Determinant Factors of Cardiovascular Mortality in Type 2 Diabetic Patients: literature review

Gina Botnariu¹,²*, Diana Bulgaru-Iliescu³

Abstract: Diabetes mellitus represents a very important cardio-vascular risk factor which produces severe myocardial and vascular lesions with lethal effect. Due to extended lesions, diabetes mellitus represents the ⁶ᵗʰ cause of death in the world. Diabetes mellitus induces injuries in all kind of vessels and cardiac nervous fibers. The cardio-vascular prognosis in diabetics without coronary artery disease is the same with a non-diabetic person with a previous myocardial infarction. Risk of death due to cardiovascular events is increased in diabetics with associated comorbidities: arterial hypertension, obesity, dyslipidemia, smoking, cardiac autonomic neuropathy. Good metabolic control may prevent the appearance of vascular complications, but medical treatment should be adapted to avoid lethal hypoglycaemia. Diabetes mellitus has a continuously increasing incidence, justifying a leading cause of death, peripheral and cerebral artery disease.

Key words: cardio-vascular risk, cardio-vascular mortality, diabetes mellitus

Diabetes mellitus represents the top sixth cause of death in the world because of the cardio-vascular complications that it causes during its evolution, (1). Numerous epidemiological studies have proved that the increased incidence of cardiovascular complications is mainly caused by atherosclerotic lesions at the level of the large vessels, to which lesions of the capillaries and of the nervous fibers are associated. In the medical literature, DM represents an independent cardiovascular risk factor (2, 3).

The impact of chronic hyperglycemia on the myocardium and the coronary vessels is extremely strong, leading to complex endemic lesions, to which the lesions of the myocardium nervous fibers can be added. The presence of type 2 diabetes mellitus increases the risk of coronary disease 2 to 4 times. A study carried out by Haffner and his collaborators proved that the cardiovascular prognosis in the case of a diabetic with no history of coronary disease is the same as in the case of a non-diabetic, but who has already has a myocardial infarction (4, 5).

The HOPE study shows that 510 persons with type 2 DM, with no previous cardiovascular events, but who associated one or more risk factors, had an annual rate of coronary events of 2, 5% and that showed that DM patients who also have cardiovascular diseases have a relatively higher rate for developing cardiac complications and events rather than persons without DM (6, 7, 8, 9).

The prevalence of cardiovascular risk factors in the case of adults with DM in the USA was also proved by the NHANES study carried out between 1971 and 2000 and they were represented in

*)Corresponding author: Associate Professor, University of Medicine and Pharmacy “Gr. T. Popa” Iasi, E-mail: gina_botnariu@yahoo.com; mobile: 0722373288
1) University of Medicine and Pharmacy “Gr. T. Popa”, Iasi, Str. Universității Nr. 16
2) University Hospital “St. Spiridon” Iasi, Clinic of Diabetes, Nutrition and Metabolic Diseases, Bd. Independentei Nr. 1
3) Institute of Legal Medicine Iasi
descending order by the increased LDL cholesterol, blood pressure above 146/86 mmHg and smoking (10, 11).

The risk is higher in the case of patients with metabolic syndrome because of the factors associated to diabetes. The same high risk also exists in the case of type 1 diabetic patients, despite the young age when the metabolic disease appears (12). The risk of developing a cardiovascular disease in the case of DM patients increases with the age and it is higher in the case of men than in the case of women (13, 14).

The Honolulu Heart Programme showed that the risk of death in the case of diabetics is 1,5-1,7 higher because of the development of silent myocardial infarction, a specific form which is caused by the association of cardiac autonomic neuropathy, which does not allow the recognition of the anginal pain in due time (15).

Besides the well-known atherosclerotic pathology (ischemic cardiomyopathy, with its forms - myocardial infarction, angina pectoris, silent myocardial ischemia, sudden death), DM patients can also develop another form of cardiac disease, called “diabetic disease of the cardiac muscle” or diabetic cardiomyopathy, which involves diffuse myocardial damage with undamaged coronaries (OMS 1977). In a statistical analysis on 37 clinical studies (16), which occurred between 1996 and 2005 and dealt with cardiovascular mortality, it was shown that the presence of type 2 diabetes mellitus doubles the risk of lethal coronary events and it is much more important in the case of women than in the case of men. The incidence of fatal events with a cardiovascular cause was of 5,4 % for persons who also had type 2 diabetes (vs 1,9%) and it was higher in the case of women (7,7% vs 4,5%).

Anatomopathological lesions characteristic to cardiovascular disease in diabetes.

The serious damage of the cardiovascular axis in the case of diabetics is caused by the generalized nature of the disease. The anatomopathological cause of diabetic macroangiopathy is atherosclerosis. There is no modification specific to diabetes, but just an increase in the extension and the distribution of damaged vessels. In the case of diabetes the atherosclerotic process is more extended for the distal arteries, it appears more often and it progresses more quickly.

Lesions of coronary arteries: in the Honolulu Heart Programme (15), the necropsy carried out on diabetics showed that there were more atherosclerotic lesions at the level of the coronaries than in the case of non-diabetics. 91% of the diabetics considered to have undamaged coronaries actually have coronary lesions which concern at least one major trunk, and Hamby pointed out the predominance of tri-truncal lesions in the case of diabetics.

Coronary atherosclerosis in the case of diabetics is diffuse and severe and the atheroma plaque can unexpectedly lead to breakage, because of the content rich in lipids, macrophages and thrombi. In the case of diabetics with unstable angor, most atherosclerotic lesions have multiple ulcerations and they are associated with thrombi in the interior of the coronaries. Consequently, the myocardial infarction can also appear in an area with reduced stenosis.

Atherosclerosis can often appear at the distal level on the coronary arteries, which makes difficult the unblocking method through angioplasty with stent and even through by-pass. The development of collateral circulation is more reduced in the case of diabetics (18).

Lesions of peripheral arteries (19, 20, 21): in the case of diabetics there is an important vascular inflammatory component with a powerful influence on the fibrinolysis process and a decrease of the muscular tonus. The vascular modifications can often be present before the diagnosis of the diabetes and they worsen according to the duration of the metabolic disease and to the precarious long-term medical examination. An early diagnosis of the peripheral arterial disease allows preventing the extension of damage to the whole inferior limb.

Peripheral arterial lesions in the case of diabetics have certain characteristics in contrast with non-diabetics, and therefore they are more serious: they are mainly distally located; this frequently leads to stenoses of the popliteal artery or to the emergence of the arteries located below the knee, the anterior or the posterior tibial artery or the peroneal artery. The damage of the distal
vessels in the inferior limbs limits the development of the collateral vessels and reduces the chance for revascularization. Intimal calcifications can diminish the precision of certain diagnosis tests. The peripheral arterial disease affects approximately 20% of the adults over 55. 20-30% of the persons with symptoms of peripheral arterial disease are estimated to have diabetes too. The prospective study FDS (Freemantle Diabetes Study) showed that in the case of diabetics the peripheral arterial disease represents a major risk factor for death caused by cardiovascular events.

Lesions of cerebral arteries (22, 23): cerebrovascular accidents (CVA) is the top 3rd death cause in the developed countries. Diabetes is an independent risk factor for the ischemic CVA, and the mortality is higher in the case of diabetics than in the case of non-diabetics and they can develop much more serious disabilities which require a longer period of recovery. Diabetics particularly develop cerebral infarction on larger areas and the risk of recurrence is bigger (15,2 %).

The diabetes mellitus remains a risk factor for the small artery occlusive disease, which also explains lesions of the lacunar infarction type detected at necropsy. In the case of diabetics who have already suffered from a myocardial infarction, the risk of developing a CVA increases from 1, 7% to 4, 5% in the first two weeks and it gradually decreases with the time (23).

Risk factors that increase the incidence of cardiovascular mortality in the case of type 2 diabetic patients

The data taken from the medical literature in the last 5 years have shown that the appearance of micro and macroangiopathic lesions is inversely correlated with the degree of metabolic control. In the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) which lasted 3, 4 years and which involved 10521 type 2 diabetic patients, the post-hoc analysis of the data showed that glycosylated hemoglobin A1c is independently correlated with cardiovascular mortality.

The values of the HbA1c higher than 7% were strongly correlated with cardiovascular mortality (24). In order to reduce microvascular complications of type 2 diabetic patients, the glycemic control is one of the fundamental factors, but, since in the case of these patients comorbidities are often associated, a strict medical examination for reducing cardiovascular complications is still debatable (25).

The decision on the degree of metabolic control has to be individualized for each patient, and the potential benefit of reducing the incidence of nephropathy is debatable compared to the risk of hypoglycemia. The data obtained 10 years after the UKPDS study was finished showed that in the case of newly diagnosed type 2 diabetic patients the very tight glycemic control is efficient when it come to long-term prevention of macrovascular disease and this led to the idea that reducing glycemia in order to lower the cardiovascular risk is efficient in the case of persons with as short period of diabetes (25). The new results obtained from the great trials ACCORD, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) and VADT (Veteran Affaires Diabetes Trial) showed that the effects of maintaining a low glycemic index on micro and macroangiopathic lesions have to be separately considered.

A good metabolic control has positive effects, especially because it prevents nephropathy, whereas in the case of macroangiopathy, the global cardiovascular risk needs to be taken into account (26). In the ACCORD study which focused on the impact of the metabolic control on the cardiovascular risk in two groups, a group with standard treatment and another one with intensive hypoglycemia treatment, it could be noticed that the annual mortality rate caused by cardiovascular events accelerated by severe hypoglycemia was higher in the second group (1,14% vs 1,42%) (27). The possible explanations offered were the induction of myocardial ischemia and of fatal arrhythmias during the episodes of hypoglycemia, especially those which were not recognized by the patient because of the co-existence of the autonomic neuropathy.

The same study showed that, by doing a simultaneous electrocardiogram and a continuous monitoring of glucose on 19 patients, in the case of the patients with coronary heart disease receiving insulin treatment there were 4 episodes of myocardial ischemia and 10 of angina pectoris
during the symptomatic hypoglycemia. During 28 episodes of asymptomatic hypoglycemia there were myocardial ischemic changes (26, 27, 28). In some other studies quoted in 27 there were extensions of the QT interval a possible indicator of arrhythmia. Steven et al (29) examined 700 diabetic patients hospitalized for unstable angor or non-Q myocardial infarction.

He noticed that the patients who underwent at least one episode of hypoglycemia during their hospitalization had a two-year longer fatal risk than the patients who had no hypoglycemia. Another study, an observational one, carried out by Ollofson et col. on 13087 type 2 diabetic patients who were overweight or obese and with cardiovascular disease, showed that the cardiovascular risk and the total mortality increases with 15% and 27% respectively for any increase of the body mass index with 5 units (30). The rate of fatal cardiovascular events is increased in the case of smoker patients (22%) in contrast with non-smokers (31).

Mechanisms of death in the case of diabetic and cardiovascular patients

Medical studies based on autopsies have proved that in the case of diabetic persons, the coronary atherosclerosis lesions are extended, diffuse and they are predominantly distally localized on more vessels; atherosclerotic plaques with multiple ulcerations lead to thromboses, which frequently accelerates the extension of the infarction areas and favors early complications, especially the mechanical ones (32, 33).

The acute coronary syndromes represent the most frequent death cause in the case of diabetics both in the immediate post-infarction period and later on after the occurrence of the acute event (34). The acute period is predominated by electrical complications: rhythm disturbances, blocks of varying degrees generated by the background ischemia, dyselectrolytemias, increased serum levels of catecholamines, lipolysis, but also the exaggerated mobilization of free fatty acids as a consequence of the rechannelling operations (34).

The extension of the myocardial infarction through multiple vascular diseases accelerates the appearance of left ventricular failure, but also of the cardiogenic shock (a loss of more than 40% of the left ventricular mass) and they are death causes in the first hours of occurrence of a myocardial infarction (34).

Mechanical complications in the case of diabetics are frequent mainly in the first week when the myocardial infarction occurs and they are responsible for approximately 15% of deaths. The main mechanisms include the production of the acute mitral regurgitation through papillary muscle rupture, ventricular septal rupture, myocardial wall rupture and left ventricular wall aneurysm (34). Thromboembolic complications are described in autopsies in approximately 20% of the cases which shows that, from a clinical point of view, the disease is underdiagnosed. Left ventricular parietal thrombosis, which is frequently accelerated by a previous extended myocardial infarction, causes cerebral accidents which accelerate death. Pulmonary embolism is a frequent death cause, being favored by deep-vein thrombosis and by right atrial thrombosis (34, 35).

Conclusions: The generalized character of the lesions induced by chronic hyperglycemia explains the severe vascular damage of the big vessels, as well as of the capillaries and it often makes that the clinical diagnosis of the cardiovascular emergencies be difficult. The association of chronic hyperglycemia with other risk factors-hypertension, obesity, dyslipidemia, smoking-worsens the long-term prognosis and it accelerates the evolution towards life-threatening cardiovascular events.

The data collected from the medical literature in the last 5 years reveal the importance of metabolic control in preventing the occurrence of cardiovascular complications and that the anti-diabetes treatment must be adapted according to the patient’s status in order to avoid life-threatening hypoglycemia. Nowadays, diabetes is a disease with growing incidence, with a serious vascular impact and it occupies an important place among major death causes worldwide.
References

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