PREDICTIVE MORTALITY RISK FACTORS IN DIABETES MELLITUS

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REZUMAT

Principala cauză de deces la pacienții cu diabet zaharat (DZ) este de natură cardiovasculară, aceştia prezentând un conglomerat de factori de risc (FR). Chiar după ajustarea pentru ceilalți FR, diabeticii rămân cu un exces de risc pentru BCV de 75-90%., ceea ce sugerează că DZ este un FR cardiovascular independent. Riscul cardiovascular indus de FR clasici este accentuat de DZ și aceasta are un efect adițional pe mortalitate. Insuccesul în obținerea unui control glicemic adecvat, adăugat altor FR, face imposibilă reducerea morbidității și mortalității cardiovasculare la pacienții diabetici, așa cum au arătat numeroase studii. Foarte adesea, riscul crescut de ateroscleroză este incriminat în augmentarea mortalității la pacienții diabetici, deși simpla existență a plăcii de aterom nu este suficientă, procesul fiind mult mai complex, contribuind la apariția evenimentelor cardiovasculare acute, cum ar fi angina instabilă și infarctul miocardic. Prevenția și tratamentul adecvat al factorilor de risc predictivi pentru mortalitatea în DZ, prin modificarea stilului de viață, ameliorarea controlului glicemic, normalizarea tensiunii arteriale și a lipidelor serice contribuie la reducerea morbidității și mortalității cardiovasculare la acești pacienți.

Cuvinte cheie: diabet zaharat, factori de risc cardiovascular, mortalitate, ateroscleroză

ABSTRACT

The principal cause of death in patients with diabetes mellitus (DM) is cardiovascular as these subjects display a plurality of risk factors (RF). Even after adjustment for the other RF, diabetics are left with an excess of risk for CVD of 75-90%., thus suggesting that DM is an independent RF for cardiovascular diseases (CVD). Cardiovascular risk determined by the classical RF is enhanced by DM, and this has an additional effect on mortality. The failure to obtain a proper glycemic control, added to the other RF, has lead to the impossibility of reducing cardiovascular morbidity and mortality in diabetes patients, as numerous studies show. Very often, the increased risk of atherosclerosis is held responsable for the high mortality in diabetes patients, though solely the existence of the atheroma plaque is not sufficient, the process being much more complex, contributing to the appearance of acute cardiovascular events like an instable angina and myocardial infarction. The prevention and adequate treatment of the risk factors predictive for mortality in DM, through lifestyle changes, an improved glycemic control, normalization of blood pressure and lipid levels contribute to a decreased cardiovascular morbidity and mortality in this group of patients.

Key Words: diabetes mellitus, cardiovascular risk factors, mortality, atherosclerosis

INTRODUCTION

The prevention and adequate treatment of the risk factors (RF) predictive for mortality in diabetes mellitus (DM) through lifestyle changes (medical education, daily physical activity, smoking cessation, an appropriate diet), an improved glycemic control checking, blood pressure (BP) and dyslipidemia treatment contribute to the decrease of morbidity and cardiovascular mortality.[1]

The principal cause of death in patients with DM is of cardiovascular nature, studies indicating as major factors for cardiovascular disease (CVD) smoking, high blood pressure and dyslipidemia. Cardiovascular risk (CVR) induced by these RF is enhanced in DM, and this has an additional effect on mortality. The failure of obtaining a proper control, over RF, has lead to the impossibility of reducing morbidity and cardiovascular mortality in diabetes patients, as numerous studies show.[2,3]

Very often, the increased risk of atherosclerosis (ATS) is considered the major culprit for the high risk of mortality in DM patients, though only the existence of the atheroma plaque is not sufficient, the process being much more complex, contributing to the appearance of acute cardiovascular events such as unstable angina and myocardial infarction (MI).

Persons suffering from DM show a plurality of RF, the excess of adjusted risk being greater, compared to that of nondiabetics, what suggests that DM is an independent RF for CVD.[4,5] Even after adjustment

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to the other RF, diabetics are left with an excess of risk for CVD of 75-90%.6 Not all cardiovascular RF (smoking, arterial hypertension, increased total cholesterol, low HDLc) are also predictive factors of mortality, a statement which is also upheld by a Finnish study, conducted in elderly persons with DM as well as by the Verona study.[7,8]

Predictive RF of mortality in patients suffering from DM are classical or specific.[9] (Table 1)

Table 1. Risk factors that predict mortality in DM.[9]

Classical	Specific for D.M.
Age and sex	Duration of D.M.
Dyslipemia	Age at the outburst of D.M.
Arterial hypertension	The seriousness of the disease
Overweight/obesity	The degree of the glycemia testing (a jeun, HbA1c)
Smoking/life style	The instability of the glycemia testing/hypoglicemia

CLASSICAL RF

Age greater than 45 in men and above 55 in women is the most important predictive mortality; moreover the risk is much higher between 65 and 74 years.[10] After menopause the CV mortality is higher, thus suggesting the protective part played by the female sexual hormones in the development of ATS.[1]

Dyslipidemia

The UKPDS has established the RF involved in the appearance of CVD: high LDL cholesterol (LDLc); a high total cholesterol (TC), a low HDL cholesterol (HDLc), high blood glucose values, arterial hypertension and smoking. The lipid profile of a diabetic person is described as follows:[11,12]

- The TC concentrations similar to that of non diabetics, but having a different HDLc composition, with a lower concentration of the big antiatherogenic particles;
- An important factor in the appearance of ATS, a marker of CVR, is the high level of cholesterol, especially of that which is part of the lipoproteins with low density (LDLc);
- The value of over 60 mg/dl of HDLc is a protecting factor against ATS, its low value being an important cardiovascular RF in DM;
- High concentrations of tryglicerides; their role in the appearance of ATS is debatable, they are present in the composition of lipoproteins with very low density (VLDL) which supply very aterogene remnants. There are also opinions supporting the role of TG as a marker for ATS.

In patients who have suffered a MI, the TC values, as well as those of LDLc, are RF for recurrent coronary events.[13]

The first intention of the treatment of dyslipidemia, in all patients with DM and CVD, are statins because they reduce TC and LDLc, and increase HDLc. The Scandinavian Simvastatin Survival Study (4S) and Cholesterol and Recurrent Events Study (CARE) show that, in diabetics, the benefits of statines are similar, or even greater than in non diabetics.[14,15] The mortality in diabetic patients was 43% lower compared with 29%, in the case of non diabetics (4S).[14]

In the CARE study, the treatment with pravastatine has resulted into a 24% reduction of coronary heart disease and non fatal MI.[15] After adopting an appropriate diet, at a TC value of 5.2 mmol/l, a statin will be chosen; if the rising of TG continues, fibrates will be preferred; the simultaneous rising of both TC and TG, needs an association of statin and fibrate. Large clinical studies uphold that, the administration of statines, in case of a TC smaller than 6.2 mmol/l, has no benefits on the consecutive CV events or an CV mortality.

Watching 35 years the evolution of the RF and their influence on CV morbidity and mortality (the Framingham study), lead to the conclusion that, there is a greater tendency of LDLc reduction in diabetics, as compared to nondiabetics, as a consequence of the growing number of treated patients, though the percentage of those who have achieved the targeted objectives was very low (the same results are revealed also in former studies, e.g NHANES).[16]

Arterial hypertension is a RF for CVD, the rise of the risk is connected to the increase of the BP values; the mortality and stroke in DM patients falls, if BP values are controlled.[1,17] When patients with CVD suffered an MI, the presence of a arterial hypertension represents a major RF for the appearance of other consecutive CV events.[18]

According to ADA, the BP treatment target in DM patients is 130/80 mm Hg, and even lower in patients with altered kidney function.[19,20] Many studies indicate, as first choice, ACE inhibitors, very beneficial in patients with DM, both because of their neutral metabolic effect (no effect on carbohydrate and lipid metabolism), and because of their CV benefits: an efficient lowering of BP, reduce the risk of the appearance and development of microvascular complications in diabetics, and promote a higher survival period in patients with CVD.[21-23] At the same time, ACE inhibitors hinder the development and progression of renal excretion of abumine, thus contributing to reducing CVR.

Obesity is a RF for DM and a vast array of cancers and it is associated with a reduced life expectation. Obesity, especially the abdominal one form, is an important RF for DM, strongly connected to the other cardiovascular RF (hypertension, dyslipidemia).[1] The relationship between the body mass index (BMI) and mortality is represented by a curve, with the lowest mortality at a BMI under 25 kg/m^2; the risk rises with a BMI over 25 kg/m^2 and, over 30 kg/m^2 the curve becomes very steep.[25] The lowering of the BMI leads to a better glycaemic control, also a better BP an associate dyslipidemia, thus resulting into a reduced general risk of the diabetic patients.[1]

Comparing persons with normal body weigh with obese persons of the same age and sex, the latter (1st degree obesity) have a death rate 2-8 times higher, those with 2nd degree obesity a rate 4-7 times higher, while those with 3rd degree a rate of 9 times higher.

In the case of heart failure the link between obesity and mortality is not yet established as there have been controversies concerning the benefit of losing weight in subjects with this condition. Many epidemiologic studies have shown (among which the Framingham study), paradoxically, a decrease in survival through the loss of weight (a similar effect have also correction of other RF).[24,26]

After adjusting to age, sex, IMC, smoking and other RF, the mortality rate was higher at patients who have lost weight (with 44% in the case of men and with 38% in women), irrespective their initial weight, probably due to the fact that the loss of weight was unintentional.[24] The situation is changed when the loss of weight is intentional, the data obtained by the American Cancer Society Prevention Study I pointing to a 25% cut of the CV mortality and a 28% of the CVD.[27] In the case of type 2 DM, the intentional loss of weight determines a lower rate of mortality, by reducing BP values, improving the lipid metabolism, and decreasing the circulant insulin level, all of them leading to a reduced risk of CVD and cancer, and to lower levels of estrogen and inflammatory cytokines. Besides we can speak about a direct diminuation of cancer risk, the improvement of thrombotic profile, reduction of the oxidative stress and of sleep apnea.

Smoking contributes to the rise of CVR thus being a RF for all causes of mortality, quitting is one of the most important and approachable methods for prevention of ATS.[1,28] It also disturbs the lipid profile, causing the rise of CT and VLDL, the decreased of HDLc and, the alteration of the sensitivity to insulin.[29] In patients with DM, smoking (through a yet unknown mechanism) worsens the glycemic control; the risk of micro and macrovascular complications grows; in patients with type 1 DM, smoking rise urinary albumin excretion (after banning smoking, the albumin level is that of nonsmokers, also through the improvement of the glycemic control), as well as the risk of nonproliferative diabetic retinopathy; the risk of diabetic neuropathy grows, a persistent effect also after giving up smoking; it hastens the risk of progression towards end stage diabetic renal disease; with patients on dyalisis, the persistence in smoking reduces the survival period.[30-34]

The mortality combined by associating smoking and DM is much greater than their sum or even multiplied.[35,36]. The mortality risk of smoking is equal or even greater than that produced by DM. A new concept, called "the equivalent in glucose of smoking" is under discussion now, with a view to giving a prevailing place to stopping this harmful habit, within the clinical management of DM.[35]

In a multinational WHO study, the authors evaluated the reduction of the death risk of any kind, dependind on the period which has elapsed since smoking was stopped: the highest risk was observed in long-term smokers (1.7 RR), then in those who had recently abandoned smoking (1. 5RR), compared with those who had abandoned smoking 10 years before (1.2 RR), and with the non-smokers (1 RR).[35]

Changing life-style through a large consumption of fruits and vegetables, avoidance of alcohol excess, doing physical activities at the tolerated level (walking, jogging, swimming, cyclism) are essential means to reduce mortality.

CVR is higher in person who have, in their family history, first degree relatives who have been diagnosed with precocious CD, men earlier than 55 of age, women than 65.[1]

DIABETES MELLITUS SPECIFIC RISK FACTORS

The duration of DM

The improvement of the glycemic control (evaluated by the value of HbA1c, fasting and postprandial glycemia), has reduced the risk of appearance of microvascular complications.[17] Milestone studies performed on patients with type 1 DM (DCCT) and type 2 DM (UKPDS) have proved the beneficial effect of bettering the glycemic control, on microvascular complications (retinopathy, nephropathy, neuropathy).[17,36-39] On the other hand, the worsening of the glycemic control, not only determines a higher risk of complications, but it also amplifies the effect of other RF, such as DM duration and microalbuminuria.[7,40] Some studies have

pointed out the growing importance of postprandial glycemia, as opposed to the fasting blood glucose, as a cardiovascular RF, and its role in the growing number of CV events.[41]

Many epidemiological studies have tried to establish a glycemic threshold for the increased CVR, showing that the risk of macrovascular complications progresses with the glycemic values, even within limits, which are under the values which justify a DM diagnosis. Though the improvement of the glycemic control has reduced atherothrombosis and CV events, the above mentioned studies have not proved a significant impact on the CV complications. DCCT has confirmed the very important part the glycemic control plays in reducing major CV events,and UKPDS asserts the improvement of the outcome of type 2 DM patients, by reducing complications and CV accidents.[17,39] In Stockholm Diabetes Intervention Studies, an intense glycemic control has reduced the thickness of the intima of the carotid artery, a marker of arteriosclerosis risk.[42] There are also contradictory data which show that the improvement of glycemic control does not influence CV mortality and morbidity.[43,44]

In the time interval between the biological and the clinical DM onset, the mortality in future patients is higher, compared to the mortality in already diagnosed patients, treated for DM.[45] If we do not take into consideration the beneficial influence of the applied treatment on the reduction of the mortality risk, the duration of DM is a RF, which raises this risk.[45] The Wisconsin study has shown that, irrespective of the patient'age, the risk of death, especially of CV cause, is correlated to the HbA1c increase.[46] It has been established that, on a long-term basis, the degree of metabolic control expressed by the variation coefficient of the fasting glycemia (CV=DS/averagex1000) is correlated much better with mortality than the average of the fasting glycemia.[47]

The antidiabetic treatment is a marker of the disease and of the mortality risk, many studies trying to correlate the type of treatment and this risk. It seems that patients who have been treated by diet, have a lower mortality rate, as compared to those on oral antidiabetic drugs.[45,47,48] An appropriate diet implies the consumption of the large quantities of vegetables and fruits, mono- and polinesaturated fats, which provide vitamins, minerals and bioflavonides and reduce the ingestion of saturated and transnesaturated lipids, which raise the ATS risk. At the same time, sedentarism must be avoided (a factor favoring CVD) through moderate physical effort.

UKPDS has shown that metformin has considerably reduced mortality caused by MI,49 by lowering the insulin-resistance, improving associated RF (atherothrombosis risk profile, BP) and, by its effect on excessive body weight.[50]

A subject long discussed, and still controversed, is the role of insulin in promoting atherogenesis, some epidemiologic data showing the existence of a link between the plasma level of insulin and CD in nondiabetic, a hypothesis which has not been confirmed in diabetics.[51-53] At the same time, some studies have found a higher mortality in those treated on insulin, but its increase was not parallel to the dose of insulin (consequently, the relationship cause-effect could not have been proved).[10,54]

The predictive RF of atherogenesis and, implicitly, of CVR are: the inflammation markers (reactive C protein and fibrinogen) which in high concentrations are s associated with a risk of CVR (proved by clinical studies); a high Lp(a) with atherogenic role; hyerhomocisteinemia, a marker with a low predictive value and incompletely evaluated; the markers of the fibrinolitic function (PAI-1); insulin-resistance; microalbuminuria, a marker of generalized endothelial disfunction, continual, an independent RF of ATS, causing a 2-4 times increase of CV and general mortality; the emotional stress, which produces a growth in the oxygen consumption of the myocardis, by stimulating SNS, contributes to the triggering of acute vascular events; toxic factors- high intake of ethanol enhances the risk of CV mortality; the atmospheric pollution, through the particles resulting from burning, has direct toxic and proinflammatory effect, leading to a rise of CVR; the sleep apnea syndrome, leads to type 2 DM, hypertension, acute MI and stroke; diabetic retinopathy, associated with coronary subclinical pathology.[55-58] Its presence in patients with type 2 DM raises the risk of CVD, independent of other RF, supporting the role of the microvascular disease in the CVD pathogenesis in diabetics.

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