Dermatology and Diabetes

Emilia Noemí Cohen Sabban
Félix Miguel Puchulu
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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.

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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.

Etiologic Classification

1. Type 1 diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation)

Type 1 Diabetes (T1DM)

T1DM is characterized by the sudden onset of severe symptoms associated with the absolute deficiency of insulin secretion, tendency to ketosis and dependence on exogenous insulin to sustain life. Represents around 10% of all cases of diabetes and is one of the most common chronic childhood conditions. T1DM is an auto-immune condition in which the immune system is activated to destroy the pancreatic cells which produce insulin. The cause of this auto-immune reaction is unknown. T1DM is not linked to modifiable lifestyle factors. There is no cure and it cannot be prevented yet.

The histopathology of T1DM is defined by a decreased β-cell mass in association with insulitis, a characteristic lymphocytic infiltrate limited to Langerhans islets and prominent in early stage of the disease in children.

It has similar characteristics with autoimmune inflammatory processes found in certain thyroid diseases (thyroiditis) and adrenal (adrenalitis). Insulitis is characterized by infiltration and resulting disruption of islets with destruction of beta cells by T lymphocytes of various types.

Pancreatic deficiency of insulin secretion is the main cause in this type of diabetes, is due to the specific loss of beta cells, with conservation within almost normal mass of alpha cells (glucagon), delta (somatostatin) and PP (pancreatic polypeptide). This can be demonstrated by measuring blood insulin (in patients who have not received the hormone exogenously, either fasting or basal, as to different stimuli for release (e.g., administration of glucose or glucagon). Also can measured values of C peptide, the residual product in the conversion of proinsulin to insulin, since they are not altered or masked by receiving replacement therapy.

T1DM usually occurs abruptly, with overt signs of hyperglycemia, and sometimes with significant deterioration of clinical status.

Hyperglycemia is the result of the destruction of 80–90% of the functioning beta cells mass.

Only the clinical manifestation is acute, there is a silent preclinical period and can be recognized by different immunological markers that reveal the underlying autoimmune process.

Most cases of T1DM are due to the autoimmune process and the destruction of beta islet cells in genetically susceptible individuals, autoimmune pathogenic process is called "type 1a" in the classification. It should be noted that not all T1DM 1 diabetes have the same clinical evolution.

Not all individuals with pathogenic autoimmune process of T1DM progress to clinical DM1 or they do it slowly, with a prior relatively long period without insulin dependence.

Antibodies have been detected years before the onset of hyperglycemia. Functional studies, such as intravenous glucose tolerance test, reveal a decrease in the first phase of insulin secretion months or weeks before the clinical onset of the disease or the presence of fasting hyperglycemia, according to the magnitude and extent of damage caused in the beta cells.

It must be considered a preclinical period in the natural history of the disease, which can be identified through different immunological and genetic markers.

Genetic Determinism

Autoimmune diabetes is a T-dependent specific organ disease, polygenic, mainly restricted by the human leukocyte antigen (HLA). **HLA-DR** is an MHC (mayor histocompatibility complex) class II cell surface receptor encoded by the HLA on chromosome 6 region 6p21.31. The complex of HLA-DR (**H**uman **L**eukocyte **A**ntigen—antigen **D R**elated) and its ligand, a peptide of nine amino acids in length or longer, constitutes a ligand for the T-cell receptor (TCR). HLA-DR molecules are upregulated in response to signaling.

While HLA genes are the most important genetic factors that determine predisposition or protection to T1DM, it is clear that predisposition is necessary, but is not enough.

It has been found other important genes that also confer susceptibility to T1DM: CCR5 (C-C motif chemokine receptor 5), CTLA4 (Cytotoxic T Lymphocyte Antigen 4), FOXP3 (forkhead box P3), HNF1A (HNF1 homeboxA), IL2RA (interleukin 2 receptor subunit alpha), IL6 (interleukin 6), INS (insulin gene), ITPR3 (inositol 1,4,5-trisphosphate receptor type 3), OAS1 (2′-5′-oligoadenylate synthetase 1), PTPN22 (protein tyrosine phosphatase, non-receptor type 22), SUMO4 (small ubiquitin-like modifier 4).

The VNTR region (variable number tandem repeat) which is adjacent to the 5′ end of the insulin gene is also related to T1DM predisposition.

It has also been found influence of the gene encoding the protein CTLA-4.

The HLA region is located in the short arm of chromosome 6. The association between HLA and T1DM was initially demonstrated by Nerup. Patients with T1DM have DR3 and/or DR4 by 94% compared with 60% in the healthy population.

People with positive HLA DR3 have a relative risk (RR) of 6.4 and diabetes carriers HLA DR4 3.7.

The presence of both markers increases the susceptibility to develop the disease, more than the sum of the relative risks (RR) of DR3 and DR4.

There are also markers that express a lower chance of developing diabetes. It has been found less frequently HLA DR2 in patients with T1DM, determining a RR for the disease of 0.26, so is considered as a protection factor.

HLA-DQB1 belongs to the HLA class II beta chain paralogs. This class II molecule is a heterodimer consisting of an alpha (DQA) and a beta chain (DQB), both anchored in the membrane. It plays a central role in the immune system by presenting peptides derived from extracellular proteins. Class II molecules are expressed in antigen-presenting cells (APC: B lymphocytes, dendritic cells, macrophages).

Different allelic variants of polymorphic gene DQB are circumscribed to the second exon of the gene and are encoding the amino terminal region of the antigen-presenting molecule.

Several alleles of HLA-DQB1 are associated with an increased risk of developing T1DM. The locus is the highest genetic risk for type 1 diabetes. Again, the DQB1*0201 and DQB1*0302 alleles, particularly the phenotype DQB1*0201/*0302 has a high risk of late onset type 1 diabetes. The risk is partially shared with the HLA-DR locus (DR3 and DR4 serotypes).

HLA
Predisposition: HLA DR3 (DQB1 0201) /DR4 (DQB1 0301).
Protection: DR2 (DQB1 0602).

Autoimmunity

T1DM can be induced by a process of autoimmunity directed against the insulin-producing beta cells. This mechanism could be triggered by certain environmental factors in genetically determined individuals. The classic biomarkers that "predict" type 1 diabetes are serum autoantibodies against β-cell antigens, including insulin, GAD, IA-2, and zinc transporter 8. Autoantibodies to other antigens have been reported, but either occur infrequently or have been inadequately validated and are not used for prediction. The suspicion of an autoimmune process came from the striking association between T1DM and other endocrine autoimmune diseases, such as those affecting thyroid and adrenal, as the high percentage of specific antibodies present in the patient's serum. This event marks a discrete start of the disease process and is associated with a marked increase in the risk of the development of diabetes. The presence of two or more of the four autoantibodies can be considered asymptomatic disease, and usually progresses to hyperglycemia.

The first description of autoimmunity in diabetes was made in 1974 with the ICA (Islet Cell Antibodies). ICA are present in a 0.5–1.7% of the general population and 15–30% in T1DM, but at the time of onset of the disease, in patients less than 30 years, this percentage rises to 60–85%, descending to lower values after 2–3 years.

They are IgG class non-specific beta-cell autoantibodies, produced by activated T lymphocytes. They are determined by indirect immunofluorescence (IFI) and measured in JDFunits, values under 10 UJDF are considered negative. Currently this determination has been replaced by other antibodies described below.

The GADA (Glutamic Acid Decarboxylase Antibodies) of which there are two isoforms described, 65 kD (specific for diabetes) and 67 kD, are the most useful because of the ease of its determination. They can be measured by radiobinding assay (RBA).

GAD antigen is not beta cell specific, and participates in the formation of Gamma-Aminobutyric acid (GABA).

Islet antigen-2 (IA-2), previously known also as ICA-512, is a major target of islet cell autoantibodies.

They are present in 45–75% of the cases at the beginning of the disease. They are determined by RBA.

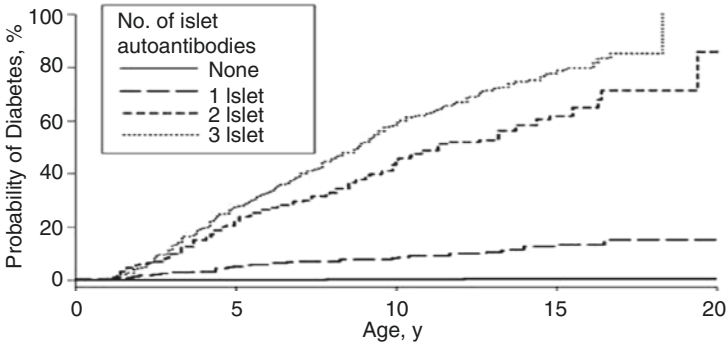
Insulin autoantibodies (IAA) are positive in 20–50% of patients with recent onset diabetes. They are positive previous the treatment with insulin. The use of insulin determines the presence of insulin antibodies (IA) to the exogenous insulin (IA instead of IAA) as they would be related of the exogenous antigen of the hormone injection. They are measured by RBA. They have inverse correlation with age, being more common at younger ages.

It has recently been discovered the antibodies against the Zinc transporter 8 islet (ZnT8A) that also predicts T1DM. ZnT8 is specifically expressed in the pancreatic β-cells and has been identified as a novel target autoantigen in patients with T1DM. Antibodies to ZnT8 have been detected in 60–80% of Caucasian and 33–58% of Asian population with T1DM.

IAAs are the first to appear, GADAs and IAAs are the most frequent islet autoantibodies in childhood, GADA is the hallmark of adult-onset type 1 diabetes, and IA-2 antigens are very specific for the development of diabetes. A study by Annette and coworkers showed that the age of onset of antibodies, and the association between them determined a greater predisposition to develop T1DM, and also that some antibodies are more specific to develop it. They showed that the subgroup of children with two islet autoantibodies, progression to diabetes within 10 years after seroconversion was increased in children with the combination of autoantibodies against insulin and IA2 than in children with autoantibodies against insulin and GAD65 and children with autoantibodies against GAD65 and IA2.The addition of zinc transporter 8 autoantibodies identified seven more children (6%) who progressed to diabetes but did not substantially alter the estimates of diabetes progression.

The sensitivity and predictive capacity increase with the association of markers. The association of GADA, IA- 2A and IAA determines a sensitivity of 90% and a positive predictive value close to 100% for the next 5 years (Fig. 2.1).

The appearance of autoantibodies does not follow a distinct pattern; the presence of multiple autoantibodies has the highest positive predictive value for T1DM.



No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44

Fig. 2.1 Development of Diabetes in Children Stratified for Islet Autoantibody Outcome The numbers at risk represent the children receiving follow-up at age 0, 5, 10, 15, and 20 years. Positive predictive value (PPV) for the development of T1DM in a risk group (Ziegler et al.)

Environmental Factors

Given the evidence of the genetic predisposition for diabetes and autoimmune origin, is still in search those factors that act as trigger determining the process of aggression to the pancreas to generate diabetes.

The mechanism of action involved in environmental factors is not known precisely, but it is postulated that they may act in two different ways: by direct toxicity against beta cell; and by triggering the autoimmune mechanism against beta cell.

Age is an important factor, being less common to develop T1DM in the first 9 months of life, probably related to the protection provided by the maternal antibodies to the newborn. There is an increase incidence at 5–6-year-old, a peak at 12–14-year-old and a slight decrease between 20 and 35 years comes later. There are also geographical variations, with significant differences between different areas; (e.g., in Finland the incidence is 29.5/100,000 people per year while in Hokkaido, Japan, is 1.6/100,000 per year). Migrant studies indicate that the incidence of T1DM has increased in population groups who have moved from a low incidence region to a high incidence area, also emphasizing the influence of environmental conditions.

There have been described factors as chemical agents and specific drugs (alloxan, streptozotocin, pentamidine and a rodenticide vacor).

A large number of epidemiological studies were conducted to determine the influence of viral infections in the development of T1DM in humans, accepting its association mainly with four viruses: mumps, coxsackie, rubella and cytomegalovirus, which would act as a trigger for immune process.

Currently, although genetic and immunological markers are involved, the use of immunosuppressants in the preclinical period is not approved, since its safety and effectiveness are not demonstrated, and that might be unnecessary in patients who undergo to an spontaneous remission without developing the disease.

Type 2 Diabetes Mellitus (T2DM)

T2DM is a chronic metabolic condition characterized by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). When insulin resistance is present, the β-cell maintains normal glucose tolerance by increasing insulin output. It is only when the β-cell is incapable of releasing sufficient insulin in the presence of insulin resistance that glucose levels rise. T2DM is commonly associated with obesity, physical inactivity, hypertension, disturbed blood lipid levels and a prothrombotic state, and therefore is recognized to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, along with poor quality of life and life expectancy reduced.

T2DM has a polygenic origin of variable expression, where environmental factors play an important role in its determinism.

The variable expression of genes implies that the presence of the predisposition not invariably determines an evolution towards the disease, and that their presence only involves the risk of developing T2DM. This risk is enhanced with some environmental factors as unhealthful food, refined carbohydrates, barriers to physical activity and stress.

T2DM accounts for 90–95% of all diabetes types. This form encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. Insulin resistance alone is insufficient to develop diabetes, so it requires the alteration in insulin secretion. The IR has two determining factors, the genetic, and the environmental, which is influenced by diet, sedentary lifestyle, overweight, medication, etc. It is more common in adults; its onset is insidious by the lack of symptoms, being common to ignore the presence of the disease.

T2DM= Insulin Resistance + β-cell dysfunction

Other Specific Types

Among the other specific types of diabetes, it is important to identify the monogenic types of diabetes.

It is worth noting the MODY diabetes (Maturity Onset Diabetes of the Young), which is characterized by diabetes that appears early in life, but behaves like type 2 diabetes and not as Type 1, and are characterized by impaired insulin

Table 2.2 Genetic classification and clinical phenotypes of the MODY subtypes (Attiya K. et al.)

Type	Gene name	Locus	Gene function	Primary defect
MODY 1	Hepatocyte nuclear factor 4α (HNF4A)	20q	Transcription factor (nuclear factor)	Pancreas
MODY 2	Glucokinase (GCK)	7p15-p13	Hexokinase IV	Pancreas/liver
MODY 3	Hepatocyte nuclear factor 1α (HNF1A)	12q24.2	Transcription factor (homeodomain)	Pancreas/kidney
MODY 4	Insulin promoter factor-1 (IPF-1)	13q12.1	Transcription factor (homeodomain)	Pancreas
MODY 5	Hepatocyte nuclear factor 1 β (HNF1B)	17q12	Transcription factor (homeodomain)	Kidney/pancreas
MODY 6	Neurogenic differentiation 1 (NEUROD1)	2q	Transcription factor(bHLH)	Pancreas
MODY 7	Kruppel-like factor 11 (KLF11)	2p25	Transforming growth factor-beta-inducible-early growth response 2.	Pancreas
MODY 8	Bile salt dependent lipase (CELL)	9q34.3	The endocrine cells of pancreas synthesize insulin and are involved in the pathogenesis of diabetes mellitus and exocrine cells are involved in the pathogenesis of pancreatic malabsorption	Pancreas
MODY 9	Paired domain gene 4 (PAX4)	7q32	Transcription factor (paired domain gene 4)	Pancreas
MODY 10	Insulin (INS)	11p15.5.	Beta cells of the islets of Langerhans	NF-kappa-B
MODY 11	Tyrosine kinase, B-lymphocyte specific	8p23-p22	Tyrosine kinase (B lymphocytes)	MIN6 beta cells

secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern, MODY is caused by a mutation in a single gene. If a parent has this gene mutation, their offspring has a 50% chance of inheriting it from them.

It commonly appears before 25 years of age, usually occurs in three or more generations of the same family. It is monogenic type, with dominant inheritance,

They have been described 11 types of maturity onset diabetes of the young whose recognition is difficult to perform, but is important to consider the presence of this type of DM because their treatment and prognosis differ from the T1DM (Table 2.2).

The diagnosis of monogenic diabetes should be considered in children with the following findings:

- Diabetes diagnosed within the first 6 months of life
- Strong family history of diabetes but without typical features of type 2 diabetes (non-obese, low-risk ethnic group)
- Mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), especially if young and non-obese
- Diabetes with negative autoantibodies and without signs of obesity or insulin resistance

Gestational Diabetes (GD) GD has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. It has 7% prevalence with a range from 1 to 14%, depending on the population studied and the diagnostic criteria used. For the diagnosis of GD an oral glucose tolerance test is performed between weeks 24 and 28 of pregnancy; if negative and there are risk factors for, is repeated between 31 and 33 weeks. It is made with 75 g of anhydrous glucose dissolved in 375 mL of water, to be ingested in 5 min (Table 2.3).

The diagnostic criteria are different according to different medical societies that are considered.

Classical risk factors for developing gestational diabetes are:

- Policystic Ovary Syndrome
- A previous diagnosis of gestational diabetes or prediabetes, impaired glucose tolerance, or impaired fasting glycemia.
- A family history revealing a first-degree relative with T2DM
- Maternal age—a woman's risk factor increases as she gets older (especially for women over 35 years of age).
- Ethnicity (those with higher risk factors include African-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders, and people originating from South Asia).
- Being overweight, obese or severely obese increases the risk by a factor 2.1, 3.6 and 8.6, respectively.
- A previous pregnancy which resulted in a child with a macrosomia [high birth weight: >90th centile or >4000 g (8 lbs 12.8 oz)].
- Previous poor obstetric history.

Table 2.3 Oral glucose tolerance test for the diagnostic of Gestational Diabetes

Time (min)	ADA (75 g OGTT) (2 h) (mg/dL)	Carpenter (100 g OGTT) (3 h) (mg/dL)
0	≥92	≥95
60	≥180	≥180
120	≥153	≥155
180	–	≥140

- Other genetic risk factors: There are at least ten genes where certain polymorphism are associated with an increased risk of gestational diabetes, most notably TCF7L2.

LADA: In the classification of the ADA the place of this type of diabetes is not defined. It is known as LADA for its acronym in English Autoimmune Latent Diabetes of the Adult. It is characterized, as indicated by its name, its autoimmune origin that occurs in adults, but with a less abrupt onset and may not require the use of insulin than 6 months periods. It is important to consider this possibility in adult individuals (over 35 years) and who are not overweight. GADA determination is indicated in this group of patients, being important to understand the type of diabetes present because they tend to insulin dependence and must be distinguished from T2DM with failure to oral agents. Other antibodies that may be useful for diagnosis include IA-2A and ZnT8-A. The determination of IAA is not recommended (less frequent in adults).

Considerations

Diabetes is the generic name of a syndrome that is defined by a blood glucose value, however it can be concluded that there are different causes of this condition so should be identified the type of diabetes in a newly diagnosed diabetic patient, to understand the nature of the disease, since this knowledge will make a difference in the treatment, prognosis and complications.

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Basic Concepts in Insulin Resistance and Diabetes Treatment

3

Fernando Bril and Kenneth Cusi

Introduction

Type 2 diabetes mellitus (T2DM) should be understood as the final common pathway that results from an imbalance between increased insulin resistance (i.e., decreased insulin action) and relative insulinopenia (i.e., impaired insulin secretion) [1].

There is consensus that for most patients with T2DM the earliest defect observed is insulin resistance. For many patients this is genetically determined, but a common acquired factor that worsens insulin resistance is obesity [2]. However, the relative contribution of acquired versus genetic factors is unclear and varies from patient to patient. At early stages, the pancreas is able to compensate for insulin resistance by increasing insulin secretion so that glucose tolerance is preserved. Thus, a state of normal glucose tolerance is maintained at the expense of hyperinsulinemia. Over time, and by mechanisms that are still incompletely understood, pancreatic β-cells fail to maintain this high rate of insulin secretion, and impaired glucose tolerance and overt T2DM develop [3].

In the current chapter, the mechanisms leading to insulin resistance and the spectrum of therapeutic approaches for patients with T2DM will be described.

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Causes of Insulin Resistance: Acquired vs. Genetic

The interplay between acquired and genetic defects in the development and promotion of insulin resistance is complex and incompletely understood [4–6]. Moreover, the relative contribution of each of these factors varies from case to case, and ranges from monogenic insulin resistance syndromes to fully-acquired cases in the setting of obesity.

Monogenic syndromes of insulin resistance are rare, but they have been consistently reported in the literature in the last few decades [6]. Over 15 different culprit genes have been identified including insulin receptor, peroxisome proliferator-activated receptor-γ (PPAR-γ), pericentrin, perilipin, protein kinase B (Akt2), etc. Of note, most single-gene causes of insulin resistance do not affect insulin signaling pathways, but adipose tissue function, inducing insulin resistance only as a consequence of the dysfunctional adipose tissue. Other responsible genes identified are involved in DNA repair, but their link to severe insulin resistance has not been fully elucidated [6]. These genetic syndromes range from infantile fatal disease to mild insulin resistance in later life, and have been reviewed in depth elsewhere [7, 8].

As for the acquired defects, obesity has received significant attention, as it is commonly associated with insulin resistance [4, 5]. However, teasing out the contribution of genetic factors from that directly attributed to obesity has been difficult. Moreover, the severity of obesity does not always correlate with the severity of insulin resistance, implying that there are other mechanisms that regulate the degree of obesity-related insulin resistance. Accumulating evidence suggests that the initiating event of insulin resistance may not be the presence of obesity itself, but the presence of dysfunctional adipose tissue [4, 5]. This concept helps to explain why non-obese individuals with a family history of T2DM (i.e., with a genetic background) are insulin resistant long before the development of obesity [9]. Based on the same principles, the development of obesity (even in the absence of a genetic background) results in adipose tissue insulin resistance due to a distinctive fat distribution (favoring visceral accumulation, in contrast of subcutaneous adipose tissue), but most importantly, due to the development of ectopic accumulation of fat in insulin sensitive tissues, such as the liver and skeletal muscle [4, 5]. Other common causes of insulin resistance include some medications and are described in Table 3.1 [8, 10].

Physiology of Insulin Resistance

Adipose Tissue

As mentioned above, adipose tissue is likely the tissue where insulin resistance begins [5]. By molecular mechanisms that are beyond the scope of this article and that have been reviewed elsewhere [5, 11, 12], adipose tissue can become insulin resistant in the setting of obesity and/or genetic predisposition. As a

Table 3.1 Causes of insulin resistance

Genetic causes of insulin resistance
Mutations in insulin receptor or insulin pathway 1. INSR [insulin receptor]—autosomal recessive (e.g., Donohue and Rabson Mendenhall syndromes) 2. INSR [insulin receptor]—autosomal dominant (e.g., type A IR and HAIR-AN syndromes) 3. IRS-1 4. Akt/PKB (e.g., Lipodystrophy with familial diabetes) 5. Insulin receptor kinase inhibitor (PC-1)
Mutations directly affecting adipose tissue function 1. Genetic lipodystrophy (generalized or partial) (e.g., PPAR-γ, perilipin1, etc.) 2. Genetically determined obesity (e.g., Alstrom syndrome)
Mutations affecting DNA repair 1. WRN gene (adult progeria or Werner syndrome) 2. BLM gene (DNA helicase) (Bloom syndrome) 3. ATM gene (ataxia-telangiectasia)
Acquired causes of insulin resistance
Obesity ± sedentary life
Increased plasma FFA (i.e., "lipotoxicity")
Hyperglycemia
Subclinical/clinical inflammation
Pregnancy
Medications 1. Highly active antiretroviral treatment (e.g., protease inhibitors) 2. Glucocorticoids 3. Nicotinic acid 4. Atypical antipsychotics (e.g., olanzapine)

consequence of this, hormone-sensitive lipase fails to be inhibited by insulin, which results in increased rates of lipolysis. This, in turn, results in an oversecretion of free fatty acids (FFA) into the circulation, where they can reach other organs promoting lipotoxicity [5]. The term "lipotoxicity" was originally introduced by Unger [13] to describe the harmful effects of increased FFA levels on β-cell function. However, since its original use, the term lipotoxicity has attained a much broader meaning, and it is now applied to any deleterious effects of FFAs on tissues that would not normally be destined to store large amounts of lipids, such as the liver [14, 15].

In addition to FFA oversecretion, insulin-resistant adipose tissue is also characterized by a pro-inflammatory phenotype [5, 12]. Adipocytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 are secreted by dysfunctional adipocytes and may contribute to insulin resistance in an autocrine, paracrine, and endocrine fashion. This consolidates a "closed loop" in which insulin resistance promotes inflammation, and inflammation reinforces insulin resistance. Reduced levels of beneficial molecules, such as adiponectin, have also been described in obesity and insulin-resistant states [16]. Moreover, there exists a closed cross-talk between adipocytes and macrophages in the adipose tissue, further expanding the systemic impact of adipose tissue-derived inflammation [11, 12].

Liver

The liver receives FFAs from three different sources: adipose tissue lipolysis, diet, and *de novo* lipogenesis [14, 17]. Of these, adipose tissue lipolysis is the most important one, contributing with approximately ~60% of all FFAs in normal conditions. In the setting of adipose tissue insulin resistance (increased lipolysis, as described above), the flux of FFA to the liver increases. When FFA supply surpasses the metabolic needs of the organ, the liver begins to accumulate them as triglycerides, which results in hepatic steatosis [18]. In addition, increased hepatic FFA oxidation leads to an incomplete oxidation, with the generation of lipid intermediates (e.g., ceramides and diacylglycerols) and reactive oxygen species (ROS) that promote hepatic insulin resistance and inflammation [18].

Hepatic insulin resistance translates into increased rates of hepatic glucose production (HGP) and of very low density lipoprotein (VLDL) secretion, as insulin is unable to suppress them as under normal conditions [19, 20]. In turn, increased HGP promotes a compensatory hyperinsulinemia in order to maintain normal plasma glucose levels. However, such hyperinsulinemia turns to be deleterious as it increases the rate of intracellular *de novo* lipogenesis (DNL), further contributing to hepatocyte triglyceride accumulation.

Nonalcoholic fatty liver disease, defined as an intracellular triglyceride accumulation greater than 5.5% in the absence of any secondary cause of steatosis (e.g., alcohol, drugs, viral hepatitis, autoimmune hepatitis, etc.), is increasingly common in patients with obesity and/or T2DM [17, 21–23]. It is closely linked to insulin resistance, and in some patients, it can progress to its more severe form known as nonalcoholic steatohepatitis (NASH), characterized by the presence of hepatic steatosis combined with inflammation, necrosis, and /or fibrosis [21, 22]. In the absence of treatment, this liver condition may progress to cirrhosis and hepatocellular carcinoma [21, 22].

Skeletal Muscle

In the setting of this "lipotoxic" environment promoted by insulin resistance, skeletal muscle insulin resistance also develops, resulting in impaired insulin-stimulated muscle glucose uptake. Several factors contribute to the development of insulin resistance in this tissue. For instance, increased plasma FFA levels promote intramyocellular steatosis and impaired insulin signaling. This is observed among healthy lean individuals, in a dose-dependent manner, when plasma FFA are experimentally increased during an intravenous lipid infusion [24]. This also occurs within 24–48 h after plasma FFA are just slightly increased experimentally to achieve plasma FFA levels typically observed in obesity [25, 26]. However, intramyocellular triglyceride accumulation *per se* appears not to play a role in the development of insulin resistance. Human studies report that athletes paradoxically have a high triglyceride content despite their normal (or above normal) insulin sensitivity [27]. Thus, the current hypothesis is that insulin resistance-related

steatosis is characterized by accumulation of toxic lipid metabolites and pro-inflammatory lipid intermediates that impair insulin signaling and are responsible for insulin resistance [27].

Chronic hyperinsulinemia, secondary to increased hepatic glucose production, can also promote insulin resistance by downregulating the number of insulin receptors and their downstream signaling steps. An approximately 2 to 3-fold increase in plasma insulin levels causes skeletal muscle insulin resistance after a 72-hour insulin infusion in otherwise insulin-sensitive individuals [28]. The combination of elevated FFA and hyperinsulinemia is the perfect storm for skeletal muscle insulin resistance, which in turn contributes to glucose intolerance.

Pancreatic ß-Cells

In order to keep plasma glucose levels in the normal range in the setting of insulin resistance, a compensatory hyperinsulinemia is required, which results in a demanding burden to the pancreatic ß-cells [29]. While ß-cells can keep up with the workload, glucose tolerance remains within the normal range. However, when this compensation fails, hyperglycemia develops. However, subtle defects in ß-cell function can be detected long before the development of frank hyperglycemia [29]. The underlying mechanisms responsible for this relentless decline in ß-cell function over time are incompletely understood. However, basic and clinical evidence suggests that hyperglycemia (i.e., glucotoxicity) and chronic elevated plasma FFAs (i.e., lipotoxicity) play key roles in this progression [30–32].

In the setting of obesity and insulin resistance, ß-cells are forced to manage the FFA oversupply. In ideal conditions, this chronic increase of plasma FFA should enhance basal and glucose-stimulated insulin secretion. However, in predisposed patients (e.g., family history of T2DM) increased plasma FFA produces the opposite effect, inducing insulin secretion impairment and favoring the progression to T2DM [31]. These patients appear to have a genetically-determined reduced ß-cell adaptation to excess FFA supply. Once hyperglycemia develops, this generates a positive feedback, where hyperglycemia impairs ß-cell function, further perpetuating the increased plasma glucose levels [30].

Management of T2DM

The management of T2DM requires a multidisciplinary approach, focused on lifestyle modifications, as well as diabetes self-management education and support [33]. At center stage of this approach are nutrition therapy, physical activity, and smoking cessation counseling [33]. Health care providers should focus on how to optimize lifestyle in every patient with T2DM, as modest weight reductions have been shown to improve glycemic control and reduce the need for glucose-lowering medications [34]. Relatively modest reductions of body weight (of approximately 5%) are frequently enough to observe beneficial effects in glycemic control, although weight