Low-dose estrogen and drospirenone combination: effects on metabolism and endothelial function in postmenopausal women with metabolic syndrome

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Summary

Purpose: Metabolic syndrome and endothelial dysfunction play a relevant role in the cardiovascular risk in post-menopause. The aim of the study was to assess the effects of a low-dose hemihydrate estradiol and drospirenone combination on cardiovascular risk parameters in postmenopausal women with metabolic syndrome. *Materials and Methods:* Twenty-eight healthy women (group A) and 28 women with metabolic syndrome (group B) were treated with hemihydrate estradiol one mg + drospirenone two mg. At recruitment and after six months, clinical and laboratory parameters of metabolic syndrome were evaluated. Endothelial function was assessed measuring the flow-mediated dilatation of the brachial artery and the intima-media thickness of the common carotid artery. *Results:* After six months an overall improvement of metabolism was observed in both groups reaching statistical significance for triglycerides, total cholesterolemia, and systolic pressure in group B. A trend to lower baseline flow-mediated dilatation was also found in group B. *Conclusions:* Drospirenone improves cardiovascular risk factors and does not impair endothelial function in menopausal women with metabolic syndrome.

Key words: HRT; Drospirenone; Metabolic syndrome; Cardiovascular risk; Endothelial dysfunction.

Introduction

The association of insulin resistance, abdominal obesity, dyslipidemia, hypertension, inflammatory and prothrombotic state, defined as metabolic syndrome, is associated with a significant increase in cardiovascular disease (CVD) , the leading cause of morbidity and mortality in Western countries [1]. The prevalence of this condition increases during postmenopause in relation to the endocrine-metabolic changes induced by hypo-estrogenism. In addition to classical cardiovascular risk factors, endothelial dysfunction is a relevant factor of cardiovascular damage [2].

In postmenopausal patients, hormone replacement therapy (HRT) should be used with extreme caution: all the latest clinical recommendations indicate the opportunity to treat postmenopausal symptoms with the lowest effective dose in the shortest possible time [3]. Low-dose estradiol (E2) may be prescribed in a continuous combined regimen both with different types of progestins. In women with cardiovascular risk, in order to maximize the benefits and reduce the risks of HRT, a careful selection of patients and choice of progestin is mandatory because of its potential detrimental impact on metabolic cardiovascular risk [4]. To date, progestins derived from progesterone (P) are preferred to the androgenic progestins used in contraception therapy for their lower metabolic effect [5].

Drospirenone (DRSP) is a progestin with anti-androgenic and anti-mineralocorticoid, recently used in combination to hemihydrate E2 for the therapy of climacteric disorders. Preliminary studies suggest beneficial effects of DRSP on the cardiovascular profile in relation to the antialdosterone activity able to counteract the estrogen-induced activation of the renin-angiotensin system, and then the retention of sodium and water, resulting in reduction of blood pressure in postmenopausal women with hypertension [6]. It has been speculated that the ability to preserve the homeostasis Na-K could counteract the pro-inflammatory activity of the endothelium [7], while the antiandrogen properties may counteract the android distribution of adipose tissue and the atherogenic lipid metabolism occurring in the postmenopause [8]. In a previous study, a low-dose hemihydrate E2/DRSP treatment did not reveal any negative effect in healthy postmenopausal women on carbohydrate metabolism, acting in a neutral way on insulin sensitivity, while the treatment induced favorable changes in lipid profile and showed a significant improvement of vascular reactivity [9]. To date, data on the impact of low-dose hemihydrate E2/DRSP in women with metabolic syndrome are lacking. The aim of this study was to evaluate the effects two mg of DRSP in combination with one mg hemihydrate E2 on clinical and laboratory parameters of cardiovascular risk and on endothelial function in postmenopausal women with metabolic syndrome.

Materials and Methods

Twenty-eight healthy patients (group A) and 28 patients with metabolic syndrome (group B) who had attended the outpatient menopausal clinic of the Second University of Naples for treat-

Revised manuscript accepted for publication October 11, 2012

ment of menopausal symptoms were enrolled in the study protocol. Before beginning the study, assessment of plasma follicle-stimulating hormone (FSH) (> 40 IU/l) and E2 (< 30 pg/ml) concentration, mammography, cervical cytology, and transvaginal ultrasound (TVUS) examination were performed. These parameters were found to be normal and compatible with the menopausal status.

Patients of group A were healthy, did not show signs of diabetes or impaired glucose tolerance, breast cancer, liver or kidney parameter alterations, history of major thromboembolism, thyroid disease, uncontrolled or treated hypertension (systolic blood pressure > 140 mmHg or diastolic > 90 mmHg), and were not smokers. Patients of group B had metabolic syndrome defined by the presence at least three of the following disorders: waist circumference > 88 cm, fasting blood glucose > 110 mg / dl, triglycerides > 150 mg/dl, high-density lipoprotein (HDL) cholesterol < 50 mg/dl, blood pressure (BP) > 130/85 mmHg (National Institues of Health - NHI, 2001) (References for the NHI 2001). Represented exclusion criteria established diabetes, triglycerides > 200 mg/dl, total cholesterol > 300 mg/dl, BP levels > 150/90 mmHg, smoking, alcohol intake (> 40 g/day), contraindication to HRT, use in the three months prior to the study of hormonal therapies for cholesterol-lowering drugs, antidiabetic, anti-hypertensives, aspirin, Nonsteroidal antiinflammatory drugs (NSAIDs), and antioxidant vitamins.

All patients were treated for six months with two mg DRSP in combination with one mg hemihydrate E2. At enrollment (T0) and at six months (T1) the following parameters were evaluated:

– clinical parameters (waist-to-hip ratio (WHR), blood pressure);

– fasting laboratory parameters (triglycerides, HDL cholesterol, total cholesterol, low-density lipoprotein (LDL) cholesterol, apo-A, apo-B, blood glucose);

– endothelial function (EF) through the measurement of brachial reactivity as changes of diameter and the flow of the artery at rest and after compression (flow-mediated dilation - FMD); these data were expressed in percent value;

– atherosclerosis progression by B-mode ultrasonography measuring the intima-media thickness of the carotid arteries [2].

The data were entered into a database and expressed as mean ± SD For the statistical analysis the parametric Student t-test was used for paired data and for unpaired data, Mann-Whitney test for analyzing the non-parametric, and the Wilcoxon matched-pairs test for comparisons between groups and within groups.

Results

Table 1 describes the characteristics the two study groups at baseline and after six months therapy. An overall improvement in lipid profile and blood pressure was observed in both groups reaching statistical significance only for triglycerides, total cholesterolemia, and systolic blood pressure in patients of group B. With regards to the endothelial function, a lower baseline FMD was observed in group B and a trend to a better response to compression in healthy patients (from 6.1% to 9.3%) compared to those with metabolic syndrome (from 4.7% to 6.6%), although not statistically significant (Figure 1). No change was observed in the intima-media thickness of the carotid arteries.

Table 1. — *Clinical, laboratory, and instrumental data.*

Parameter	Group A		Group B	
	Baseline	After six months	Baseline	After six months
Age	49.9 ± 4.8		51.6 ± 4.1	
Years of menopause	3.5 ± 2.0		3.2 ± 2.0	
Waist circumference	82.7 ± 7.9	83.0 ± 7.8	90.8 ± 11.0	90.3 ± 9.8
Fasting glucose (mg/dl)	88.8 ± 9.9	90.1 ± 9.7	103.2 ± 14.7	92.8 ± 13.9^
Triglyceridemia (mg/dl)	88.4 ± 23.8	88.9 ± 28.0	119.3 ± 48.8	110.2 ± 50.3
Total cholesterol (mg/dl)	216.9 ± 24.5	215.9 ± 22.6	214.9 ± 14.5	194.4 ± 26.0^
HDL cholesterol (mg/dl)	46.3 ± 7.0	46.8 ± 7.8	51.1 ± 6.5	59.2 ± 12.4
Systolic blood pressure (mmHg)	132.7 ± 11.2	136.9 ± 15.6	136.9 ± 13.7	120.5 ± 12.8^
Diastolic blood pressure (mm/Hg)	85.9 ± 8.2	84.7 ± 7.0	83.4 ± 6.7	78.6 ± 5.9
Thickness of the carotid arteries (mm)	0.39 ± 0.11	0.39 ± 0.13	0.38 ± 0.12	0.39 ± 0.1

^$p \leq 0.05$ group B; *$p \leq 0.05$ vs group A.

Discussion

CVD is the leading cause of death in women in Western countries and its incidence is highest in postmenopausal women when the prevalence of the metabolic syndrome increases and contributes significantly to the alteration of the parameters of cardiovascular risk induced by estrogen deficiency [10]. It is believed that alterations of lipid metabolism, central obesity, insulin resistance, and hypertension, that are the most important features of metabolic syndrome, represent a substantial component of the cardiovascular risk, worsened also by hypoestrogenism. Endothelial dysfunction is undoubtedly one of the key elements in the pathophysiology and progression of vascular damage.

HRT is the gold standard for the treatment of symptomatic menopausal patients [11], and is also considered the gold standard therapy for menopausal osteoporosis even if recent studies suggest new potential target for osteoporosis therapy as modulators of the endovanilloid/endocannabinoid system [12, 13]. In women in which HRT is contraindicated, phytoestrogens are the most used alternative therapy [14, 15]. Nowdays, the impact of HRT on cardiovascular risk is controversial [16]: HRT is not currently indicated for the prevention of CVD, but it can play a role of primary prevention in healthy subjects in perimenopause or early postmenopause before endothelial damage occurs [9]. The literature today suggests the use of estrogens and progestins used at the lowest dosages and with lowest metabolic impact [4]. DRSP is a novel synthetic progestin structurally similar to spironolactone, which differs from classical progestin because it has both antiandrogenic and anti-mineralocorticoid effects. Such action could contribute to the control of endothelial dysfunction because it may antagonize the renin-angiotensin-aldosterone system by blocking the action of aldosterone at the receptor level resulting in renal reuptake of sodium and fluids, by promoting NO activity resulting in smooth muscle relaxation and vasodilation. It is also hypothesized that the ability to preserve Na-K homeostasis could counteract the pro-inflammatory endothelial activity [6-8].

Clinical evidence on the impact of DRSP on cardiovas-

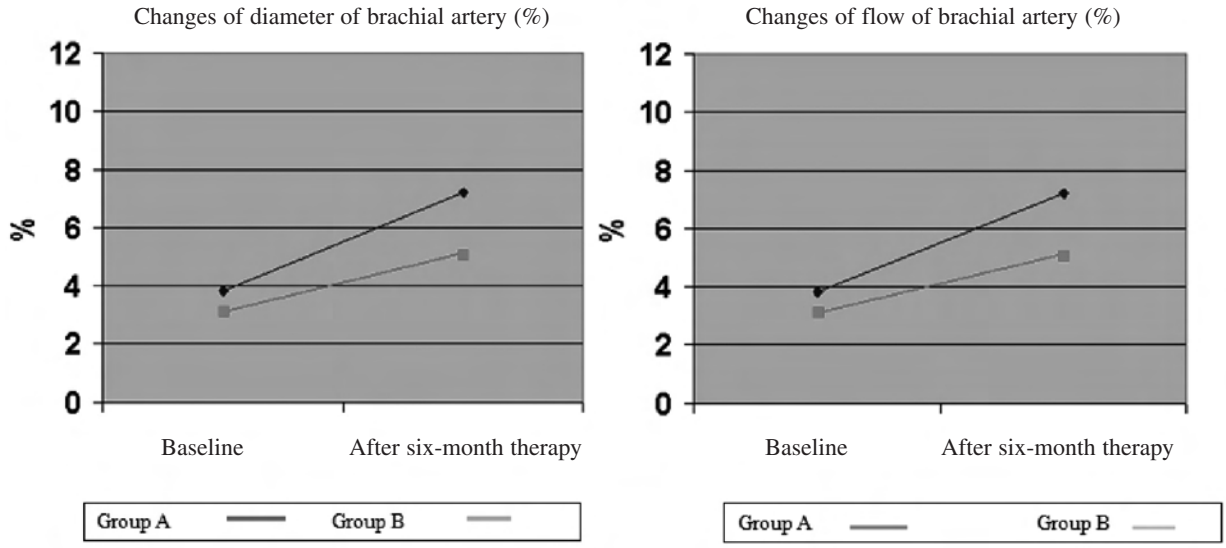

Figure 1. — Changes of diameter and flow of brachial artery (%)

cular risk in healthy postmenopausal women show a favorable change in the lipid profile and an improvement of vascular reactivity [9], but data on women at risk of CVD are lacking. The present study shows that the two mg DRSP + one mg hemihydrate E2 has a good impact on metabolic cardiovascular risk factors because it improves the metabolic parameters in patients with metabolic syndrome compared to healthy controls, with a greater impact on blood pressure, while endothelial function as measured by brachial artery reactivity is not impaired. These results may be due to the new profile of activity of DRSP which seems to be preferable to other progestins for the association in HRT in postmenopausal patients at risk of CVD, even if the influence of E2 cannot be excluded. In conclusion, this study, although carried out in a selected and limited population, and lasting only a brief period, indicated an overall remarkable beneficial effect of DRSP on several determinants of cardiovascular diseases and encourage further investigations.

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