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LONG TERM COMPLICATIONS OF DIABETES – A REVIEW

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Abstract

It is estimated that subclinical DM (diabetes mellitus) has the onset about 10 years before the appearance of actual clinical manifestations, leading to uncontrolled chronic complications. Many trials have pursued the onset and evolution of the DM chronic complications in order to obtain a full picture that allows the development of prevention strategies, treatments and DM costs reduction.

key words: *clinical manifestations, diabetes mellitus, chronic disease, treatment.*

Background and aims

This article is a review of the literature about chronic diabetic complications, their managemenet and monitoring of associated risk factors.

Material and methods

A literature search was performed using the NCBI PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Diabetes Care (http://diabetes.diabetesjournals.org) databases for „diabetes classification", „diabetes treatment", „chronic diabetic complications" and „diabetes risk factors" keywords.

Results

Macrovascular complications of diabetes

Cardiovascular disease (CVD) is the major cause of morbidity and mortality for persons with Diabetes Mellitus (DM), both Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D), and also the largest contributor to the direct and indirect costs of DM [1,2]. CVD can be approximated using various risk factors, and a therapeutic strategy for prevention can be initiated before the complication occurs. Many studies indicate the efficiency of individual cardiovascular risk control in preventing and slowing the CVD for patients with DM [2].

Coronary Heart Disease

Coronary heart disease is liable for 14-25% of overall mortality worldwide, Romania having probably the highest mortality rate in Europe. In Europe, among the cases of diabetic adults, the coronary heart disease death is over 50%, both in T1D and T2D [3,4]. The risk for developing a coronary heart disease is two or three times

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higher for persons which are suffering of diabetes [4]. The risk of coronary heart disease for patients suffering of T1D increases dramatically with the onset of nephropathy. Up to 29% of T1D patients who developed nephropathy in childhood will develop a coronary disease in 20 years' time, in comparison with only 2-3% of the patients with diabetes but without nephropathy [5].

Patients suffering of T2D and/or a history of artery disease have very high risk of death due to coronary heart disease [3,6]. The study of a large cohort (51.735 Finnish people, 25.215 men and 26.520 women), aged 25-74 years, tracked for a period of 17.2 years, was realized to determine if there is a synergy between type 2 diabetes and coronary heart disease in increasing the risk of death. During the study there were 9201 deaths (3039 heart disease, 917 strokes and 4580 cardiovascular disease). Hazard rates for mortality from coronary heart disease adjusted for other risk factors in men with diabetes only, myocardial infarction (MI) only and with both diseases were: 2.1, 4.0 and 6.4, while in women they were: 4.9, 2.5 and 9.4 respectively. Hazard ratios for total mortality were: 1.8, 2.3 and 3.7 for men and 3.2, 1.7 and 4.4 for women [6].

Stable Angina and DM

Angina pectoris, also known as stable angina, is a clinical syndrome characterized by precordial chest pain, usually accentuated by stress or physical activity. Normally, this type of chest discomfort is relieved with rest, nitroglycerin or both. Angina pectoris is more common in men with diabetes mellitus, with maximum incidence in their 50's and 60's [7]. Coronary atherosclerosis is the main cause of angina pectoris in patients with diabetes mellitus. Characteristic lesion of atherosclerosis is atherosclerosis plaque, which causes loss of elasticity and narrowing of the lumen (stenosis) [7,8]. For diabetes mellitus the glucose changes in blood is causing: impairment of energy substrate metabolism and insulin, an increasing concentration of non-esterified fatty acids (NEFA), emphasizing the oxidative stress, and the release of free radicals [7]; all favouring to atherosclerosis and angina pectoris development.

Diabetic Cardiomyopathy

Diabetes mellitus increases the probability of heart failure of any etiology. Cardiomyopathy in diabetes is characterized by the presence of myocardial dysfunction (left ventricle diastolic dysfunction) in the absence of coronary atherosclerotic disease and/or hypertension [9]. The prevalence of heart failure in individuals with DM is 2-fold higher in men and 5-fold higher in women, aged between 45-74 years compared to the general population [10].

Several studies in asymptomatic patients with T2D, without hypertension, coronary atherosclerotic disease, valvular heart disease or other known cardiovascular disease, used a Doppler ultrasound to assess the functioning of the left ventricle. For more than 50% of the subjects, results pointed out to the left ventricular diastolic dysfunction as an indicator of diabetic cardiomyopathy [11,12].

Cerebrovascular Disease and DM

The term cerebrovascular disease includes any affection of the brain induced by a pathologic process of the blood vessels. Cerebrovascular disease contributes to development of vascular dementia and Alzheimer's disease. In the USA it is the third cause of death, after heart disease and cancer. The risk factors for cerebrovascular disease can be found in details, in dedicated speciality guides [13,14].

Diabetes mellitus, both T1D and T2D, is an independent risk factor for cerebrovascular disease of 1.8 to 6 times higher compared to

non-diabetic individuals. Diabetic patients, without a history of cardiovascular disease show a risk of fatal strokes similar with non-diabetic individuals with a history of stroke episodes. Epidemiological studies have found that DM is a risk factor for ischemic stroke and there is no, or rare association with hemorrhagic stroke. In current clinical practice, glucose metabolism disorders are often undiagnosed or underestimated, therefore the stroke is considered a "severe form of heart injury", although detailed analyses specificities of the substrate would show the long way of chronicity [15].

Peripheral Artery Disease (PAD)

PAD is one of the most important causes of foot ulceration, intermittent claudication, pain and lower-extremity amputation, among both diabetics and the non-diabetics individuals. It represents the peripheral type of the clinical symptoms of atherosclerosis. Morpho-pathologically, atheromatous lesions are identical to those in non-diabetics, but they develop earlier, evolving more quickly and severely. Arteriopathy of the lower limbs is 2 to 4 times higher among people with diabetes and increases with age and diabetes duration. The prevention of PAD involves the removal of the risk factors: quitting smoking, glycemic control, the control of hypertension and the control of dyslipidemia, maintaining an ideal body weight, fighting against a sedentary lifestyle [16].

Metabolic syndrome components

In 1988, Reaven describes a syndrome based on the combination of the following: resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hyperglycemia, increase of VLDL (very low density lipoprotein triglycerides), low HDL (high-density lipoprotein) cholesterol concentrations and hypertension [17,18]. This syndrome was named "metabolic syndrome" [18]. More recently, new components were included: inflammation markers, microalbuminuria, hyperuricemia, fibrinolysis and procoagulant changes [19].

According to the definition of IDF (International Diabetes Federation) from 2005, the diagnostic criteria for metabolic syndrome are: abnormal fat distribution, insulin resistance, atherogenic dyslipidemia, hypertension, prothrombotic state and proinflammatory state [20].

Hypertension in Diabetic Patients

The Framingham Study showed that the incidence of cardiovascular diseases has doubled (39.1‰ vs. 19.1‰) for man suffering of DM and tripled (27.2‰ vs. 10.2 ‰) in women with DM in comparison with non-diabetic subjects [21].

In the EPIDIAB study, by analyzing dates from 2001, it was found that 49.9% from the 16.394 newly diagnosed diabetes patients have had raised blood pressure (BP) [22]. For patients suffering of DM, the blood pressure should be measured at every routine medical visit. Patients with systolic blood pressure (SBP) ≥130 mmHg and patients with diastolic blood pressure (DBP) ≥80mm Hg will be reevaluated.

The therapeutic goal is to lower BP <130/80 mmHg. The results of the Hypertension Optimal Treatment Trial (HOT) and the results of UKPDS Trial provide strong evidence that the target of the DBP level is 80 mmHg [23,24]. These studies have shown that lowering diastolic BP value close to 80 mmHg has reduced significantly the frequency of micro- and macro-vascular complications, cardiovascular deaths and deaths from diabetes-related causes in patients with DM. The ACCORD study showed that patients suffering of T2D that maintain the systolic BP value <120 mm Hg have greater cardiovascular protection compared to the SBP values between 130-140 mm Hg [25,26].

Dyslipidemia in Diabetic Patients

Dyslipidemia is a major risk factor for coronary heart disease, which is the most common cause of mortality in patients with DM. In addition to glycemic, weight and blood pressure control, lipid control is also a part of the intensive multifactorial clinical management for DM. Usually, the lipids are measured every year. For people without risk (LDL-c < 100 mg/dl, HDL-c > 50 mg/dl, triglycerides < 150 mg/dl) the analysis can be repeated every 2 years [27].

In a meta-analysis of population-based cohort studies, the ratio of the average excess risk with an increase of 1 mmol/L (89 mg/dL) in the triglyceride level was 32% in men and 76% in women. After adjustment for HDL cholesterol, the risk was halved to 37% in women and 14% in men, but remained statistically significant [28].

In the Epidemiological Dynamics Study of DM (EPIDIAB) in several counties from Romania, by analysing dates from 2001, it was found out that 48.8% of newly diagnosed patients have dyslipidemia [22].

Heart Protection Study (HPS) followed-up the highest number of people suffering from DM and receiving lipid-lowering therapy. The study showed that lowering LDL-cholesterol by 29%, increasing HDL cholesterol by 3% and decreasing triglyceride levels by 14% resulted in a 22% reduction in major cardiovascular events [29].

Microvascular complications

Diabetic Chronic Kidney Disease

Pathological processes that cause the affection of renal function are diabetic microangiopathy (glomerulosclerosis) and diabetic macroangiopathy (atherosclerosis of renal arteries) which often coexist in different degrees. Early diagnosis is made by detection of microalbuminuria (30-300mg/24 h). The manifestations of diabetic chronic kidney disease are defined by persistent albuminuria (> 30 mg/24 h), the increase of serum creatinine, the decrease of creatinine clearance and the decrease of glomerular filtrate [30]. 30% of patients suffering from T2D and diagnosed with microalbuminuria, develop chronic renal disease in the absence of a treatment, and 20% of renal disease patients progress to more advanced stages of renal impairment [30].

Many studies have shown that albuminuria is not a parameter of the progression of diabetic nephropathy towards renal impairment. The predictor for the development of nephropathy is serum creatinine, which must be included in routine measurements of the diabetic patient [31]. All diabetics should be considered as potential patients with renal impairment. The administration of intravenous non-steroidal anti-inflammatory drug will be avoided [32]. Protein restriction is recommended for all patients with microalbuminuria (< 0.8 g/kg body weight per day; 10% of daily caloric intake) [33,34], but recent data question the beneficial effect of this restriction [35].

Diabetic Retinopathy

Diabetic retinopathy is the result of pathological vascular retinal changes. Clinically is classified as: nonproliferative diabetic retinopathy (progresses from mild to moderate and severe abnormalities) and proliferative diabetic retinopathy (characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous) [36,37]. From the total of patients with diabetic retinopathy 10-15% are patients with T1D and 85-90% are patients with T2D [38].

The incidence of visual impairment was analysed in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) on 2364 patients, during 20 years (1980-2000). The

patients were divided into two groups: group 1, patients with DM, under 30 years of age and group 2, patients over 30 years of age; the last mentioned group was subdivided into: patients that were treated with insulin and patients that no insulin was administrated. Impaired vision was divided into four categories, ranging from healthy to blindness. Examination of patients was done at the beginning of the study, at 4 years and at 10 years, to analyze the diabetic retinopathy incidence and prevalence. The incidence of all types of retinopathy, in diabetic people, with a start before 30 years of age, measured at 4 and at 10 years, is 59%, respectively 90%, and the incidence of diabetic retinopathy is 11%, respectively 30%. The incidence of all types of retinopathy, in diabetic people, with a start after 30 years of age, analyzed at 4 and at 10 years, is 34-47%, respectively 67-80%, and the incidence of diabetic retinopathy is 2-7%, respectively 10-23% [39,40].

Diabetic retinopathy is characterized by microaneurysms, hemorrhages, exudates, venous changes, formations of new vessels and retinal spots. It may involve the peripheral retina or macula, or both [26,41]. High blood pressure is a significant risk factor in the occurrence of retinopathy in people with T1D and T2D. UKPDS Study (The UK Prospective Diabetes Study) proved that the risk of developing retinopathy in diabetic patients with an average BP of 154/87 mmHg is 47% higher than for diabetic patients with an average BP of 144/82 mmHg [26].

The patient should be informed about the importance of the ophthalmologic examination, and that an early laser treatment prevents the risk of visual loss [26,42]. For prevention of diabetic retinopathy, optimal levels of blood glucose and BP are recommended to be maintained [26,43].

Diabetic neuropathy

Diabetic neuropathy is defined as a "neurological disorder, clinical or subclinical, common in diabetic patients, in the absence of other neuropathic causes that is characterized by manifestation of the component somatic and / or autonomic of nervous system" [44].

The prevalence of peripheral neuropathy is 16.8-26.4% for DM patients and 2.9-4.9% for non-DM patients, meaning a relative risk of 6 times higher for developing peripheral neuropathy in patients with DM. An important factor in the pathogenesis of diabetic neuropathies is the duration of diabetes, which is 6-8% at the onset of diabetes, 20% at 10 years and 50% at 25 years after onset [44].

In a cross-sectional study, the prevalence of diabetic autonomic neuropathy considered to amend two of the six tests was 25.3% in T1D patients and 34.3% in T2D patients, and the modification of three of the six tests was 16.8% in T1D patients and 22.1% in T2D patients [44,45].

The clinical manifestations are varied and progressive: tingling, burning, muscle weakness, lack of coordination, changes in mobility, loss of ability to detect pain, temperature, dry skin, cracks in the foot, bone deformities, severe pathology of the nails. In patients with DM an annual sensory examination is required. Inexpensive methods of sensory testing are: the monofilament sensory testing (testing protective sensitivity) and tuning fork test (vibration sensitivity testing). Differential diagnosis with other neuropathies of various causes must be considered: alcoholism, vitamin B12 deficiency, hypothyroidism, vasculitis.

Diabetic foot

Diabetic foot includes a group of foot problems in patients with diabetes, in which neuropathy, ischemia and infections lead to

tissue damage and ulceration that can lead to amputation. Epidemiological dynamics of ulceration and amputation in diabetic patients is worrying. The general prevalence of ulcers in DM persons ranges from 4% to 10%, with an annual incidence of 1% to 4,1% [46]. Incidence of all forms of lower extremity amputation ranges from 46.1 to 9600 per 10^5 in the population with diabetes compared with 5.8-31 per 10^5 in the total population. Major amputation ranges from 5.6 to 600 per 10^5 in the population with diabetes and from 3.6 to 68.4 per 10^5 in the total population [47]. In non-diabetic individuals the major cause of leg amputation is chronic arterial arteriosclerosis obliterans.

The treatment of diabetic foot is complex and involves both the diabetic patient and a team of specialists. Litzerman et al. found in a randomized study on 352 diabetic patients that the intervention group which received regular foot care had fewer foot injuries [48].

Erectile dysfunction

Erectile dysfunction (ED) is defined as "the inability to develop and/or maintain a penile erection sufficient for a satisfactory sexual performance" [49]. A variety of diseases are causing erectile dysfunction, including DM. In fact the prevalence of erectile dysfunction is three times higher in diabetic patients (28%) than non-diabetic subjects (9.6%) [50]. The prevalence of erectile dysfunction, in DM patients is 15% at the age of 30 years and 55% at the age of 60 years [49,50]. DM induces erectile dysfunction by a number of several pathophysiological mechanisms: changes in mental behavior, androgen secretion, peripheral neuropathy, impaired of the endothelial function and the contractility of cavernous muscle.

Epidemiological studies on the prevalence of erectile dysfunction in diabetic patients are not very conclusive and reliable, due to the fact that prevalence is influenced by the sensitivity and specificity of the methods used for determining ED: some studies were based on hospital admission sheets, others on anonymous questionnaires, others based on direct queries addressed to diabetic patients (with sincere affirmative or negative answers). The location and the scale of a study are very important in highlighting the prevalence of erectile dysfunction (ED). Siu et al. studied 500 Chinese diabetic men (97% with T2D) registered at a single medical clinic in Hong Kong during 1999, and found the overall prevalence of ED to be 63.6%. In contrast, Fedele et al. who studied 9.756 diabetic men (86% with T2D) selected from 178 diabetes centers in Italy, found that only 37% reported ED, considerably less than in the Chinese study [50].

Complications of DM are associated with an increased risk of erectile dysfunction. Erectile dysfunction negatively affects the quality life of both the patient and his partner/s. A study of diabetic complications in diabetic men orederd these complications according to their importance to the people indicated the following ranks: kidney disease, blindness, erectile dysfunction, hypertension, infections of the foot, migraines. These diabetic men prefer to pay more money on treatments in order to avoid ED, compared with paying money againstany other complications of diabetes [50].

Psychological effects of diabetes

Diabetes mellitus, as any other disease, implies a psychological or psychiatric distress manifested more or less obvious, especially according to the age of the affected person and then by professional familial and economic status.

If in other conditions/diseases, total healing might be possible, a diabetic patient understands that for him healing is not possible, but rather

diabetes can be controlled on the long term by diet, adequate nutrition, adequate exercise, medication, physical equilibrium, maintain blood sugar within normal limits, etc. As every person is different, also the psychological manifestation of the disease is different: from the denial of the disease to rebellion, acceptance, understanding and treatment administration, to anxiety, depression and personality disorders. Every person diagnosed with diabetes should receive moral support, necessary to recognize the disease and coexist with it. The current medical trend, encouraged by the large pharmaceutical industry is to stabilize as quickly as possible the organic function, but without support for the psychological function. All of these lead to a spiritual and emotional imbalance, which carry on serious consequences of the disease.

Many diabetic centers and foundations have been created specifically to support the psychological side of diabetes. They organise familiarization, integration and communication sessions, cultural activities and games, and various professional conversion programs or for the development of personal skills.

Conclusions

Glycemic control is associated with a reduced risk for the microvascular and macrovascular complications of diabetes mellitus. Early detection of microvascular and macrovascular complications and implementation of appropriate treatment strategies will reduce the risk for adverse outcomes from these complications.

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