

Hypertension in Postmenopausal Women

a report by

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The incidence of cardiovascular and cerebrovascular diseases in women is low before the menopause but after the age of 50 years they become the leading cause of mortality and morbidity for women living in most developed countries. This increased incidence is only partially explained by ageing, since the state of oestrogen deficiency developing after the menopause plays a key role in favouring the increased cardiovascular risk. Indeed, cessation of ovarian function and the consequent reduction of sex steroid hormones levels have important metabolic and pathophysiological implications that negatively influence the cardiovascular system.

It has been long known that blood pressure is typically lower in pre-menopausal women than in age-matched men, that arterial blood pressure increases after the cessation of menses and that after the menopause women develop arterial hypertension often together with changes in lipid and glucose metabolism.

However, in postmenopausal women, the prevalence of hypertension and cardiovascular disease risk increases regardless of ethnic origin. The National Health and Nutrition Examination Survey (NHANES III) showed that in Hispanic women and non-Hispanic black women, the prevalence of hypertension was similar to, or higher than, that in men by age 60 years and that in non-Hispanic white populations the prevalence of hypertension was higher in women than in men by age 70 years.

The increase in blood pressure in postmenopausal women does not occur soon after the cessation of menses, but it becomes evident over a number of years. Although the mechanisms responsible for the increased blood pressure in women after menopause are not known, it is reasonable to believe that the underlying mechanisms may be similar in the two sexes and that, in women, after the menopause the lack of oestrogens highlights the underlying defects. However, other mechanisms related to the state of oestrogen deficiency may become important. Furthermore, more recently it has become clear that hypertension and metabolic risk factors are inter-

related, influencing each other and often having similar underlying causes. The clustering of metabolic risk factors overweight and hypertension is of particular importance in women after the menopause because of the negative effect of menopause on the development of hypertension and on cardiovascular risk factors.

To this end, menopause, or more correctly oestrogen deficiency, has been considered a risk factor for coronary artery disease because of the negative impact of ovarian hormone deficiency on the development of cardiovascular disease. Menopause acts directly as a risk factor by reducing the direct beneficial effect of ovarian hormones upon cardiovascular functions and indirectly by negatively influencing other traditional risk factors for coronary artery disease (i.e. hyperinsulinaemia, blood cholesterol, blood pressure, coagulation, etc.).

Therefore, in menopausal women, there occur correlated disturbances that have their common etiological factor in the decline in ovarian function that occurs with the menopause. These disturbances will then themselves have negative effects that may augment the effect of menopause. Adverse changes in one factor may induce adverse changes in a variety of other risk factors leading to the concept that, in evaluating cardiovascular risk, it is important to consider co-ordinated changes in risk factors more than attempt to isolate single, independent factors.

The recognition of risk factor interrelationships developed in the 1980s was depicted by Reaven with the term of Metabolic Syndrome X and is now widely accepted as Metabolic Syndrome. This syndrome identifies a cardiovascular risk profile that includes insulin resistance, central obesity, increased triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels and arterial hypertension. In post-menopausal women, the state of ovarian hormones deficiency induces physiological changes leading to a greater prevalence of hypertension and metabolic syndrome compared with the pre-menopausal period. However, all changes occurring

after the menopause must be regarded under a unifying mechanism that induces changes in body weight, salt sensitivity, insulin tolerance, plasma lipids, sympathetic tone and vascular function, and these changes then interact each other, amplifying the effect of ovarian hormone deficiency and ageing.

Menopause, Obesity and Body Fat Distribution

Increase in body mass index (BMI) and an increased proportion of visceral fat are strongly correlated with the development of arterial hypertension and, a range of metabolic risk factors for cardiovascular disease. The relationship between obesity and hypertension is well documented, the Framingham study showing that the prevalence of hypertension as a function of age in both sexes increases substantially with increase in relative weight. It is important to underline that recent weight gain is a very important factor in the development of hypertension, as suggested by the fact that, in the Framingham study, obesity or recent weight gain accounted for 70% of new onset hypertension. Apart from body weight, body fat distribution is an important risk factor of hypertension. An increase in abdominal circumference or in waist-to-hip ratio, both surrogate markers for android fat distribution, is an independent factor for the development of high blood pressure values and is independently associated with other risk factors for the development of cardiovascular disease.

The relationship between obesity and blood pressure cannot be explained adequately by haemodynamics since, if it is true that obese subjects have increased blood volumes and cardiac output, these variables are within the normal range when corrected for body mass. Also, the greater intake of sodium of overweight subjects is not sufficient to explain the development of hypertension, since weight loss in overweight individuals decreases blood pressure even if the intake of sodium is not diminished. Therefore, the shift in the pressure-natriuresis curve in overweight subjects may be secondary to an increased sympathetic drive, hyperinsulinism and insulin resistance, factors that are inter-related and that, in women, are worsened by menopause like body weight.

Menopause is associated with important changes in weight and in body fat distribution, postmenopausal women tending to gain weight starting within the first year from the menopause and redistribute body fat from a gynoid to an android pattern. The increase and the change in body fat distribution occurring after the menopause are strictly related to the state of ovarian hormone deficiency, as women

taking hormone replacement therapy gain weight by a lesser extent than women not on hormone replacement therapy. The exact mechanism through which ovarian hormone deficiency may cause weight gain and android body fat distribution is not clear, although an activation of the renin-angiotensin-aldosterone system linked with an increase in salt sensitivity and a negative effect on the secretion of Leptin and the relative increase in androgens together with changes in thyroid function seem to play a key role. In men and women the increase in body fat is often coupled with negative changes on insulin resistance, plasma lipids, blood pressure and increased sympathetic drive, however, these changes are enhanced in women by ovarian hormone deficiency.

Menopause and Glucose Metabolism

The inter-relationship between insulin sensitivity and blood pressure has been long known. Patients with increased insulin resistance have a greater incidence of hypertension and hypertensive patients frequently develop alterations of glucose metabolism and diabetes. Menopause per se does not seem to affect fasting glucose but is associated with a progressive decline in glucose-stimulated insulin secretion. This decline in insulin secretion seems to be compensated, at least in the initial stages, by a reduction in peripheral insulin elimination. Several studies have reported an increased incidence of insulin resistance and a decrease in insulin sensitivity with menopause and have related these changes with both an effect of oestrogen deprivation and with the changes in body weight and sympathetic activity accompanying the menopause. Insulin resistance is a multisystem disorder that induces multiple metabolic alterations and, in women, is facilitated by the state of ovarian hormone deficiency.

Insulin resistance is an important risk factor for the development of type II diabetes mellitus and cardiovascular disease and occurs at multiple organ sites including the liver, the skeletal muscle cells and the adipocytes. As mentioned above, insulin resistance occurs in combination with a cluster of other metabolic abnormalities and arterial hypertension in the metabolic syndrome. Prospective studies have shown that hypertension develops more often in subjects with insulin resistance than in patients with normal insulin sensitivity suggesting that insulin resistance is a key factor in the development of hypertension. Furthermore, Ferrannini et al. showed that decreased insulin sensitivity (by euglycaemic clamp) is inversely associated with blood pressure. The link between hyperinsulinaemia, insulin resistance and hypertension is supported by the

observation that the worsening of insulin resistance that occurs with weight gain is associated with a greater incidence of hypertension and that an improvement in insulin sensitivity occurring with weight loss or with drugs that improve insulin sensitivity is associated with a decrease in blood pressure values.

The exact mechanism through which hyperinsulinaemia predisposes to hypertension is unclear, as insulin administration in healthy subjects induce vasodilation and may even cause a small decrease in blood pressure and attenuates the pressor effect of several hormones such as norepinephrine and angiotensin II. The vasodilator effect of insulin is mediated by the release of nitric oxide. It is probable that, in the development of hypertension, hyperinsulinaemia is consequent to insulin resistance that decreases the release of nitric oxide thereby increasing the effect of pressure hormones on vascular resistances. In hypertensive patients insulin may also affect the vasomotor tone by affecting the Calcium flux into the vascular smooth muscle cells, by increasing the sympathetic nervous system activity and the sodium and volume retention.

It becomes clear that the changes in insulin

sensitivity and body weight that occur after the menopause are inter-related and facilitated by the state of ovarian hormone deficiency; these changes, together, with the increase in sympathetic nervous activity may facilitate the development of arterial hypertension. Therefore, in women, hypertension is often the first clinical manifestation of a more complex clinical scenario, which is the metabolic syndrome. This clustering of risk factors includes unfavorable changes in lipid profile.

Autonomic Nervous Control of the Cardiovascular System

A close relationship exists between incretion of ovarian and hypothalamic hormones and the autonomic control of the cardiovascular system. Cyclical variations in the secretion of catecholamines occur during the menstrual cycle and after the menopause a clear shift of the autonomic control of the cardiovascular system towards an increased sympathetic tone occurs. This increased sympathetic tone is in part independent from the changes occurring in body weight and glucose metabolism but is, in the long term, heightened by these metabolic changes. Several studies have shown that, after the menopause, there is an increased production



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asthma; otosclerosis. Stop treatment at once if: jaundice or deterioration of liver function; significant increase in blood pressure; new onset migraine-type headache; pregnancy; symptoms that are possible prodromata of vascular occlusion; other contraindications occur. Remind patients of the need to inform doctor if they are aware of any new symptoms. Endometrial hyperplasia and carcinoma with unopposed oestrogen use is reduced by adding a progestogen for at least 12 days per cycle. Investigate irregular bleeding. Some studies have reported an increased risk of breast cancer in women taking HRT for several years. HRT is associated with an increased relative risk of developing venous thromboembolism (greater in first year of use). Risk factors include: personal or family history of thrombosis; severe obesity; systemic lupus erythematosus; immobilisation; major trauma; major surgery. Consider stopping HRT 4-6 weeks before elective surgery requiring immobilisation. Possible increased risk of cardiovascular morbidity in the first year of use of HRT. HRT is associated with an increased risk of stroke. Long term use of oestrogens in hysterectomised women is associated with an increased risk of ovarian cancer. Oestrogens may cause fluid retention. Monitor patients with cardiac or renal dysfunction. Monitor pre-existing hypertriglyceridaemia closely since large increases in triglycerides leading to pancreatitis have been reported. Certain laboratory tests may be affected. Oestrogens may increase circulating thyroid hormone, other binding proteins and some plasma proteins. Chloasma may occur. HRT is associated with an increased risk of developing dementia in women who start using HRT

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of catecholamines and a clear shift of the autonomic control towards an increased sympathetic activity of the cardiovascular system has been shown by our group. This increased sympathetic drive is closely related to the state of oestrogen deficiency as it occurs within few days from surgical oophorectomy and is reversed by oestrogens.

The increased sympathetic drive together with the metabolic changes occurring after the menopause, contribute to cause the metabolic syndrome but is also worsened by the metabolic changes. The increased sympathetic drive causes physiological and structural changes, leading to hypertension or facilitating its development (i.e. vasoconstriction, rarefaction of skeletal muscle arterioles, increase in angiotensin II plasma levels), changes in insulin sensitivity leading to reduced glucose tolerance because of the effect of sympathetic stimulation to the liver, fat tissue and muscle metabolism.

Apart from the structural changes in arterioles and their rarefaction, an important mechanism through which the increased sympathetic tone affects hypertension is related to the mutual changes induced by sympathetic stimulation on insulin sensitivity and renin activity. The adrenergic stimulation leads to both an increase in insulin and angiotensin II, which in turn act centrally and peripherally increasing SNS outflow and catecholamine release. Therefore, the reduction of sympathetic tone in women with metabolic syndrome has beneficial effect on glucose metabolism and on blood pressure. The modulation of sympathetic activity with centrally acting agents has therefore a clear indication in the treatment of hypertensive patients with metabolic syndrome.

Ovarian Hormones in Postmenopausal Hypertension

Ovarian hormones have a variety of effects that should be protective for the cardiovascular system. However, the effect of oestrogens and progestins on blood pressure are dependent on the route of administration and chemical structure. In fact, apart from selected hormone replacement therapy (HRT) preparations that have a clear effect on blood pressure, HRT has not always been shown to consistently lower blood pressure in postmenopausal women.

Many of these studies were short-term, i.e. <1 year. In contrast, Scuteri et al. studied healthy postmenopausal women who had been using HRT for at least five years and found that HRT significantly lowers blood pressure in both hypertensive and non hypertensive women. In

elderly mostly overweight post-menopausal women, some of whom with not controlled arterial hypertension, the Women's Health Initiative study found that HRT, using a progestin with mineralcorticoid properties, slightly increased systolic blood pressure. Progesterone and progestins with an anti-mineralcorticoid or anti-aldosterone effect used in HRT schemes have positive effects on blood pressure values in normotensive as well as in hypertensive women.

Renin-angiotensin-aldosterone System in Postmenopausal Hypertension

It is commonly thought that the plasma renin activity and the activity of the renin-angiotensin-aldosterone system (RAAS), decreases with age in humans and animals. However, studies that measured plasma renin activity serially for nine years in men and women found that oestrogen status influenced the renin activity as it was higher in postmenopausal than in pre-menopausal women.

It is well known that the RAAS plays a major role in control of blood pressure and body fluid volume (i.e. pressure natriuresis). Apart from its direct effect on vessels and on the release of aldosterone, Angiotensin II can also raise blood pressure in postmenopausal women by stimulating synthesis of preproendothelin or by producing oxidative stress. Therefore, activation of the RAAS may cause direct increases in blood pressure but also may stimulate endothelin and oxidative stress, further increasing blood pressure in postmenopausal women.

In women receiving HRT, oral administration of oestrogens may increase angiotensinogen production from the liver, thus facilitating the development of hypertension. This effect is buffered by the co-administration of progestins with anti-mineralcorticoid or anti-aldosterone properties. Recent studies have shown that the co-administration of Drospirenone in HRT schemes significantly reduces blood pressure in hypertensive women treated with Enalapril.

Therapeutic Approach of Menopausal Women with Arterial Hypertension and Metabolic Syndrome

Therefore, menopause is associated with unfavourable changes in a broad range of risk factors for cardiovascular disease. These disturbances may themselves be interrelated and in most case associate in the metabolic syndrome. The frequent presence of metabolic syndrome in postmenopausal hypertensive women has important implications for the therapeutic approach of these patients, as some anti-

hypertensive drugs may worsen the already altered metabolic profile of these patients while few others may have a beneficial effect.

Because of the clustering of hypertension with other metabolic risk factors, the therapeutic approach of the syndrome must include lifestyle modifications as well as pharmacological interventions. Several studies have shown that weight reduction is an effective and well-tolerated long-term treatment for hypertension in overweight patients. Moderate weight loss in overweight patients has been shown to decrease intravascular volume and cardiac output without affecting total peripheral resistances. Weight reduction has a beneficial effect on glucose metabolism and sympathetic nervous activity, as it reduces plasma insulin levels by increasing the number and the affinity of the insulin receptors and reduces sympathetic activity.

Although still under debate, several studies have suggested that weight loss is associated with a reduction in plasma renin activity, plasma aldosterone levels and intracellular sodium. Despite the beneficial effect of weight loss on glucose and lipid metabolism and blood pressure levels, several studies suggest that dropout rates in weight-loss programs range from 50% to 70% within one to two years. In order to enhance long-term maintenance of weight loss programmes, it is important to induce a gradual change in eating habits with increase intake of fruits and vegetables coupled with a gradual increase in physical activity up to 30 minutes/day. However, in patients with moderate or severe hypertension, or in those unable to lose weight, a pharmacological approach is needed

The therapeutic approach of patients with metabolic syndrome should be twofold: to improve glucose tolerance and thereby delay the onset of type II diabetes, and the other to allow an aggressive control of blood pressure values. The metabolic control of patients with metabolic syndrome and high insulin levels should be focused on drugs that improve insulin sensitivity. Several studies have shown that in patients with metabolic syndrome, therapy with metformin, acarbose and glitazones delay the onset of diabetes mellitus, also ACE-inhibitors and Angiotensin II receptor blockers have been proven effective in reducing the progression of glucose intolerance to type II diabetes.

Our group has shown that metformin improves endothelial function in patients with metabolic syndrome independently from the changes in glucose levels supporting the importance of this drug in the treatment of these patients. These

drugs, however, had been tested against beta-blockers and, since beta-blockers have a negative effect upon glucose metabolism, it is likely that the effect on glucose metabolism was the result of a neutral effect compared to a negative effect of beta-blockers.

Nowadays, it is possible to choose amongst several anti-hypertensive drug classes, all effective in the control of blood pressure. However, some drugs, such as beta-blockers and diuretics, may not be indicated in patients with metabolic syndrome because of their unwanted effect on glucose and lipid metabolism. The association of Amlodipine/Perindopril has been recently shown to be effective in reducing cardiovascular events and the new onset diabetes in hypertensive patients. However, it is most likely that the metabolic effect of this association is related to the known effect of Perindopril on glucose metabolism. ACE-Inhibitors and ATII receptor blockers are effective in controlling blood pressure and have been shown to reduce the development of diabetes mellitus. However, among ACE-inhibitors, it seems that the metabolic effect is more pronounced with those drugs that increase bradikinin while the metabolic effect of most of the ATII blockers is neutral on glucose metabolism. We have also shown that Telmisartan, an angiotensin II receptor blocker with a PPAR γ activity, improves glucose metabolism while reducing blood pressure in hypertensive patients with metabolic syndrome.

Centrally acting agents and alpha-2 blockers have been proven to effectively reduce blood pressure and to improve the glycaemic and lipid profile of hypertensive patients. Therefore, it seems that they should be indicated alone or in combination in the treatment of patients with metabolic syndrome. However, regarding the use of alpha blockers especially after the ALLHAT Study, there is no evidence to support the use of monotherapy with alpha blockers in hypertensive patients.

Studies evaluating the effect of the different classes of anti-hypertensives in patients with metabolic syndrome have always been conducted in relatively small patient populations. Therefore, at the present, as also highlighted by the recent ESH/ESC guidelines, there is no clear evidence for the superiority or inferiority of different drug classes and it appears reasonable to recommend that all effective and well-tolerated antihypertensive can be used, generally in combination. ■

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