

What the radiologist needs to know about the diabetic patient

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Abstract Diabetes mellitus (DM) is recognised as a major health problem. Ninety-nine percent of diabetics suffer from type 2 DM and 10% from type 1 and other types of DM. The number of diabetic patients worldwide is expected to reach 380 millions over the next 15 years. The duration of diabetes is an important factor in the pathogenesis of complications, but other factors frequently coexisting with type 2 DM, such as hypertension, obesity and dyslipidaemia, also contribute to the development of diabetic angiopathy. Microvascular complications include retinopathy, nephropathy and neuropathy. Macroangiopathy mainly affects coronary arteries, carotid arteries and arteries of the lower extremities. Eighty percent of deaths in the diabetic population result from cardiovascular incidents. DM is considered an equivalent of coronary heart disease (CHD). Stroke and peripheral artery disease (PAD) are other main manifestations of diabetic macroangiopathy. Diabetic cardiomyopathy (DC) represents another chronic complication that occurs independently of CHD and hypertension. The greater susceptibility of diabetic patients to infections completes the spectrum of the main consequences of DM. The serious complications of DM make it essential for physicians to be aware of the screening guidelines, allowing for earlier patient diagnosis and treatment.

Keywords Diabetes mellitus · Complications · Imaging · MRI · CT · PET · Ultrasound

Introduction

Diabetes mellitus (DM) is a major health and economic problem. It is a chronic epidemic disease occurring across the world with multiple complications. The size of the diabetic population worldwide, according to the International Diabetes Federation (IDF), is expected to consist of 380 millions people by 2025 [1]. The global cost of diabetes medication and its complications was calculated for 2007 to be 232 billion dollars.

Definition and classification of DM

According to the American Diabetes Association (ADA) and the World Health Organisation (WHO), DM describes a metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [2, 3]. The criteria that are now in use for the diagnosis of DM recommended by the ADA in 2010 are shown in Table 1 [2].

The current classification of DM distinguishes four categories of diabetes [2]. The main types are: type 2 DM, formerly called non-insulin-dependent DM (NIDDM) or adult-onset DM, is observed in 90% of the diabetic population and is characterised by insulin resistance in peripheral tissues and an insulin secretory defect of the beta cell. This form of DM develops gradually and is occult at earlier stages so that the onset of diabetes usually precedes the clinical manifestations and diagnosis for many years. The

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Table 1 Diagnostic criteria of diabetes

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1. Glycated haemoglobin (HbA1c) $\geq 6.5\%$
or
 2. Fasting plasma glucose (FPG) ≥ 126 mg/dl (7.0 mmol/l)
or
 3. Two hours plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT), using 75 g anhydrous glucose dissolved in water.
 4. If a person appears the classic symptoms of hyperglycaemia (polyuria, polydipsia, polyphagia, weight loss and blurred vision) or acute consequences of hyperglycaemia (ketoacidosis, non-ketotic hyperosmolar syndrome), one random plasma glucose ≥ 200 mg/dl (11.1 mmol/l) is enough for the diagnosis
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remaining 10% includes mainly patients with type 1 DM and also some other less frequent types such as gestational diabetes, drug-induced diabetes (thiazides, glucocorticoids, β -adrenergic agonists, etc.) and MODY (maturity-onset diabetes in youth), which is characterised by genetic defects [2].

Besides diabetes, two other relative pathological situations are recognised: pre-diabetes and metabolic syndrome. Pre-diabetes is the state in which blood glucose levels are higher than normal, but not high enough to be diagnosed as overt diabetes. Subjects with pre-diabetes are at high risk of future development of DM [2]. Pre-diabetes is defined by the ADA as either impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT; Table 2). There is also a strong relation between DM and metabolic syndrome, which is a cluster of risk factors for cardiovascular disease (CVD) and diabetes. The current definition for the metabolic syndrome is shown in Table 3 [4]. Metabolic syndrome represents a powerful predictor of type 2 DM, because insulin resistance, which is the most important disorder of the syndrome, frequently precedes the onset of diabetes and thus it confers a fivefold increase in risk for type 2 DM [4]. Patients with the metabolic syndrome are at twice the risk of developing CVD over the next 5–10 years compared with individuals without the syndrome.

Prevalence

DM affects almost 6% of the world's population, but its incidence increases every year [5]. The prevalence of diabetes is expected to increase by 54% until 2030. A 69% increase in the number of adults with type 2 DM in developing countries is estimated to occur between 2010

and 2030, and the biggest proportion of this increase will concern persons aged between 40 and 60 years. The respective increase in developed countries is estimated to be 20% and that mostly concerns people over 60 years of age. The likeliest explanations for these trends include ageing, urbanisation and the adoption of a western lifestyle leading to obesity and a sedentary life, and also the improvement of longevity of people with diabetes as a result of better health care improvement [5–7]. Type 1 DM still has the biggest prevalence among children, but in recent years this has changed because more and more children are becoming obese. The recent WHO report on Diet, Nutrition and the Prevention of Chronic Diseases placed obesity at the top of the public health agenda as a major risk factor [6]. Rising levels of obesity and type 2 DM in children are cause for concern worldwide [7, 8].

Risk factors

Lifestyle plays a crucial role in the development of type 2 DM. There is certainly a genetic predisposition for type 2 DM, but the presence of multiple risk factors is leading to the epidemic of the twenty-first century. Risk factors are distinguished as non-modifiable and modifiable ones. The first category includes the age (persons over 45 years old), the family history of type 2 DM and the ethnicity [9]. Also, a history of gestational DM is an important risk factor, because it places women at increased risk of the later development of type 2 DM [4]. Fortunately, lifestyle modifications like healthy diet, physical activity and breast-feeding can prevent it [10]. On the other hand, there are modifiable risk factors, like obesity ($BMI \geq 30$) and physical inactivity, which are considered the main non-

Table 2 Diagnostic criteria of pre-diabetes

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- IFG: Fasting plasma glucose ≥ 100 mg/dl (6.1 mmol/l) and ≤ 125 mg/dl (6.9 mmol/l) during an oral glucose tolerance test (OGTT), using 75 g anhydrous glucose dissolved in water.
- IGT: Two hours plasma glucose ≥ 140 mg/dl (7.8 mmol/l) and ≤ 199 mg/dl (11.0 mmol/l) during an oral glucose tolerance test (OGTT), using 75 g anhydrous glucose dissolved in water
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Table 3 Criteria for diagnosis of metabolic syndrome

Necessary at least three of the below:

- 1) Waist circumference ≥ 94 cm for men and ≥ 80 cm for women (IDF recommendation) or ≥ 102 cm for men and ≥ 88 cm for women (AHA/NHLBI recommendation).
- 2) Triglyceride levels ≥ 150 mg/dl (1.7 mmol/l).
- 3) HDL cholesterol levels < 40 mg/dl (1.0 mmol/l) for men and < 50 mg/dl (1.3 mmol/l) for women.
- 4) Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg.
- 5) Fasting plasma glucose (FPG) ≥ 100 mg/dl (5.6 mmol/l).

IDF International Diabetes Federation, AHA/NHLBI American Heart Association/National Heart Lung Blood Institute

genetic determinants of the disease [2]. In addition, previously identified pre-diabetes, which includes IFG or IGT, may progress to type 2 DM [4]. Finally, dyslipidaemia [11], hypertension [12, 13] and the coexistence of the components of metabolic syndrome, such as central obesity, increase the risk of the future development of diabetes [4].

Diabetic complications

The classic symptoms of hyperglycaemia include polyuria, polydipsia, polyphagia, weight loss and blurred vision, but it has to be underlined that it may not be present for years in type 2 DM. As the prevalence of DM increases, diabetes-related mortality also increases. The multimorbidity of diabetics increases mortality in all age groups [14].

Earlier exposure to hyperglycaemia has the potential to accelerate the progression and severity of vascular complications. Future generations will be burdened with the complications of diabetes at the peak of their productivity. The multimorbidity of the diabetic population is increased because of the presence of acute and chronic complications, the coexistence of hypertension and dyslipidaemia and, moreover, the high incidence of infections.

Diabetic complications are distinguished as either acute or chronic (Table 4). Acute complications resulting from acute metabolic derangement and severe hyperglycaemia include ketoacidosis and the non-ketotic hyperosmolar state [15]. Hypoglycaemia resulting from the use of insulin and oral antidiabetic agents is also an acute complication.

DM may affect almost every organ and system. Chronic complications include microvascular and macrovascular ones. Microvascular complications include retinopathy, nephropathy and neuropathy, while macrovascular include coronary heart disease (CHD), peripheral artery disease (PAD), cerebrovascular incidence and erectile dysfunction. Duration of diabetes is an important factor in the pathogenesis of these late complications. Other concomitant risk factors such as hyperglycaemia, hypertension, smoking and hyperlipidaemia, are involved in the progression of such

complications. Diabetic cardiomyopathy represents another chronic complication, developing independently of CHD and hypertension. Finally, the greater susceptibility of diabetic patients to infections completes the spectrum of the main consequences of DM.

Microvascular complications

A continuous relation exists between glycaemic control and the incidence and progression of microvascular complications. Hypertension and smoking also have an adverse effect on microvascular outcomes. There is evidence that strict glucose control reduces the development and progression of microvascular complications [16–18].

Diabetic nephropathy

Diabetic nephropathy (DN) is the most common cause of end-stage renal failure in the western world [19, 20]. It is defined as the presence of persistent proteinuria (> 0.5 g/24 h), and declining glomerular function in the absence of urinary tract infections, other renal disease, or heart failure. The annual incidence of diabetic nephropathy rises rapidly over the first 15–20 years of diabetes to decline sharply afterwards. DN

Table 4 Main diabetic complications

Acute	Ketoacidosis
	Non-ketotic hyperosmolar state
	Hypoglycaemia due to oral antidiabetic agents or insulin
Chronic	Macroangiopathy \rightarrow coronary heart disease
	stroke
	peripheral artery disease
	Microangiopathy \rightarrow diabetic nephropathy
	diabetic retinopathy
	diabetic neuropathy
Diabetic cardiomyopathy	
Increased susceptibility to infections	

affects up to 35% of type 1 diabetic patients and a smaller proportion of type 2 diabetic patients of Caucasian origin. However, because of the higher prevalence of type 2 diabetes, 50% of diabetic patients in renal replacement treatment programs have type 2 diabetes [20]. The mortality and morbidity of diabetic patients with end-stage renal disease (ESRD) are greater than those of patients with other causes of ESRD related to concomitant systemic disorders, especially coronary artery and cerebrovascular disease.

Diabetic nephropathy follows a well-outlined clinical course, starting with microalbuminuria (elevation of excretion of albumin in the urine, above what is the normal non-diabetic range, which goes up to 20 mg/ml), through proteinuria, azotaemia and culminating in ESRD [21].

The earliest morphological abnormality in diabetic nephropathy is the thickening of the glomerular basement membrane and expansion of the mesangium due to accumulation of extracellular matrix. A stage of glomerular hyperfiltration and hypertrophy precedes the glomerular sclerosis and the deterioration of the glomerular filtration rate [22, 23]. Renal ultrasound reveals a normal to increased kidney size at the initial stage of hyperfiltration, while later at the progression of renal failure kidneys are decreased or shrunken with decreased thickness of the parenchyma. According to ADA recommendations an annual assessment of urine albumin excretion has to be performed in type 1 diabetic patients with diabetes duration of 5 years and in all type 2 diabetic patients, starting at diagnosis [24].

Beyond hyperglycaemia, another crucial factor for the progression of DN is arterial hypertension. The renin-angiotensin-aldosterone system (RAAS) plays an important role in modulating the presence of microalbuminuria. RAAS-directed antihypertensive agents, including angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and renin inhibitors, have been demonstrated to have renoprotective effects [23, 25–28].

It has to be emphasised that a particularly important concern in diabetic patients, especially those with underlying renal insufficiency, is nephrotoxicity resulting from contrast agents used in imaging studies such as computed tomography (CT) or digital subtraction angiography (DSA). Clinical manifestations range from a mild and reversible impairment of the glomerular filtration rate to renal failure requiring haemodialysis. Special care should be taken in patients taking the oral hypoglycaemic agent metformin. Metformin accumulation caused by renal insufficiency can result in lactic acidosis, which is a serious and potentially fatal complication [29].

Diabetic retinopathy

Diabetic retinopathy (DR) is the leading cause of blindness in people of working age [30, 31]. Blindness results from

progressive retinopathy and macular oedema. DR is classified into two stages, non-proliferative DR (NPDR) and proliferative DR (PDR) [32]. The duration of DM and the degree of glycaemic control are mostly related to the development of DR. NPDR is usually demonstrated late in the first decade of the disease. It is characterised by the appearance of retinal vascular microaneurysms, exudates and blot haemorrhages. NPDR can progress to the more severe PDR. Neovascularisation is the hallmark of PDR. The newly formed vessels are prone to rupture leading to vitreous haemorrhage and subsequent fibrosis and retinal detachment. The prevalence of DR reaches 80% among patients with 20 or more years' duration of type 1 DM [33]. As type 2 DM usually remains unrecognised for years, a significant percentage of patients, ranging from 7% up to 38%, already have DR at the time of diagnosis [17, 34]. DR usually coexists with the other types of diabetic microangiopathy [32]. Patients with overt diabetic nephropathy are almost certain to have DR. According to the recent ADA guidelines, patients with type 1 DM should have an initial dilated and comprehensive eye examination by an ophthalmologist within 5 years of the onset of disease, while patients with type 2 DM should have an initial evaluation shortly after the diagnosis of DM [24].

Diabetic neuropathy

Neuropathy is a common disorder in diabetic patients. It results from several pathways of metabolic insult but also microangiopathy sometimes contributes to its development [35]. Besides the duration of diabetes and poor glycaemic control, other factors such as higher body mass index, smoking, hypertension, and raised plasma cholesterol and triglyceride levels are associated with the incidence of neuropathy [36]. It manifests as polyneuropathy, mononeuropathy and/or autonomic neuropathy. The most common form of diabetic neuropathy is chronic sensorimotor distal symmetric polyneuropathy, which affects 30–50% of diabetic patients [37]. It is often asymptomatic, particularly at the beginning. The most frequent presentation of distal symmetric polyneuropathy is distal sensory loss, while other symptoms include burning pain, paraesthesiae, hyperaesthesiae and deep aching pain. The symptoms are typically located in the feet and lower limbs and neuropathic pain is usually worse at night. Patients suffering from distal symmetric polyneuropathy are at high risk of foot ulceration and subsequent amputation. Another complication associated with the loss of pain sensation, proprioception and muscular reflexes that regulate joint movement is Charcot neuroarthropathy (CN) [38]. CN almost exclusively affects the foot and it is characterised by progressive cartilage and bone damage resulted from repeated trauma due to the absence of

the above-mentioned protective mechanisms. Initially, Charcot neuroarthropathy presents with a warm, swollen and painful foot, while at a more advanced stage numerous dislocations and fractures lead to severe deformity of the foot accompanied by severe disability. The plain X-ray is often impressive, while radionuclide imaging and particularly magnetic resonance imaging (MRI) can help in the diagnosis and the differentiation from osteomyelitis, which is sometimes difficult. Peripheral mononeuropathies occur less frequently and mainly involve medial, ulnar, radial and common peroneal nerves [35]. Cranial neuropathies are extremely rare. Similarly, diabetic neuropathy rarely manifests as polyradiculopathy involving intercostal, truncal, or lumbar plexus, resulting in pain over the thorax, abdomen, or in the thigh and the hip respectively [15]. In the latest cases, a rare manifestation called diabetic amyotrophy can occur, characterised by weakness and atrophy in the proximal thigh muscles.

Diabetic autonomic neuropathy is frequent and can affect multiple systems, including cardiovascular, gastrointestinal and genitourinary. Concerning the cardiovascular system, the major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance and orthostatic hypotension [35]. Moreover, silent myocardial ischaemia and sudden death have been attributed to diabetic autonomic neuropathy. Gastroparesis, constipation or diarrhoea, bladder dysfunction and erectile dysfunction are the most common types of the impairment of gastrointestinal and genitourinary systems. Diabetic autonomic neuropathy may also reduce the patient's ability to sense hypoglycaemia, thereby subjecting patients to the risk of severe hypoglycaemia.

Diabetic cardiomyopathy

The prevalence of heart failure (HF) is particularly increased in diabetic patients [39]. Furthermore, the likelihood of developing heart failure following a myocardial infarction is increased in diabetic patients [40]. Diabetes also represents a powerful risk factor for death among patients with established HF [41]. In the Framingham study, after adjustment for age, blood pressure, cholesterol level, obesity and history of CHD, the risk of congestive HF in diabetic males was over twice that of non-diabetic subjects, while in women the presence of diabetes entailed a more than five-fold increase in the risk of congestive HF [42]. It has been accepted that besides the increased prevalence of CHD and the increased likelihood of hypertension among diabetic patients there is also a distinct clinical entity called diabetic cardiomyopathy (DC). DC is now considered a common complication of type 1 DM and type 2 DM. DC is defined as a primary disease process that develops secondary to metabolic insult, occurring independently of CHD and

hypertension and leading to ventricular dysfunction [43]. The main feature of DC is the adverse myocardial remodelling, resulting in concentric left ventricular hypertrophy and leads to the development of a stiffened ventricle with diastolic dysfunction that progresses to diastolic HF or otherwise called HF with preserved ejection fraction. The impairment of diastolic function is the predominant clinical feature of DC and typically precedes systolic left ventricular dysfunction in diabetic patients. Myocyte hypertrophy, capillary basement membrane thickening and interstitial fibrosis are the prominent histological features of DC [44]. Diagnostic techniques currently used to detect the presence of DC include echocardiography and cardiac MRI [43, 45]. Echocardiography is currently the most frequently used method for the measurement of left ventricular wall thickness and pulse-wave Doppler echocardiography is the most practical method for the assessment of diastolic function. Cardiac MRI is considered the "gold standard" for measuring left ventricular mass. However, its use is mainly limited to research. The use of gadolinium allows the assessment of myocardial fibrosis (late gadolinium enhancement), while MR spectroscopy is another emerging research tool allowing the measurement of myocardial triglyceride content, which is a novel field of research concerning the diagnosis and the pathogenesis of DC [46, 47].

Macrovascular diabetic complications

There is a growing epidemic of atherosclerotic complications particularly concerning the type 2 diabetic population [48]. Macroangiopathy in diabetic patients progresses rapidly and affects multiple organs. Coronary arteries, extracranial carotid arteries and arteries of the lower extremities are mainly affected. The clinical expressions of diabetic macroangiopathy include CHD, PAD, stroke and erectile dysfunction. The coexistence of established risk factors for CHD such as hypertension, dyslipidaemia and obesity in type 2 diabetics further increases the prevalence of CVD [49]. Atherosclerosis is four times more common in patients with diabetes than in the non-diabetic population [50]. Eighty percent of deaths in the diabetic population result from cardiovascular incidents [51]. Seventy-five percent of these deaths are caused by CHD and the other 25% is due to stroke and PAD.

DM as a CHD equivalent

In the Framingham study mortality from CHD among type 1 diabetics was approximately four-times higher than that seen in non-diabetics [52]. In a meta-analysis of 37 prospective studies, which enrolled over 400,000 people

the rate of fatal CHD was 3.5-times higher in the type 2 diabetic population in comparison with non-diabetics [53]. In the Multiple Risk Factor Intervention Trial (MRFIT), the diabetic population had a risk of CHD death more than three-times higher than that of the non-diabetic population for every age and ethnic group even after adjustment for established risk factors such as age, serum cholesterol level, systolic blood pressure and smoking [54]. The presence of diabetes also results in worse outcomes during the acute phase of myocardial infarction (MI), as well as in long-term follow-up [48]. In a Finnish study, diabetes increased the 28-day mortality after an MI by 58% [55]. In a six-nation study that enrolled patients with unstable angina and non-Q-wave MI, the OASIS registry, diabetes was independently associated with a 57% increase in the risk of death [56]. In another study the 5-year mortality rate after an MI in diabetic patients was more than double that of non-diabetic patients [57]. Diabetic patients without previous MI exhibit the same risk of subsequent acute coronary events as non-diabetic patients with a history of previous MI [58]. The studies mentioned above are representative of a large amount of data that have led to the establishment of DM as a CHD equivalent mandating aggressive anti-atherosclerotic management [59, 60]. The outcomes of revascularisation procedures, either percutaneous coronary revascularisation or bypass angioplasty revascularisation, are also less favourable in diabetic patients [61, 62]. Invasive methods such as coronary angiography and intravascular ultrasound are the “gold standards” for the diagnosis of CHD, while in the recent years new non-invasive methods such as positron emission tomography (quantitative measurement of blood flow and myocardial vitality), MRI (morphology and perfusion) and CT (calcium score and morphology) have been proven valuable research tools, with CT also becoming an emerging technique in clinical practice [63–65].

DM and stroke

The CV mortality in the diabetic population is high due to the coexistence of CHD and cerebrovascular disease. In the MRFIT cohort, diabetic patients had a threefold increased likelihood of developing a stroke [54]. Particularly among subjects younger than 55 years, the risk of stroke is increased more than tenfold in diabetic patients [66]. Diabetes also increases stroke-related mortality [67], while the risk of dementia following a stroke is increased by threefold [68]. Digital subtraction angiography (DSA) is still considered the “gold standard” for assessment of carotid stenosis, but it has now mostly been replaced by non-invasive techniques, especially Doppler ultrasound and also CT angiography and MR angiography [69]. Beyond

the estimation of luminal stenosis, there is increasing interest in the assessment of plaque quality. The differentiation of high-risk, vulnerable carotid plaques from stable plaques is an emerging criterion for the identification of high-risk patients who need to undergo revascularisation, but also for the choice between endarterectomy and carotid artery stenting as there are data indicating that patients with vulnerable plaque are at increased risk of stroke in carotid artery stenting [70, 71]. The association between the presence of diabetes and the formation of vulnerable plaques is not yet elucidated, but a recent study concerning coronary atherosclerosis assessed by intravascular ultrasound reported a greater proportion of vulnerable plaques among diabetic patients compared with non-diabetic patients (21.6% vs 13.6%) [72]. In addition to B-mode ultrasound, which is the widely used technique for the identification of vulnerable plaques, carotid MRI, multidetector-row CT and nuclear imaging techniques such as (^{18}F)fluoro-glucose (^{18}F -FDG) positron emission tomography (PET) are promising methods for a more accurate evaluation of plaque quality [69, 71].

Screening for subclinical atherosclerosis

Endothelial dysfunction is probably the first demonstration in the development of atherosclerosis that can be clinically assessed. Numerous studies suggest the impairment of endothelial dysfunction and the subsequent development of arterial stiffness as premature events in the evolution of atherosclerosis and that diabetes impair endothelium-dependent vasodilatation before the formation of atheroma [48]. Several epidemiological studies have revealed that endothelial dysfunction predicts future cardiovascular events [73]. A significant amount of data has demonstrated that impairment of glucose homeostasis leads to endothelial dysfunction and arterial stiffness. DM but also IFG and IGT are strongly associated with the presence of endothelial dysfunction and arterial stiffness [74]. Non-invasive techniques using ultrasound have developed to assess endothelial dysfunction. These include the measurement of flow-mediated dilatation (FMD) or the nitrate-induced dilatation of the brachial artery, the measurement of carotid-femoral pulse wave velocity (PWV) and techniques of pulse wave analysis recording the radial pulse wave (PWA) [73]. These methods are widely used in research and they are valuable for assessing the potential anti-atherogenic efficacy of treatment options. However, the variability of the results in terms of absolute values between different laboratories and the diversity of methods in use have not yet permitted these techniques to be integrated into everyday clinical practice. The most validated of these methods is the measurement of PWV, and the European Society of

Hypertension and the European Society of Cardiology define values above 12 m/s to be a marker of subclinical cardiovascular damage [75]. On the other hand, measurement of the combined thickness of the intima and media of the carotid artery (CIMT or simply IMT as it is more frequently mentioned) is widely used not only in research but also in clinical practice. The increase in IMT is considered to be a phenotype of early atherosclerosis [76]. Several large observational studies have demonstrated IMT to be a strong predictor of future cardiovascular events [77]. As measurement of IMT by ultrasound is also a simple, non-invasive and inexpensive test, IMT is an emerging strong risk factor for cardiovascular disease. The European Society of Hypertension and the European Society of Cardiology define values of IMT above 0.9 mm to indicate subclinical cardiovascular damage [75]. Common carotid artery (CCA) IMT > 0.87 mm and internal carotid artery (ICA) IMT > 0.90 mm were found to be associated with an increased risk of cardiovascular disease [76]. IMT has been used for the evaluation of the presence of early atherosclerosis and also for the assessment of the efficacy of several treatments such as the administration of lipid-lowering agents [78, 79]. Not only type 2 DM, but also IGT are associated with an increase in IMT [78]. An increasing number of studies use IMT measurement to reclassify patients into higher or lower risk categories [80].

DM and PAD

The development of PAD is two- to fourfold more common among diabetic patients [81]. The incidence and extent of PAD correlate with the duration and severity of DM [82]. The coexistence of hypertension, dyslipidaemia and central obesity, which is common in diabetic patients, contributes to the development of PAD [83]. There is a strong association with cardiovascular morbidity [84]. PAD results in disability with serious social consequences and may require surgery. The clinical presentation of PAD typically includes intermittent claudication, which can progress to resting pain, ulceration and gangrene. The stage of intermittent claudication is characterised by pain in the legs after walking a certain distance. The characteristic symptom in critical ischaemia stage is resting pain, which leads to severe disability. Gangrene is the end stage of PAD and amputation is inevitable. Among patients with PAD, diabetic patients have worse arterial disease and poorer outcome than non-diabetic patients. The impairment of circulation frequently combined with impaired sensation due to diabetic neuropathy, commonly results in foot ulcerations. The subsequent development of infections is a major cause of morbidity in diabetics. Evaluation of diabetic foot infections often requires clinical, laboratory, microbiological and radiological assessment with

bone imaging and MRI exhibiting the best sensitivity [85]. Osteomyelitis has a profound impact on the prognosis and management of these infections and the “gold standard” for its diagnosis remains the bone biopsy. Diabetic patients are five-times more likely than non-diabetic patients to undergo an amputation [82] and, moreover, diabetes is the leading cause of non-traumatic lower extremity amputations in the United States [48]. Atheromatous disease tends to affect more distal vessels such as the tibial and the peroneal arteries, producing multiple, diffuse lesions that are less straightforward to bypass or to dilate by angioplasty [83, 86, 87].

It has to be noted that a particular type of atherosclerosis called Mönckeberg’s sclerosis can be observed in diabetic patients [88]. Mönckeberg’s sclerosis is characterised by calcification of the medial wall, mainly of medium-sized and larger arteries, leading sometimes to an impressive image of a calcified artery network on X-rays. Although it was formerly believed to be an innocuous condition, it is now considered to be a variant of atherosclerosis with predominance of calcification and a small inflammatory component [89]. Calcification in the first dorsal metatarsal artery is common in Mönckeberg’s sclerosis and, if seen on X-ray, is an indication for screening for the presence of DM [90].

Peripheral Doppler ultrasound has substituted for conventional angiography and digital subtraction angiography as the first line imaging technique for the diagnosis of PAD, while MR angiography is another non-invasive technique emerging into clinical practice [83, 91, 92]. Screening for subclinical PAD is strongly recommended in diabetic patients. Besides peripheral Doppler ultrasound, a widely used method in the evaluation of PAD in everyday practice is the ankle-brachial index (ABI) test. ABI is calculated by dividing the systolic blood pressure measured at the level of the ankle by the systolic blood pressure measured in the brachial artery. As it is a simple, rapid, inexpensive, and reliable method of screening asymptomatic patients for PAD, the ABI test is ideal for implementation in the primary care physician’s office [93]. An ABI < 0.9 is accepted as an indication of the presence of PAD, while values < 0.5 and < 0.3 indicate severe disease and critical ischaemia respectively [83, 93]. Values > 1.4 may be associated with arterial incompressibility due to Mönckeberg’s sclerosis, which can be seen in diabetic patients as well as in patients with chronic renal insufficiency. It has to be underlined that the early detection of PAD and the subsequent medical management is of great importance in preventing vascular morbidity and mortality of diabetic patients.

Erectile dysfunction

Erectile dysfunction is a common complication of diabetes, occurring in $\geq 50\%$ of men with DM, and DM is one of the greatest risk factors for erectile dysfunction [94]. Pathogen-

esis is multifactorial, with autonomic neuropathy, vascular insufficiency and psychological factors contributing to the clinical picture [94, 95].

Diabetes and infections

Diabetes is associated with a greater frequency and severity of infections. Several abnormalities regarding the phagocyte function and cell-mediated immunity are implicated [96]. Skin, mucus, nails and soft tissues are frequently affected predominantly by staphylococcal and fungal infections, especially candidal infections. Pneumonia is caused by a similar spectrum of microorganisms as in the non-diabetic population, but with an over-representation of *Staphylococcus aureus* and Gram-negative bacteria such as *Klebsiella pneumoniae* [15, 96, 97]. Pneumococcal pneumonia occurs more commonly in the diabetic population and diabetics are also more susceptible to developing tuberculosis [96]. Lower tract urinary infections and pyelonephritis are common and they have as additional casual factors the presence of glucosuria and bladder dysfunction due to autonomic neuropathy. Diabetic foot infections are very common and can lead to serious consequences such as osteomyelitis and amputation.

Besides common infections, several less frequent infections are particularly associated with the presence of diabetes. These include emphysematous infections of the gall bladder and urinary tract, alithiasic cholecystitis, “malignant” or invasive otitis externa and the rare but frequently fatal rhinocerebral mucormycosis [15]. Finally, it has to be noted that diabetics are at greater risk of nosocomial (especially wound) infections [96].

Conclusion

DM is an epidemic disease. The increasing prevalence of obesity, especially that concerning childhood, as well as physical inactivity are mainly responsible for the increased incidence of DM. The prevalence of DM is expected to increase by 54% by 2030. Future generations will be burdened with the complications of diabetes at the peak of their productivity. The multimorbidity of the diabetic population is increased due to the presence of acute and chronic complications and the high incidence of infections. The presence of hypertension and dyslipidaemia is common and increases the prevalence of CVD. Eighty percent of people with diabetes will die of CVD.

DM can affect almost every organ. The intersection of several types of complications increases the burden of the disease. The coexistence of micro- and macroangiopathy represents a major reason for the increased severity and the

worst outcomes of CAD and PAD in diabetic patients. Microangiopathy further reduces vascularisation and impairs the development of collateral vessels in ischaemic tissues and thus amplifies the severity of macroangiopathy, promoting tissue hypoxia and reduced wound healing. Autonomic neuropathy also contributes to the impairment of cardiac function. Besides PAD and microangiopathy, diabetic polyneuropathy and the increased susceptibility to infections are other significant causal factors in the pathogenesis of the diabetic foot, which is a very common situation that is frequently difficult to treat. Diverse imaging techniques are in use in clinical practice and research. The contribution of these imaging studies is of great importance for the diagnosis and, more importantly, the early detection of diabetic complications, which is increasingly considered to be the hallmark of the treatment of diabetic patients.

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