Dermatology and Diabetes

Emilia Noemí Cohen Sabban
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Preface

When we thought about this book on diabetes, our desire was to achieve something that would help the reader understand the disease from a wider point of view. Hence, this work, contributed by dermatologists and specialists in diabetes, not only reviews the dermatological manifestations of diabetes mellitus but also includes contributions from diabetologists, since we consider the disease in all its aspects in patients with diabetes. Thus, we approach the same issues from the perspective of both specialties, in the same way we face the daily task of taking care of our patients in a multidisciplinary team.

The book comprises a broad spectrum of skin conditions related to diabetes, its comorbidities, its most common complications—vasculopathy and neuropathy—as well as basic and necessary concepts regarding the epidemiology, classification, diagnosis, and treatment of the disease.

We hope that the effort invested in this work will be of great help to all those who, in one way or another, feel responsible for improving the quality of life of these patients.

Buenos Aires, Argentina — Emilia Noemí Cohen Sabban
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Epidemiology of Diabetes

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Mariano Javier Taverna

Introduction

Diabetes mellitus is a chronic, metabolic disease defined by increased concentrations of blood glucose which leads, over time, to progressive damage in most tissues and organs including heart, blood vessels, eyes, kidneys, skin, and nerves. The most common is type 2 diabetes, commonly in adults, which occurs as result of the combination of insulin resistance with pancreatic beta cell insufficiency, with 50% of patients requiring insulin treatment within 10 years [1]. Type 1 diabetes, more frequent in children and adolescents, is a chronic autoimmune disease in which autoreactive T lymphocytes and inflammation cause severe loss of beta cells [2]. The incidence of diabetes exhibits an alarming pandemic scenario, in large part due to the global obesity epidemic [3]. Diabetes causes premature death, severe disability and great economic burden. Therefore, there is a globally agreed target to stop the growing incidence of diabetes and obesity by 2025 [4].

Global Burden

The number of adults living with diabetes has approximately quadrupled since 1980 (108 millions) to 2014 (422 millions). The age-standardized prevalence of diabetes has nearly doubled since 1980, increasing from 4.7 to 8.5% in the adult population (Table 1.1) [3]. This is consequent to a rise in associated risk factors such as

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Table 1.1 Global estimates of people with diabetes (adults 18+ years) in 1980 and 2014

	Prevalence (%)	Number (millions)		
World Health Organization region	1980	2014	1980	2014
African region	3.1	7.1	4	25
Region of the Americas	5	8.3	18	62
Eastern Mediterranean region	5.9	13.7	6	43
European region	5.3	7.3	33	64
Western Pacific region	4.4	8.4	29	131
South-East Asia region	4.1	8.6	17	96
Total	4.7	8.5	108	422

sedentary lifestyle, greater longevity, poor eating habits (high in salt, low in fiber, and rich in saturated fats and sugar) and, especially, overweight/obesity. Indeed, the obesity pandemic explains a large part of the global epidemic of diabetes (especially type 2 diabetes) [1, 3]. In 2014, global estimates showed that more than one in three adults aged over 18 years were overweight (body mass index, BMI 25–29.9 kg/m^2), and 10% were obese (BMI ≥30.0 kg/m^2). Both overweight and obesity were higher in women than men, lowest in the WHO South-East Asian region, and highest in the WHO region of the Americas. Moreover, the prevalence of overweight/obesity rises with country income level [3]. Physical inactivity is more common in women (27%) than men (20%) across all country income groups from all WHO regions, and is more common among adolescents (78% of boys, and 84% of girls), especially from high-income countries [5].

In the last decade, diabetes prevalence, in a pandemic scenario, has increased less faster in high-income nations than in low- and middle-income countries, including Africa and Asia, where most diabetic patients will probably be found by 2030. This rising incidence of diabetes in developing countries accompanies the trend of unhealthy lifestyle changes (low physical activity and Western pattern eating habits) and urbanization [3, 6]. The WHO Eastern Mediterranean region has showed the highest increases in diabetes prevalence, and nowadays exhibits the highest prevalence (13.7%) [3]. Of note, the risk of type 2 diabetes is strongly associated with lower socio-economic status [7].

Diabetes generated approximately 1.5 million deaths in 2012. In addition, suboptimal high blood glucose caused 2.2 million deaths, by increasing the risks of heart disease and other associated conditions such as kidney failure, stroke and tuberculosis. Forty-three percent of these 3.7 million deaths arise before the age of 70 years. The percentage of deaths secondary to hyperglycemia or diabetes that appear prior to age 70 is greater in low- and middle-income countries than in high-income countries. In 2012, diabetes was the eighth leading cause of death among both sexes and the fifth leading cause of death in women in 2012 [8].

Importantly, separate global estimates of diabetes prevalence for type 1 and type 2 do not exist. Approximately, 85% of people with diabetes, mostly adults and elderly people, are affected by type 2 diabetes. Unfortunately, in last decade, there is also a rising incidence of type 2 in children [9], especially in children of ethnic minority and from lower income families. Type 2 diabetes is frequently undiagnosed; therefore

there are almost no data about its true incidence. Recently, it was reported that between 24 and 62% of diabetic patients from seven countries were undiagnosed and untreated [10]. A high proportion of undiagnosed diabetes can be found even among individuals from high-income countries [11]. Even though the prevalence of type 2 is frequently highest in wealthy subjects, this trend is changing in some middle-income countries. In addition, in high-income populations, type 2 diabetes is highest among individuals who are poor [12].

Type 1 diabetes occurs especially in children and adolescents [2, 3]. Most evidence about the incidence of type 1 diabetes has been obtained from population-based registries of new cases worldwide, such as the WHO DIAMOND project [13]. These registries reported large differences in the incidence of type 1 diabetes, ranging from under 0.5 to over 60 cases annually per 100,000 children (under 15 years). According to the WHO DIAMOND project, Scandinavia, Sardinia and Kuwait exhibit the highest incidence for type 1 diabetes, while is much less common in Asia and Latin American [13]. The worldwide epidemiology of type 1 diabetes shows a pandemic scenario with an annual increase of ~3%, especially in children from high income countries [14, 15].

Diabetic Complications

Chronic hyperglycemia, if not well controlled, may cause kidney failure, nerve damage, blindness, lower limb amputation, heart disease, stroke and several other long-term consequences that seriously affect the quality of life and induce premature death. There are no global estimates of diabetic complications. Where data are available—mostly from high-income countries—incidence and prevalence of chronic complications vary largely between countries [16–18].

End-Stage Renal Disease

Epidemiological data from 54 countries show that approximately 80% of cases of end-stage renal disease (ESRD) are secondary to diabetes and/or high blood pressure [7]. The percentage of ESRD due to diabetes alone ranges from 12 to 55%, and is ≤10 times higher in diabetic patients than non-diabetic individuals, especially in type 1 diabetes, elderly people, longer duration of diabetes, high blood pressure, obesity and low-income populations [19].

Loss of Vision

According to the WHO, prevalence of any retinopathy in persons with diabetes is 35% while vision-threatening retinopathy (proliferative retinopathy) is 7% [20, 21]. The proportion of diabetic retinopathy is higher among individuals with type 1 diabetes, longer duration of diabetes, high blood pressure, Caucasian populations, and among low-income populations [20, 21].

Lower Extremity Amputations

Diabetes strongly increases the risk of lower extremity non-traumatic amputation because of severe infected foot ulcers [18]. Amputation in diabetic patients is 10–20 times higher than in non-diabetic individuals. Its incidence ranges from 1.5 to 3.5 amputations per 1000 diabetic patients [18]. Amputation is higher in peripheral arterial occlusive disease, sensorimotor diabetic polyneuropathy, previous ulceration, elderly people, late complications of type 2 diabetes, male gender, long diabetes duration, and low-income populations [22].

Cardiovascular Events

Cardiovascular disease (CVD) is the leading cause of death in diabetes. Adults with diabetes (especially type 2 diabetes) have approximately three times higher incidence of cardiovascular events (myocardial infarction, stroke or CVD mortality) than non-diabetic adults [23]. The risk of cardiovascular disease rises continuously with increasing fasting plasma glucose concentrations [24, 25]. Two-thirds of deaths in diabetic patients are due to cardiovascular disease: 40% are from coronary artery disease, 15% from other types of heart disease, especially congestive heart failure, and ~10% from stroke [26]. Of note, a better management of diabetes and associated CVD risk factors has lead to a large reduction in thee incidence of cardiovascular events over the past 20 years, in particular in Scandinavia, United Kingdom and USA, in both type 1 and type 2 diabetes, albeit less reduction in non-diabetic people [27].

Economic Impact

Diabetes causes a great economic burden on the health care system that can be measured through direct medical costs, indirect costs associated with productivity loss, early mortality and the negative effect of diabetes on country's gross domestic product (GDP).

Direct medical costs secondary to diabetes include expenditures for preventing and especially treating diabetes and its complications, in particular outpatient and emergency care, inpatient hospital care, medications and medical supplies (self-monitoring consumables, injection devices etc.). Recently, it has been reported that the direct annual cost of diabetes to the world is more than US$ 827 billion [28, 29]. Moreover, total global health-care spending on diabetes more than tripled over the period 2003–2013 because of pandemic diabetes, according to the International Diabetes Federation [30].

It was reported that losses in GDP worldwide from 2011 to 2030, including both the indirect and direct costs of diabetes, will total US$ 1.7 trillion, including US$ 800 billion for low- and middle-income countries and US$ 900 billion for high-income populations [31].

Conclusions

Diabetes is a prominent cause of early death and disability. Chronic complications secondary to diabetes and associated CVD risk factors include, among others, heart disease, stroke, kidney failure, blindness, lower limb amputation, and nerve damage. In 2012, diabetes and associated conditions caused 3.7 million deaths. In 2014, 422 million people had diabetes (~85% type 2 diabetes), with a global prevalence of 8.5%. The global obesity epidemic explains, in large part, the current pandemic scenario of diabetes (especially type 2 diabetes). The growing epidemic of diabetes is higher in low- and middle-income countries than in developed populations.

Finally, diabetes is one of four priority noncommunicable diseases (NCDs) proposed by world leaders according to the 2011 Political Declaration on the Prevention and Control of NCDs. This declaration highlights that diabetes and its complications can be reduced and/or prevented with an appropriate strategy that include evidence-based, cost-effective, and population-level interventions [4].

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Definition, Diagnosis and Classification of Diabetes Mellitus

2

Félix Miguel Puchulu

Introduction

Diabetes Mellitus (DM) is a syndrome characterized by hyperglycemia and impaired metabolism of carbohydrates, proteins and fats, due to an absolute or relative deficiency of the secretion and/or insulin action.

Its prevalence is 7–10% approximately, of which 90% corresponds to type 2 diabetes and the rest is distributed among the different types of diabetes.

Diagnosis of DM

DM is defined by blood glucose levels. Patients with fasting plasma glucose (FPG) values ≥126 mg/dL (7.0 mmol/L) twice or 2 h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT) or glucose values ≥200 mg/dL (11.1 mmol/L) at any time of the day, will be considered diabetic.

Normal values are below 100 mg/dL fasting or under 140 mg/dL 2 h of testing glucose tolerance.

There are some people with glucose levels between 100 and 126 mg/dL on the fasting state, or ≥140 mg/dL but <200 mg/dL after 75 g of glucose (OGTT), they are considered non-diabetic but with alterations in carbohydrate metabolism. Both disorders are called prediabetes.

The first alteration is impaired fasting glucose (IFG), in which insulin resistance plays the most important role; the second disturbance is called impaired glucose

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Table 2.1 Oral Glucose Tolerance Test for the diagnostic of alterations on carbohydrate metabolism

Glycemia (min)	Normal (mg/dL)	IFG (mg/dL)	IGT (mg/dL)	Diabetes (mg/dL)
0	≤99	100–125	≤99	≥126
120	≤139	≤139	140–199	≥200
		Pre-diabetes		

OGTT oral glucose tolerance test, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance

tolerance (IGT), in which a disturbance in the normal secretion of insulin to the stimulus with glucose has the prevalence.

Both alterations can also be present in the same individual. The presence of IFG and IGT indicate a higher probability of evolving to T2DM. In the case of presenting one of the alterations, it has been seen that the IGT has a higher incidence of T2DM that the IFG (Table 2.1)

Current diagnostic criteria of the American Diabetes Association propose adding glycosylated hemoglobin A1c (HbA1c) within them. Values above 6.5% would define the presence of disease. In Argentina, due to the lack of standardization of the method for the determination of HbA1c, Argentine Diabetes Society (SAD) decided to exclude this criterion.

DM diagnostic criteria of the American Diabetes Association (ADA)

- FPG ≥ 126 mg/dL (7.0 mmol/L) Fasting is no caloric intake for at least 8 h*
- 2 h PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT (according to the technique described by WHO, using a glucose load of 75 g anhydrous dissolved in water)*
- A1c ≥ 6.5% (48 mmol/L) in laboratories with standardized methods*
- Classic symptoms of hyperglycemia or hyperglycemic crisis glucose and a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia results should be confirmed by repeat testing.

Classification

The former classification of DM based on dependency insulin was modified with the intention of eliminating denominations as insulin dependent diabetes mellitus and non-insulin dependent diabetes mellitus (IDDM and NIDDM), taking into account the diversity of response to therapeutic. The current classification of DM is based on the etiology of the disease, considering than type 1 diabetes is the result of the destruction of pancreatic beta cells (autoimmune or unknown cause, etc.) and type 2 diabetes is related to the association of insulin resistance and insulin deficiency.