

Arterial Hypertension, Major Multiplier Risk Factor for Micro and Macrovascular Complications of Diabetes Mellitus

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Abstract

Hypertension and diabetes are the most frequent diseases that affect the world population, while cardiovascular morbimortality has seen some stagnation in the recent years, diabetes is on the increase both in number worldwide, but also in severity of complications. While both entities pose a significant risk, their association is by far on the long term from every point of view a serious health risk. The common denominator in this equation is atherosclerosis, which both diseases initiate, amplify and contribute to progression, but there is compelling evidence that these two when acting together increase several folds the cardiovascular risk. In this review we highlight some of the recent published work regarding the association between diabetes and hypertension with highlights on the microvascular and macrovascular complications.

Keywords: hypertension, complications, atherosclerosis, microvascular, macrovascular

Introduction

The guidelines of the European Society of Cardiology (ESC) published in 2018 brought a new guideline for monitoring, evaluation and treatment of essential and secondary hypertension. Compared to the previously published guideline, this guide brings some new modifications and concepts while

maintaining the classification according to the measured blood pressure values. For example, if in the previous guideline normal high blood pressure was not required to be treated (class III), in the present guideline it is recommended in the presence of a very high cardiovascular risk or coronary heart disease to initiate treatment even from this stage of normal high blood pressure (class IIb) [1].

The current population models of National Societies of Diabetes, Cardiology and other medical fields involved in the treatment of complications caused by high blood pressure, atherosclerosis and diabetes, as well as the World Health Organization in particular, predict in the short term a significant increase in the number of cases of diabetes, and in the medium term this forecast shows a slight

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reduction in growth. If in 1980 there were about 108 million patients in 2014, it reached a number of about 422 million, with a prevalence of 8.5% in 2014. By the year 2045 models predict a 50% increase in the current number of patients with diabetes, reaching around 630 million, of which about 70 million only in Europe. In Romania, the average estimate from 2017, in the age group 20–79 years is 1.78 million patients with limits between 1.1 and 2.2 million [2–3]. These figures are practically a population and epidemiological bomb, which automatically leads to increased pressure on health systems both in terms of costs and the prospects of aging population, with a direct impact on mortality and morbidity.

Hypertension and risk

The 2018 ESC Guideline automatically introduces the vast majority of middle-aged adults into the medium-risk group, with an average SCORE risk of between 1 and 5%, while diagnosed diabetes mellitus automatically increasing the risk, making the patient included in the high and very high risk classes high. If the hypertensive patient with diabetes has no complications and no other major risk factors are present with the exclusion of young type 1 diabetes patients, the risk is considered high with a SCORE risk calculated between 5–10%. If the same patient for example had diabetes with angiographically proven plaque with stenosis > 50% of the lumen or hypercholesterolemia or proteinuria he automatically presents a very high risk (> 10%) of cardiovascular events. This profile corresponds to diabetes with already established subclinical organ lesions [1]. Basically, it is noted that regardless of the complications that diabetes has already caused or if there are still no visible complications, the risk is much more increased from the beginning and the combination of diabetes and hypertension through the process of atherosclerosis that sometimes involves systemic forms is a combination that causes serious and most often fatal complications.

Recent studies

A recent meta-analysis of Emdin et al. [4] published in 2015 in the Journal of the American College of

Cardiology (JACC) based on a grant from the National Institute for Health Research (UK) showed some interesting results. Basically, the meta-analysis consisted of evaluating during the a period of 23 years, between 1990 and 2013, 4.6 million patients without diabetes and high blood pressure, who developed during this period one of these diseases, including in the final meta-analysis about 4.1 million of the 4.6 million initially identified. The results showed that those with a systolic blood pressure (SBP) higher than 20 mmHg and a diastolic blood pressure (DBP) with 10 mmHg higher was enough to be associated with a 58% and 52% higher risk of developing diabetes, respectively. (SBP hazard ratio: 1.58; 95% [CI] 1.56 to 1.59; DBP hazard ratio: 1.52; 95% [CI] 1.51 to 1.54). As the person aged and/or gained in body mass, the strength of this association decreased, but estimates were maintained even after initiating antihypertensive treatment even in association with statins. The relative risk of diabetes for a SBP greater than 20 mmHg than normal BP was 1.77. The diminished power of the association between the increase of SBP and the risk of diabetes observed in the case of increasing body mass or aging may be due to other factors involved, which makes the relationship not necessarily causal, but these results are based on a large cohort of over 4 million participants. The comparison with other studies that identified approximately the same results confirm the blood pressure - diabetes binomial. This lack of causality can be explained by the interference of other biological parameters or constants, for example the weak blood pressure control in the patients with hyperuricemia, data that suggested from the national study SEPHAR III (Study for the Evaluation of Prevalence of Hypertension and cArteriovascular Risk in Romania [12]).

Another meta-analysis published in 2010 in Lancet that included 102 prospective studies totaling approximately 700,000 patients showed that diabetes once adjusted for age, sex, smoking, blood pressure and body mass index carries a hazard ratio (HR) of 2 for ischemic coronary artery disease, a 2.27 fold increase for ischemic vascular attacks, a 1.56 fold increase for hemorrhagic vascular attacks and 1.73 fold increase for the rest of vascular events (combined), which accounted for more than 50,000 fatal and nonfatal vascular events [5].

In the LIFE (Losartan Intervention for Endpoint) study, a 20 mmHg increase in blood pressure

resulted in a 39% higher risk for diabetes (HR: 1.39; 95% CI: 1.25 to 1.56), and in the Women's Health study, hypertensive individuals had double the risk of developing diabetes compared to those with blood pressure values between 120 and 129 mmHg. (HR: 2.03; 95% CI: 1.77 to 2.32) [6-7].

Microvascular complications

Once cardiovascular risk is multiplied by association of diabetes and high blood pressure, this risk is mediated by complications. These complications are due to atherosclerosis and are divided into microvascular complications and macrovascular complications. The microvascular complications are those that lead to nephropathy and retinopathy, to mention two of the most affected organs, and the macrovascular ones frequently lead to cerebral infarcts, myocardial infarctions, amputations on atherosclerotic background or sudden cardiac death. Established diabetic nephropathy is characterized by increased glomerular pressure and clinically objectified since the early stages by albuminuria, which induces chronic lesions on the filter barrier. Changes such as thickening of the basement membrane, deletion of podocyte processes or mesangial expansion under the influence of pro-inflammatory signals are just a few of the mechanisms involved [8]. In this situation, diabetes alone would be sufficient to induce injury, but the association with uncontrolled blood pressure values has an exponential effect to the pathogenesis of nephropathy, even if only through pressure-hydrostatic mechanisms. There is a plethora of studies regarding chronic kidney disease in which the stage of dialysis replacement therapy can be delayed to some extent only by optimal blood pressure control without optimal diabetes control. Retinopathy, the main cause of blindness, has largely identical mechanisms with nephropathy. At the level of the retinal capillaries there is a decrease in the density of pericytes, acellular capillaries, the formation of advanced glycosylation end products (AGEs) and the formation of neovessel inflammatory stimuli [9].

One of the major complications of diabetes with perhaps the greatest impact on the quality of life is diabetic retinopathy. This condition is supposed to

affect over 90 million diabetic patients worldwide, to varying degrees, with an increasing trend. The proportion is between 30% and 50% depending on the populations studied [13], a recent meta-analysis of more than 20,000 type 2 diabetic patients reported a 35% proportion of this condition in this population in different degrees, with 7% proliferative diabetic retinopathy, macular edema 6.8% and approximately 12% patients with diabetic retinopathy at risk of visual acuity loss. Practically only about 10% of these patients had a form of uncomplicated retinopathy. This meta-analysis is interesting because in the case of diabetic retinopathy, the control of hypertension, dyslipidemia and hyperglycemia all contribute to reducing the severity of retinopathy. Hypertensive patients had a rate of diabetic retinopathy of 30.8% at systolic blood pressure <140/90 mmHg compared to those with values above 140 / 90mmHg, where the rate was approximately 40% [14].

Macrovascular complications

Regarding the macrovascular complications, the central mechanism is atherosclerosis based on the current concept of inflammatory atherosclerosis. This concept is based on the fact that a lesion of the endothelium under a chronic stimulus induces an inflammatory response that is self-sustaining, self-potentiating and producing atheromatous plaques. To plaque formation contributes platelet adhesion, impaired fibrinolysis, and hypercoagulability, which are increasingly evident as part of the inflammatory mechanisms in the diabetic vascular wall [10].

A study of approximately 1200 patients that followed the characterization of macrovascular lesions in diabetes mellitus and hypertension showed that the prevalence of macrovascular complications (atherosclerotic coronary disease, significant or insignificant carotid stenosis, cerebrovascular disease, peripheral arterial vascular disease, arterial arterial vascular disease) was 46.4%, (p <0.001) with a majority of individuals in the polyvascular arterial disease group and a predominance of the male sex. The authors defined as polyvascular arterial disease in this study any at least two pathological entities from those mentioned above [11].

The Pittsburgh Epidemiology of Diabetes Complications prospective study, which has tracked patients with type 1 diabetes for 25 years before age 17, has presented some findings that actually sum up the risk of diabetes in combination with other risk factors or if target organ damage develops. Basically, the 500 participants were divided into 5 groups, according to severity, duration of diabetes mellitus, albumin / creatinine ratio. The evolution duration of diabetes considered as a cut-off in this study for group division was 20.9 years. Two main conclusions are drawn from this study: the overall rate of cardiovascular events was 46.9% at 25 years and the Kaplan-Meier survival analysis showed that the group with the least complications still has a rate of cardiovascular events of over 25%, in stark contrast with the group with the most complications which presents almost 85% cardiovascular events [15].

Conclusion

Aging population, the increase of survival after cardiovascular events, the better palliative care have a paradoxical effect in patients with diabetes: an increase in the complications both in number and severity, that they present themselves with. The progression of chronic kidney disease, accelerated atherosclerosis, blindness, Alzheimer’s degenerative diseases and vascular dementia or peripheral arterial disease all rely on the complex physiopathological interrelationship, both directly and indirectly between diabetes regardless of its etiology and hypertension. .

It is necessary that the approach of these patients be multilevel, multidisciplinary and with rapid and correct interventions based on the calculation of risk scores, which unfortunately take into account only certain parameters, considering other factors as negligible, which in reality is most likely an incorrect approach.

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