Hormones and cardiovascular aging: from prevention to therapies

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ABSTRACT

Cardiovascular disease increases with aging in both men and women, but the menopause has an additional effect in women. Loss of ovarian function leads to an increase in the risk of coronary heart disease (CHD) due to changes in metabolic risk factors and in vascular function. There are adverse changes in lipids and lipoproteins, glucose and insulin metabolism, body fat distribution and haemostatic factors. An increase in blood pressure and a deterioration in vascular endothelial function add to the CHD risk. The latter changes accentuate those observed due to the aging process. Whilst aging cannot be reversed, the effects of the menopause may be ameliorated by the replacement of female sex steroids, hormone replacement therapy (HRT). Improvements in the lipid profile, in insulin resistance, in atheroma development and in vascular function are seen, varying with the types, doses and routes of administration of estrogens. The addition of progestogens may modify the responses to estrogens, with the more androgenic progestogens having the greater adverse effects. HRT can result in reductions in CHD events when introduced in the early postmenopausal period. Randomized clinical trials have clearly shown a reduction in surrogate CHD risk markers and in CHD events, including death, when HRT is initiated in postmenopausal women aged below 60 years or within 10 years of onset of menopause. It is likely that the greatest benefits for CHD prevention would be seen with the use of estradiol, either oral or transdermal, and the addition of non-androgenic progestogens when necessary. Ideally, large randomized clinical trials of such forms of HRT should be undertaken to confirm such benefits, but at present these are unlikely to be carried out. Nevertheless, the totality of the current evidence suggests that consideration should be given for the use of HRT in the primary prevention of CHD in postmenopausal women.

KEYWORDS

Menopause, coronary heart disease, hormone replacement therapy, estrogen, progestogen.

Introduction

The risk of cardiovascular disease increases with aging in both men and women. There are a number of risk factors common to both genders, including obesity, hypertension, diabetes mellitus, dyslipidemia, smoking and lack of physical exercise [1]. But for women, the menopause is an additional factor. Loss of ovarian function leads to adverse changes in metabolic risk factors and in arterial function. These changes result in increased risk of cardiovascular disease, particularly coronary heart disease (CHD), superimposed on the risk resulting from aging alone.

Metabolic and vascular changes with menopause

Loss of ovarian function results in increases in total and low-density lipoprotein cholesterol (LDL-C), decreases in high density lipoprotein cholesterol (HDL), and increases in triglycerides [2,3]. There are other changes such as increases in lipoprotein (a), impaired clearance of atherogenic particles and increased oxidative damage to lipoproteins which will contribute to increased CHD development. Insulin resistance is an important risk factor for atheroma development; insulin resistance increases with aging and with time since menopause [4]. Redistribution of body fat results in an increase of central (male pattern, android) fat which reflects an increase in visceral fat [5]. Blood pressure tends to increase after menopause [6], and there is impairment of arterial function [7].

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Effects of hormone replacement therapy (HRT)

Metabolic effects

Estrogen administration results in decreases of total and LDL-C cholesterol and increases in HDL cholesterol. These changes are more pronounced with the oral administration. However, oral administration results in increases in triglyceride concentrations whereas transdermal administration results in a decrease [8].

These effects of estrogens on lipids and lipoproteins may be modified by progestogen administration. The type of progestogen added will determine whether or not such changes are beneficial or adverse. Oral administration of the more androgenic progestogens such as norgestrel, norethisterone acetate and medroxyprogesterone acetate will blunt or even reverse the beneficial increases in HDL-C induced by estrogen [8]. However, they will also prevent or limit the increases in triglycerides induced by oral estrogen. In contrast, the addition of non-androgenic progestogens such as oral micronized progesterone or the very similar dydrogesterone does not have detrimental effects on HDL-C [9].

The effects of estrogens and progestogens on glucose and insulin metabolism vary according to the type of steroids and the route of administration. Estradiol 17-beta improves glucose tolerance and reduces insulin resistance as shown by an increase in insulin sensitivity and a decreased insulin response to a glucose challenge, with oral administration having a greater effect than transdermal [10]. Conjugated equine estrogens at lower doses are fairly neutral in their effects on glucose and insulin. The addition of oral androgenic progestogens to estradiol negates the beneficial effect on insulin resistance whereas the transdermal addition or the use of non-androgenic progestogens has little or no negative effect [10,11].

Other CHD risk factors

HRT does not result in an overall gain in weight and produces a relative decrease in android fat distribution [12]. Blood pressure usually shows no change or a small decrease in response to estrogen administration [13]. A small fall in blood pressure may be enhanced by the addition of progestogens which have anti-mineralocorticoid effects [14]. Concerns have been raised about the increase in circulating C-reactive protein (CRP) concentrations seen with the oral, but not transdermal, administration of estrogen [15]. However, this appears to be a local hepatic effect of the first-pass metabolism of estrogen and does not reflect any increase in vascular inflammation as evidenced by the complete lack of any increase in a number of other vascular inflammatory markers [16].

Atheroma

The effects of HRT on atheroma have been studied using animal models. The development of atheroma in cynomolgus macaques has been produced by feeding atheromatous diets coupled with surgical menopause. The administration of estrogen has been shown to reduce atheromatous plaque development, an effect not impeded by the addition of non-androgenic progesterone [17] but inhibited by the addition of androgenic medroxyprogesterone acetate [18].

Venous thromboembolism

HRT may influence the risk of venous thromboembolism (VTE) according to the type of hormone and the route of administration. The effects of different types and doses of HRT were examined in an analysis of almost 472,000 postmenopausal women aged between 40 and 80 years from UK databases [19]. A significant increase in VTE was seen with oral estrogen, with higher doses having a greater effect and conjugated equine estrogens having a larger increase than estradiol 17-beta. Transdermal estradiol 17-beta was not associated with any increase in VTE. With the addition of progestogens to oral estrogen, significant increases were seen with all combination except for estradiol and dydrogesterone.

Vascular function

Estrogen has direct arterial effects [20]. It improves nitric oxide-dependent endothelial function and increases endothelial nitric oxide synthase production, thereby increasing vasodilatation. It reduces the endothelial release of endothelin-1, a potent vasoconstrictor. It inhibits calcium channels and enhances potassium-dependent channels, both vasodilatory effects.

Timing hypothesis

The timing of initiation of HRT in relation to the onset of menopause may be important in determining cardiovascular benefit. A group of different animal studies have examined this issue. Female cynomolgus macaques were rendered surgically menopausal, fed an atherogenic diet and randomized to treatment with placebo or conjugated equine estrogens for 2 years. Coronary artery plaque size was measured and those monkeys given estrogen had a 70% reduction in plaques size compared with placebo [21]. In a second study, monkeys were given an atheromatous diet for 2 years before surgical menopause and then randomized to conjugated equine estrogens or placebo for 3 years. Those monkeys given estrogen had around a 50% reduction in plaque size compared with placebo [22]. In a third study, monkeys were made surgically menopausal and fed an atherogenic diet. After 2 years the monkeys were randomized to no treatment or conjugated equine estrogens for 3 years. There was no difference in plaque size between monkeys given estrogens or not, suggesting that the delay in giving estrogen after menopause obliterated its benefit on atheroma progression [23]. These findings have given rise to the timing hypothesis that HRT will give coronary benefit only if started close to the menopause.

Clinical trials

The large, randomized HRT trials in the Women's Health Initiative (WHI) showed a non-significant increase in CHD events with estrogen-progestogen [24] and a non-significant decrease with estrogen alone [25], suggesting a negative effect of the progestogen (medroxyprogesterone acetate). With estrogen alone, in those initiating treatment below age 60 years there was a non-significant decrease in myocardial infarction and death, a significant decrease in coronary interventions and a significant decrease in a composite of these outcomes whereas there were no significant changes in these outcomes on those initiating treatment above age 60 years [26], in keeping with the timing hypothesis. With long term follow-up, those initiating estrogen alone below age 60 years continued to have a significant reduction in CHD events compared with those who were randomized to placebo [27]. Thus 7 years of estrogen-alone therapy initiated below age 60 years results in CHD benefit for at least 13 years. In keeping with this, Alexanderson and colleagues [28] found that 2 to 3 years of HRT given to women in their early fifties re-

sulted in a decreased cardiovascular mortality compared with those who had been randomized to placebo during an observational study with follow-up of up to 15 years [28]. Thus, HRT is of benefit to the age-related risk of CHD. The Danish Osteoporosis study (DOPS) was a randomized trial of HRT in over 1,000 women in the very early postmenopausal period treated for 10 years [29]. There was a significant reduction in a composite endpoint of myocardial infarction, death or hospital admission for heart failure with HRT compared with no treatment. The early versus late intervention trial with estradiol (ELITE) also examined the timing hypothesis by including a group of women within 6 years of menopause compared to a group beyond 10 years postmenopause who were randomized to either oral estradiol or placebo [30]. Over a 5-year study period the increase in carotid artery intima-media thickness was significantly lower with estrogen use in the early starters but not in the late starters. Finally, meta-analyses of randomized trials in postmenopausal women have demonstrated a significant decrease in myocardial infarction or cardiovascular death in women initiating HRT below age 60 years or within 10 years of onset of menopause compared with those initiating later [31,32]. Observational studies of over 90,000 women have also shown a significant reduction in CHD death in those initiating HRT below age 60 years [33]. Taken overall, these studies clearly show a CHD benefit of starting HRT early in menopause. It should be noted that HRT initiation above age 60 years, whilst not showing benefit in risk reduction, did not show any increased risk. Can there be any CHD benefit of HRT in older women? Secondary prevention trials have not shown any overall benefit; although there have been trends towards reduced events [34]. Low dose non-oral estradiol, combined with a non-androgenic progestogen, would seem a logical approach for older women, including those with established CHD, who need to take HRT.

Conclusions

The totality of evidence shows that HRT can be of benefit for the primary prevention of CHD in postmenopausal women. The timing of the intervention, the type of hormones used and the doses at initiation are probably crucial and need to be determined. It is not feasible to conduct separate large randomized clinical trials using clinical events as hard endpoints to examine various types of HRT; we will need to be guided by smaller studies using surrogate endpoints.

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