prevalent in people with diabetes; it is estimated that up to 87% experience some form of diabetic neuropathy, and one quarter of them suffer from painful diabetic neuropathy [38]. It is strongly associated with diabetic foot complications and PVD.

A systematic review has reported an increase of 23.5% in the decade between 2000 and 2010 in the number of people living with PVD, and it is the most common initial manifestation of CVD in people with type 2 diabetes [39, 40].

The outcome of individuals with PVD depends on the comorbidities, advanced age, smoking and glycaemic control [41]. Inadequate control of metabolic parameters was associated with a greater need for lower extremity bypass surgery and amputation, and worse outcomes following vascular surgery [42].

People with diabetes have 10 to 20 times higher risk for lower limb amputation compared to people without diabetes [43]. It has been estimated that one amputation of the lower limb as a complication of diabetes occurs every 30 s globally [44].

Diabetic foot ulcers and amputations are more common in low- and middle-income countries than in high-income countries [45]. The prevalence of diabetic foot ulcers is higher among people with type 2 diabetes compared with those with type 1 diabetes [46]. People with diabetes who have foot ulcers have health expenditures five times higher than those without foot ulcers [1, 47].
Examination of the feet of people with diabetes and evaluation of circulation in lower extremities, in addition to education on self-inspection of feet, provides a cost-effective strategy for early diagnosis and treatment of PVD in a setting with limited resources.

Diabetes and related complications are exerting a huge economic impact on the healthcare systems and national economies. Total diabetes costs are composed of direct and indirect costs. Direct costs of diabetes include all diabetes related healthcare expenditures from both public and private sources [1, 48]. The indirect costs of diabetes include loss of production resulting from disability, mortality, absenteeism (absence from work), and presenteeism (reduced productivity when at work) [1, 49].

Historically, direct diabetes costs have been continuously rising, from USD 232 billion worldwide in 2007, to USD 727 billion in 2017, and USD 760 billion in 2019, for the age group 20–79 years. The trend of rising costs is expected to continue to reach USD 825 billion by 2030, and USD 845 billion by 2045 [1].

Diabetes treatment is a small portion of the healthcare budget allocated for diabetes in developed countries, at a level of approximately 10%. Majority of the diabetes related direct costs in developed countries are due to diabetes complications and resulting hospitalizations [1, 50].

Situation is different in the developing countries where diabetes treatment takes a higher portion of the healthcare budget. The example of the Republic of North Macedonia was already mentioned with the tremendous cost of insulin and related supplies at the level of 40% of the budget allocated for all reimbursed, non-hospital medications (Fig. 1.4) [22, 51].

Furthermore, approximately 20% of the total healthcare budgets in South and Central American countries and 15% in Middle East and North African countries are allocated for diabetes, compared to 8.3% in Europe [1].

Although screening of early diagnosis of diabetes complications is associated with certain healthcare costs, their late diagnosis and treatment results in even higher costs, largely contributing to the overall economic impact.

These significant economic effects of diabetes complications on direct costs have been reported from the developed countries, such as Germany, the UK, the US and Italy [1, 52–59]. Studies of the economic impact of diabetes in developing countries also indicate a large economic burden [60]. Healthcare expenditures for diabetes and its adverse effects on the labor market are expected to increase over time and with disease severity, indicating that early investments into prevention and disease management may be particularly cost-effective in countries with limited resources [60].

Treatment of diabetes complications is a major driver of direct costs, and the main complications identified include: CVDs, diabetes foot complications, including amputations, diabetic retinopathy, and diabetic nephropathy. Direct costs are clearly related to the number of complications present, with mean annual healthcare expenditures for people with four or more complications being 20 times higher than in people with diabetes without complications [1, 52–59].

Control of major risk factors in people with type 2 diabetes can be cost-effective strategy in reducing CVDs. Screening for diabetic retinopathy is very cost-effective
compared with no screening; and comprehensive foot care reduces costs by prevent-
ing ulcers and amputations in high-risk people with diabetes [61]. Improved care
and subsequent prevention of complications results not only in better healthcare
outcomes, but is also highly cost-effective [61].

The highest overall diabetes-related costs on a country level were estimated for
the US with USD 294.6 billion, followed by China and Brazil, with USD 109.0 bil-
lion and USD 52.3 billion, respectively [1]. The countries with the lowest diabetes-
related costs are lower resource countries, such as Sao Tome and Principe, and
Tuvalu, with estimates of USD 1.1 million and USD 1.8 million [1].

There is a huge difference if we compare the countries according to the diabetes
related expenditures per person in 2019. Countries with the highest annual expendi-
ture per person are Switzerland with USD 11,916, followed by the US and Norway
with USD 9,506 and USD 9,061; respectively [1]. Countries with the lowest annual
expenditure per person are Bangladesh (USD 64), Central African Republic (USD
72) and Nepal (USD 80) [1]. Understandably, lower resource countries are spending
less for diabetes per person, which affects the quality of care and increases the risk
for even more costly diabetes complications.

It is worth mentioning that indirect costs add up to the overall diabetes burden,
and need to be taken into consideration when evaluating the cost-effectiveness of
diabetes care. Latest estimates suggest that indirect costs contribute with close to
35% of total diabetes costs, calculated at USD 1.31 trillion in 2015 [1, 62].

In high-income countries indirect costs were estimated at a level of 36.5%, com-
pared to 31.7% in middle-income and 37.8% in low-income countries. Although
there is a small difference between these groupings in terms of the share of the
indirect costs, there is a considerable variation in the structure of the indirect costs
[1, 62].

Disability and mortality are dominant in the global figures for indirect costs with
48.5% and 45.5%, respectively. Situation with structure of indirect costs is similar
in high-income countries (59.2% and 35.5%). However, mortality contributes with
63.6% of indirect costs in middle-income countries, and 90.6% in low-income
countries. Absenteeism and presenteeism together contribute 6% globally and less
than 3% in low-income countries [1, 62].

It is important to estimate the economic impact of undiagnosed diabetes on the
healthcare costs, since it could result in diagnosing diabetes complications at an
advanced stage which is associated with higher costs.

Diabetes complications, due to their enormous impact on both direct and indirect
costs, have to be included in the National Diabetes Plan. Efforts should be made by
each developing country to estimate the prevalence of diabetes complications.
Procedures for screening diabetes complications have to be included in the National
Diabetes Care guidelines.

Frequent screening for diabetes complications results in early diagnosis and
treatment that is a cost-effective compared to their treatment at a more advanced
stage. Meticulous screening is particularly valuable under the conditions with lim-
ited resources.
What should be done to manage the impact of diabetes complications?
Each developing country should …

- … evaluate the prevalence of diabetes complications;
- … implement mandatory screening for CVD, retinopathy, nephropathy, PVD, as stipulated in the National Diabetes Care guidelines;
- … define screening frequency for diabetes complications;
- … determine the total cost, including direct and indirect costs;
- … empower National Diabetes Committee to monitor adherence to National Diabetes Care guidelines related to the screening of diabetes complications.

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