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Hypertension and cardiometabolic disease

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1. ABSTRACT

Hypertension has a central role in cardiometabolic disease and is usually associated with metabolic disorders, such as insulin resistance, obesity, and dyslipidemia. Hyperinsulinemia may increase cardiovascular (CV) risk through its promotion of hypertension, which is possibly a result of chronic enhancement of sympathetic nervous system activity, stimulation of the renin-angiotensin-aldosterone system leading to increased renal tubular sodium reabsorption, modulating cation transport, or inducing vascular smooth muscle cell hypertrophy. The body mass index value is associated with hypertension, but additional analyses showed that the strongest link existed between visceral obesity and hypertension. In a cross-sectional study, we have already shown that pulse pressure (PP) amplification, heart rate (HR), and pulse valve velocity (PWV), but not augmentation index (Aix), are increased in patients with metabolic syndrome (MS). The basis of therapy for hypertension in MS lies in a changed way of life, involving caloric intake reduction, increased quality of food, increased physical activity, and medicamentous therapy. Such a therapy has a favorable impact not only on blood pressure (BP), but on all the components of MS, and is able to delay the onset of diabetes.

2. INTRODUCTION

At the beginning of the twentieth century cardiovascular (CV) disease was responsible for approximately 10% of all deaths. In the last hundred years, this Figure increased rapidly to 35 – 40% becoming the most common cause of mortality worldwide. CV disease occurs in susceptible patients in whom classical risk factors, such as hypercholesterolemia, hypertension, and diabetes have been present. However, it is important to emphasize that availability and popularity of very high caloric fast food, and the reduction in physical activity, epidemic of obesity began to grow at an alarming rate. Percent of overweight and obese has almost doubled in the past ten years. A cluster of risk factors including insulin resistance, central obesity, dyslipidemia, impaired glucose tolerance, hypertension and inflammation is associated with increased cardio metabolic risk that is now present in at least one quarter of the adult population.

Nevertheless, the problem with cardio metabolic disease is recognizing by the recommendations and this changes our view on the problem. It is well known that the Framingham Heart Study forever changed our approach to coronary

artery disease (CAD) by identifying major risk factors such as hypertension, smoking, hypercholesterolemia, diabetes and family history. Since then, countless other risk factors and markers of disease have been identified. In this manuscript, we cover many aspects of cardio metabolic risk factors and therapy as well.

3. ASSOCIATION OF HYPERTENSION WITH METABOLIC SYNDROME

3.1. Association of hypertension with insulin resistance

Cardiometabolic diseases represent a wide array of diseases which usually start with insulin resistance in early periods of life and progress later into conditions which can be identified clinically as metabolic syndrome, prediabetes, type 2 diabetes mellitus (T2DM), and CV disease. Metabolic syndrome (MS) is defined as a cluster of risk factors for CV disease and T2DM and involves elevated blood pressure (BP), dyslipidemia (high triglycerides and low HDL cholesterol), high fasting glucose, and central obesity.

Etiology of hypertension in cardiometabolic syndrome is complex and multifactorial. In a way, hypertension has a central role in cardiometabolic disease and is usually associated with a metabolic disorder, especially with insulin resistance, obesity, and dyslipidemia.

Reduced insulin sensitivity leads to compensatory hyperinsulinemia. Hyperinsulinemia may increase cardiovascular CV risk through its promotion of hypertension, possibly a result of chronic enhancement of sympathetic nervous system activity, stimulation of the renin-angiotensin-aldosterone (RAS) system thus increasing renal tubular sodium reabsorption, modulating cation transport, or inducing vascular smooth muscle cell hypertrophy (1-3).

Park *et al.*have reported in their clinical study the association of the baseline insulin level and onset of hypertension. High baseline and continuously increasing fasting insulin levels appeared to be independent determinants for the future development of hypertension during this 4-year follow-up study in normotensive, non-diabetic, healthy adults (4). However, this association is much stronger in younger patients, suggesting that the mechanism of onset of hypertension is different in the young compared to the old.

3.2. Obesity and hypertension

Epidemiological studies have demonstrated the association between obesity and risk of fatal and non-fatal CV events. The results of the Framingham study best illustrated this association, showing that obese men have the chance to live 6 years shorter, and women 8 years shorter than non-obese persons (5). Pathophysiological mechanisms linking obesity, CV disease, and hypertension are diverse and involve insulin resistance, diabetes, inflammation, and dyslipidemia. However, the real risk associated with obesity lies in the type of obesity. The large INTERHEART study (6) conducted in 52 countries showed the association of abdominal obesity with the risk of myocardial infarction for both genders, all ages, and all participant countries. Visceral obesity located intraabdominally and retroperitoneally carries a greater risk than subcutaneous obesity about the hips or lower limbs. A simple measurement of the waist circumference and waist-hip ratio can reveal abdominal obesity, but a true measurement of the quantity and localization of visceral fat can be performed nowadays with modern imaging modalities, such as nuclear magnetic resonance, or x-ray densitometry (magnetic resonance and x-ray densitometry have enhanced the anatomic compartmentalization of fat depots). In the Dallas Heart Study, the investigators characterized 903 obese, nonhypertensive participants, at baseline, by multiple biomarkers and by defining fat depots using magnetic resonance with proton-spectroscopic imaging and assessing lower body fat by dual energy x-ray absorptiometry (7). The study showed an association between the body mass index value with hypertension, but additional analyses showed that the strongest link existed between visceral (especially retroperitoneal) obesity and hypertension. This observation directly linked the type of obesity with its potential compressive effect on the kidney and suprarenal glands, which might disturb renal function, produce salt retention, or activate the pathways associated with increased renin excretion. These results confirm the necessity of using simple, practical methods to measure fat depots in epidemiological studies. Abdominal obesity, especially of visceral type, is directly linked to metabolic syndrome and one of its principal components.

3.3. Atherogenic dyslipidemia and hypertension

Hyperinsulinemia is frequently associated with dyslipidemia. The condition of insulin resistance and hyperinsulinemia is associated with high triglycerides. This is commonly accompanied by decreased high-density lipoprotein (HDL) cholesterol levels. Low HDL cholesterol is promoted by insulin resistance through diminished activity of lipoprotein lipase, which may result in excessive transfer of triglycerides from chylomicrons and very low-density lipoprotein (VLDL) particle from cholesterol esters from HDL particles thus reducing HDL-cholesterol (8). Although the level of low-density lipoprotein (LDL) cholesterol is similar to that in general population, LDL compositional differences may make these particles more atherogenic. Insulin resitance has also been

associated with this preponderance of small dense LDL particles, and it is the small dense LDL particle that has been suggested to be the more atherogenic LDL (9).

The San Antonio Heart Study (10) showed that higher levels of triglyceride and fasting insulin predicted the development of hypertension.

In the Physicians' Health Study (11), total cholesterol, non-HDL-cholesterol and HDL-cholesterol predicted the onset of hypertension in 3110 men without self-reported hypertension.

Dyslipidaemia characteristic of the MS predicts the development of hypertension during a 7-year follow-up of eastern Finnish men, independently of features related to insulin resistance (12).

How does dyslipidemia provoke the onset of hypertension? The mechanism has not yet been fully elucidated, but endothelial damage has certainly a major role in the process. Endothelial dysfunction is important not only in the onset of atherosclerosis and thrombosis, but in the onset of hypertension as well. Lipoproteins rich in triglycerides and LDL cholesterol have a toxic effect on endothelial cells, while HDL cholesterol has a protective role (13). Long-term endothelial damage increases peripheral vascular resistance, leading to arterial hypertension.

3.4. Hypertension and impaired glucose tolerance, impaired fasting glucose, insulin resistance and diabetes

Disorders of the glucose metabolism, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), often referred to as „pre-diabetes", reflect the natural progression from normoglycaemia to T2DM. IGT can only be recognized using an oral glucose tolerance test (OGTT): 2-hour post-load plasma glucose (2hPG) ≥7.8. and <11.1. mmol/L (≥140 and <200 mg/dL). IFT is defined using only the criterium of fasting plasma glucose of 6.1.-6.9. mmol/l (14).

The DECODE study showed evidence of an increased risk for coronary heart disease (CHD) in patients with abnormal glucose tolerance. The project involved 10 prospective cohort studies with more than 22,000 subjects. Death rates from all causes, CV disease and CHD were significantly higher in subjects with impaired glucose tolerance, whereas there was no difference in mortality between the subjects with impaired fasting glycaemia and those with normal fasting glucose (15). Fasting-glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycaemia. The oral glucose tolerance test provides additional prognostic information and enables detection of individuals with impaired glucose tolerance who have the greatest attributable risk of death (16).

A study of 63,443 relatively healthy men has detected IFT in 10,773 subjects (17%). The examinees with IFT had a higher body mass index, higher serum cholesterol and triglycerides, systolic and diastolic blood pressure (BP) than those with normal glucose levels. The relative risk of cardiovascular mortality after 8-year follow-up of individuals with moderate hypertension (systolic BP, 140-159 mmHg), compared to normotensive individuals, was very dependent on the glucose level: 2.9.7. (95% CI: 1.5.8. to 5.5.5.) for men with impaired fasting glucose, compared with 1.3.5. (95% CI: 0.8.4. to 2.1.8.) in those with normal fasting glucose (17).

IGT, IFT, insulin resistance and diabetes represent a spectrum of disorders that is associated with an elevated risk of CV complications (18).

While diabetes has been a well established CV risk factor, IGT, IFT and insulin resistance is emerging risk factors are also associated with MS as well as the development of diabetes. In general, IGT test is determined with an oral glucose tolerance test (OGTT), impaired glucose is detected by serum glucose after a fast and insulin resistance is suggested by an elevated fasting serum insulin levels.

The impact of overt diabetes and poor glycemic control on the risk of cardiovascular disease is well established in the literature. Among patients with type 2 diabetes, some studies demonstrated a significant increase in coronary artery disease (CAD) related death and coronary events associated with HbA1c levels of greater than 7 % compared with lower levels (18).

The UKPDS study evaluated a panel of proposed risk factors for CAD among patients with non-insulin dependent diabetes (19). In addition to increased levels of LDL cholesterol, decreased levels of HDL cholesterol, hypertension and smoking hyperglycemia as determined by glycated hemoglobin A1c (HbA1c) levels was a significant predictor for the incidence of CAD (19).

Another study demonstrated that hyperglycemia as detected by HbA1c was also a strong predictor of stroke in patients with T2DM (20).

In the Munich General Practitioner project several risk predictors for macrovascular mortality were evaluated among patients with T2DM (21). After follow up of 10 years, HbA1c was demonstrated to be a significant risk predictor for CV disease mortality.

In the study of diabetic patients in USA investigated the relationship of hyperglycemia to all cause and CV mortality (22). The study reported that while diabetes was itself a strong predictor of all cause mortality, patients with a baseline fasting plasma glucose experienced a 4.9. fold increase in all cause mortality and 4.7. fold increases in CV mortality (22).

More recent UKPDS study was designed to determine the relationship between hyperglycemia and the risk of macrovascular and microvascular complications in patients with T2DM. The investigators found a significant relationship between increasing HbA1c levels and the incidence of both macrovascular and microvascular disease [23]. Furthermore, they found that each 1% reduction in mean HbA1c was associated with a 14% reduction in the risk of myocardial infarction (23). In addition to hyperglycemia, microalbuminuria has also been shown to be a significant independent predictor of CAD related events in patients with diabetes (24).

Based on the large number of studies linking disorders of glucose metabolism to the incidence of CVD, the assessment of cardio metabolic risk factors should include consideration not only for overt diabetes mellitus, but also for other disorders on spectrum such as impaired glucose tolerance, impaired fasting glucose and insulin resistance.

3. 5. Hypertension and metabolic syndrome

The impact of MS and its components on hypertension is complex, and the values obtained with traditional brachial artery measurements can only partly show the impact of MS on macro-microcirculation. MS involves structural changes of arterioles and capillary rarefaction that in turn are associated with an increase in vascular resistance and a resultant increase in mean arterial pressure (MAP) (25). Within the macrocirculation (26), a similar process of vascular remodeling occurs and increases arterial stiffness, which favors an increase in systolic BP but also a decrease in diastolic BP. In MS, diastolic BP level is the result of 2 mechanisms, an increase of systemic vascular resistance, which tends to increase diastolic BP, and an increase of arterial stiffness, which is associated with low diastolic BP (27).

Modern BP measurement methods have shown that individuals with MS have macro-and microcirculatory dysfunction, even in the absence of diabetes and CVD macro-and microcirculatory dysfunction has an impact on arterial stiffness, disturbed wave reflections, and altered systolic BP and/or pulse pressure (PP) amplification. Aortic pulse wave velocity (PWV), an index of large artery stiffness, is highly dependent on age and mean arterial pressure (MAP) (28). Augmentation index (AI) is a measure of systemic arterial stiffness derived from the ascending aortic pressure waveform, an indicator of pressure wave reflections, and is influenced by the amplitude and timing of forward and backward travelling pressure waves. In addition to arterial properties, heart rate (HR), body height and gender are also important modulators of AI.

Measurement of the PWV is a surrogate of aortic stiffnes. PWV increases in MS in proportion to the number of MS criteria and increases with age more rapidly in patients with MS than in patients without MS for the same MAP (29, 30).

In a cross-sectional study, we have already shown that PP amplification, HR, and PWV, but not AIx, are increased in patients with MS compared with control patients without MS but of the same age, sex, and MAP(31, 32).

3.6. Therapy of hypertension in metabolic syndrome

Treatment of hypertension depends on the possible concomitant presence of MS and T2DM. Numerous factors, complex mechanisms and specific BP characteristics in these patients require a more complex therapeutic approach, affecting all the risk factors involved in the onset and progression of MS. Most patients with MS are obese and lead sedentary lifestyles. Urbanization and increased availability of unhealthy, cheap food, created the MS pandemic. The basis of therapy for hypertension in MS lies in a changed way of life, reduction in dietary sodium intake, involving caloric intake reduction, increased quality of food, increased physical activity, and medicamentous therapy. Such a therapy has a favorable impact not only on BP, but on all the components of MS, and is able to delay the onset of diabetes.

Observational follow-up trials of hypertension prevention (TOHP) have shown that in addition to BP reduction, a restricted sodium intake can reduce the long term risk of cardiovascular events (33).

Increased physical activity of MS patients reduces the risk of atherosclerotic cardiovascular disease. The mechanisms of favorable impact of physical activity are the consequence of its beneficial effect on BP values. A recent meta-analysis has demonstrated that endurance, dynamic resistance, and isometric resistance training lower systolic BP and diastolic BP, whereas combined training lowers only diastolic BP. BP reductions after endurance training were greater in groups of hypertensive subjects than in groups of pre-hypertensive subjects and groups of subjects with normal BP levels. BP reductions after dynamic resistance training were largest for pre-hypertensive participants compared with patients with hypertension or normal BP (34).

The type of training to be administered in hypertensive patients is an individual decision that should be made based on the severity of hypertension, BP response to stress, and the affinity of individual patients. Aerobic training of moderate intensity can be beneficial in the prevention of hypertension and should help in the treatment of stage 1 hypertension. A properly determined and well-dosed dynamic resistance exercise can produce both systolic and diastolic BP reduction. There have not been sufficient evidence about the safety and effectivity of isometric resistance training in hypertensive patients (35).

A reduced caloric intake has been confirmed to have a beneficial effect on BP reduction. A realistic advice to all the patients is 7-10% weight reduction in the period of 6-12 months as the effect of combined physical exercise and restricted caloric intake.

A modified diet plan such as DASH diet, has been created for the patients with hypertension and involves a healthy salt intake level, caloric restriction, and reduction of saturated fat (36). The Mediterranean diet is rich in fruits, vegetables, legumes, cereals, and olive oil, with moderate amounts of fish and dairy products, and small amounts of red meats. It has a favorable impact on atherogenic dyslipidemia in MS patients, with a beneficial effect on BP valuesas well (37). Some of the latest results have shown that the traditional Mediterranean diet, especially when enriched with virgin olive oil, improves HDL atheroprotective functions in humans (38). It has been shown that having a Mediterranean diet supplemented with either nuts or extra-virgin olive oil, as opposed to eating a low-fat diet, was more likely to reverse MS 5 years later (39).

A large Spanish study of 7447 persons (of whom 57% were women) at a high cardiovascular risk showed that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major CV events (40).

Finally, the study participants who followed a Mediterranean diet had a lower incidence of major CV events (myocardial infarction, stroke, or CV death; hazard ratio (HR), 0.7.1.; 95% confidence interval (CI), 0.5.6. - 0.9.0.), breast cancer (HR, 0.4.3.; CI, 0.2.1. - 0.8.8.), and diabetes (HR, 0.7.0.; CI, 0.5.4. - 0.9.2.) (41).

Current dietary guidelines advice reduced intake of simple carbohydrates and increased intake of fruits, vegetables and whole grain foods. Hercberg *et al.* (42) have studied the impact of dietary patterns on PWV. The study lasted for 7.5. years, and a positive correlation was established for a diet high in alcohol and meat, and inverse correlation with diets that included fiber, vitamin B9 and C, beta-carotene, and calcium. The study suggested a major role of diet in the stiffening of large arteries.

Regretfully, the percentage of patients who regularly engage in the prescribed physical activity and reduce their energy intake is low, and the average duration of abidance by the recommended interventions is less that 6 months.

3.7. Medicamentous therapy of MetS

In the selection of the first drug or combination of drugs as the initial treatment of hypertension in MS patients, it is necessary to avoid the drugs confirmed to increase the risk of developing new-onset diabetes and which may worsen the lipid profile.

The latest ESH-ESC guidelines for hypertension in 2013 (43) recommended RAS blockers and calcium antagonists as the first-line treatment for MS patients in whom lifestyle changes could not produce target BP values lower than 140/90 mmHg. They potentially improve – or at least do not worsen – insulin-sensitivity, while beta-blockers (with the exception of vasodilating beta-blockers) and diuretics should only be considered as additional drugs, preferably at low doses. If diuretics are used, the association with a potassium-sparing agent should be considered, as there is evidence that hypokalaemia worsens glucose intolerance. It has been shown that diuretics increase the risk of new-onset diabetes compared with placebo (23% increase for diuretics). Combinations of thiazide diuretics with beta-blockers should be avoided.

In contrast, calcium channel blockers and especially RAS blockers – angiotensin receptor blockers (ARBs) and angiotensin-converting-enzyme (ACE) inhibitors – decrease this risk (33% decrease with ACE inhibitors and 43% decrease with ARBs). Telmisartan, an ARB, is an especially interesting drug in this group. This agent also acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPAR-γ), a regulator of insulin and glucose metabolism (44). Because of this latter action, this agent might be useful in the treatment of MS (45).

4. SUMMARY AND PERSPECTIVE

In conclusion, hypertension is closely related to all factors of MS. Therapy of the hypertension should be adequate and should include all aspects of MS as well as should focus on specific drugs.

5. ACKNOWLEDGEMENTS

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Abbreviations: CV: cardiovascular; CAD: coronary artery disease; T2DM: type 2 diabetes mellitus; BP: blood pressure; HDL: high-density cholesterol; VLDL: very low-density lipoprotein; LDL: low-density lipoprotein; IFG: imparied fasting glucose; IGT: imparied glucose tolerance; MS: metabolic syndrome; HbA1C: glycated hemoglobin A1C; MAP: mean arterial pressure; PP: pulse pressure; PWV: pulse wave velocity; AI: augmentation index; HR: heart rate; RAS: renin-angiotensin system; ARBs: angiotensin receptor blockers; ACE: angiotensin converting enzyme; PPAR-γ: peroxisome proliferator-activated receptor gamma

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