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Effects of estradiol and norethisterone on lipids, insulin resistance and carotid flow

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Abstract

Objectives: To evaluate the lipid profile, insulin resistance and vasomotricity, and the interaction between these factors, in postmenopausal women receiving hormone therapy.
Methods: A prospective, randomized, double-blind study was carried out in which 77 postmenopausal women received one of the three treatment regimens: (A) 2 mg oral micronized estradiol (E_2) ($n = 25$); (B) 2 mg oral E_2 + 1 mg oral norethisterone acetate (NETA) ($n = 28$); or C) placebo ($n = 24$), daily for 6 months. Evaluations were carried out at baseline and at the end of treatment on lipid and lipoprotein profiles, homeostasis model assessment of insulin resistance (HOMA-IR) and pulsatility index (PI) of the internal carotid artery by Doppler ultrasonography.
Results: Mean increases of 15.6% and 2.4% and a reduction of 6.4% in high-density lipoprotein (HDL) levels were found for the E_2, E_2 + NETA and placebo groups, respectively. Reductions of 9.5% and 3.7% and an increase of 12.1% in low-density lipoprotein (LDL), and reductions of 20.0% and 3.8% and an increase of 28.8% in the LDL:HDL ratio were found for the E_2, E_2 + NETA and placebo groups, respectively ($p < 0.001$ in all cases). Insulin levels and HOMA-IR decreased 12.8% and 12.3% in the E_2 group and increased 12.9% and 16.0% in the E_2 + NETA group ($p < 0.05$), respectively. Carotid PI following treatment was 1.18 ± 0.23, 1.38 ± 0.20 and 1.41 ± 0.21 for the E_2, E_2 + NETA and placebo groups, respectively ($p = 0.0006$).
Conclusions: Oral estrogen therapy led to an improvement in lipid profile, insulin resistance and carotid blood flow, which was cancelled when NETA was associated.

Keywords: Hormone therapy; Estradiol; Norethisterone; Cardiovascular risk; Diabetes; Menopause

1. Introduction

Cardiovascular diseases in general are the principal cause of death in both men and women of the western

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world [1]. In addition, this group of diseases incurs serious social and economic consequences, particularly among the surviving victims who may then have to live with sequelae and limitations.

Cardiovascular mortality is low in women of reproductive age; however, the incidence increases rapidly following the onset of menopause. During reproductive years, the incidence is much lower than that of men of similar age [1].

The serum levels of estrogen present in women of reproductive age appear to offer a cardioprotective effect. In addition, it has long been known that deterioration occurs in lipid and lipoprotein profiles following menopause, principally a decrease in the levels of high-density lipoprotein (HDL), and estrogen therapy is known to revert this deterioration [2].

For some time, the role of progestagens in reversing the benefits of estrogen in lipid metabolism has been questioned. It was initially believed that 19-nortestosterone derivatives were more detrimental than 17-hydroxyprogesterone derivatives since the former may offer slight androgenic activity; however, no consensus has yet been established with respect to the alleged poorer profile of the former.

It should be remembered that the risk of cardiovascular disease depends on many other factors, carbohydrate metabolism deserving particular mention. An increase in insulin resistance and deterioration in glucose tolerance is known to occur with advancing age, although the effect of the menopause remains controversial [3]. Moreover, lack of estrogen tends to promote an accumulation of abdominal fat, which is a major cardiovascular risk factor and one of the criteria for the diagnosis of metabolic syndrome [4].

In carbohydrate metabolism, estrogen may have beneficial effects, while the progestagen may be deleterious; however, results may differ depending on the type of progestagen used [5].

Another important aspect with respect to cardiovascular risk is the effect of hormones on arterial flow, estrogen having been shown to reduce flow impedance [6]. Little is known, however, with respect to the beneficial effect of the simultaneous administration of progestagens on arterial blood flow.

In view of the gaps that exist in current knowledge with respect to the effects of postmenopausal hormone therapy (HT) on factors related to cardiovascular risk, particularly carbohydrate metabolism, and the effects of 19-nortestosterone-derived progestagens on these parameters, the present study was developed to evaluate the serum levels of atherogenic markers, insulin resistance and vasomotricity in postmenopausal women not using HT, in women using estrogen-only therapy and in a group using combined estrogen–progestagen HT.

2. Methods

For this prospective, randomized, double-blind, placebo-controlled study, initial sample size was calculated at 16 women for each group, in order to have a power of 80% to detect a difference of 0.15 in pulsatility index of carotid artery (type I and II error rates: 5% and 20%, respectively, and S.D. of 0.24). This sample size was also calculated as being able to detect a difference of 7.5 mg/dL in high-density lipoprotein with a power of 90%, considering a S.D. of 10.0 (type I and II error rates: 5% and 10%, respectively).

Inclusion criteria comprised: age 40–60 years; postmenopausal; last menstrual period at least 1 year previously; not having been in use of postmenopausal hormone therapy for at least 3 months prior to inclusion in the study. The exclusion criteria adopted were non-spontaneous menopause; practice of any physical exercise other than walking; endometrial thickness >5 mm as measured by transvaginal ultrasonography; presence of obstructive lesion with carotid vascular flow restriction detected by Dopplerfluxometry; abnormal mammography or cervical cytology; fasting glucose >99 mg/dL; medical history of cardiovascular disease, venous or arterial thromboembolism, carotid occlusive disease, *diabetes mellitus*, acute or chronic liver disease, alcohol consumption; use of any of the following medications: vitamin supplements (B_6, B_{12} or folic acid), androgens, raloxifene, tamoxifen, statins, barbiturates, hydantoins, carbamazepine, phenylbutazone, meprobamate and rifampicin.

All participants were from Jundiaí, a city of metropolitan São Paulo. They signed an informed consent form prior to inclusion in the study. The study was conducted at Gynecologic Clinic of Jundiaí School of Medicine. The study protocol and the consent form were approved by the Institution's Internal Review Board.

The medical history of all participants was registered at admission and complete general physical