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Journal of Steroid Biochemistry & Molecular Biology 74 (2000) 387–393

The Journal of Steroid Biochemistry & Molecular Biology

www.elsevier.com/locate/jsbmb

Cardiovascular effects of oestrogens

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Keywords: Cardiovascular; Oestrogen; Lipids; Insulin; Vascular function; Coronary heart disease

Coronary heart disease (CHD) is the leading cause of death in women as it is in men in Northern Europe and North America. Cardiovascular disease is the most common cause of morbidity and mortality in postmenopausal women, with approximately 50% developing CHD in their lifetime, 30% dying from the disease and 20% developing a stroke [1–3].

2. Effects of menopause

Loss of ovarian function at menopause is a specific risk factor for CHD in women, and postmenopausal women have perhaps double the incidence of CHD seen in premenopausal women, independent of age. This age-independent increase in CHD which is associated with the menopause [4–8] is paralleled by metabolic disturbances similar to those found in men. Menopause results in adverse changes in lipids and lipoproteins [9], with increases in total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol, and decreases in high-density lipoprotein (HDL) and HDL_2 cholesterol. Menopause also results in changes in insulin metabolism. Whilst there is no immediate change in circulating insulin concentrations, this disguises a decrease in pancreatic insulin secretion which is accompanied by a decrease in insulin elimination [10]. However, as a function of time since menopause, there is a decrease in insulin sensitivity [10] and an increase in the insulin response to a glucose challenge [11]. Thus postmenopausal women become increasingly insulin resistant, which in turn results in a relative hyperinsulinaemia. The observation that diabetic women have a higher incidence of CHD than diabetic men [12] is in keeping with the notion that the central metabolic disturbance of diabetes, namely insulin resistance, may be particularly important in women. In fact, most metabolic risk factors for CHD in women have now been linked to oestrogen deficiency [13].

3. Hormone replacement therapy

Postmenopausal hormone replacement therapy (HRT) appears to reduce the risk of cardiovascular disease, as evidenced by many epidemiological studies. There is a very consistent agreement in these studies that postmenopausal oestrogen-use results in a decrease in cardiovascular-disease incidence by 40–50% [14]. This effect does not seem to be reduced by addition of progestogen in the HRT. Concerns have been expressed that these apparent reductions in CHD with HRT reflect a healthy cohort bias. Indeed, a recent study showed that women choosing to start HRT had better CHD risk profiles [15]. However, there are large studies where attempts to remove this bias have been made by matching cases and controls for equally healthy lifestyles [16] and for the presence of major risk factors [17]. These case control studies have also shown reductions in CHD risk of about 40% with use of HRT.

Estrogen may improve myocardial ischaemia in postmenopausal women with CHD [18] and may help to relieve angina. Indeed, benefits of oestrogen have been shown on various surrogate endpoints in small controlled clinical trials. Yet trials with hard clinical endpoints, such as death, provide the most convincing evidence of a true beneficial effect. Data from randomised controlled clinical trials are currently regarded as the 'gold standard' evidence for proof of effect. But

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PII: S0960-0760(00)00117-5

even these studies have their limitations. Unlike epidemiological studies, clinical trials require volunteers to participate, which immediately produces a selected, and therefore biased, population. Furthermore, they test effects of an intervention against a placebo which itself may have its own effects compared with no treatment. For example, it is well established that placebo causes a reduction of vasomotor symptoms of around 50% in postmenopausal women, not an insubstantial effect [19].

A recent prospective randomised clinical trial of HRT (HERS) [20] showed some initial adverse cardiovascular effects, possibly due to the dose of oestrogen being too high. The HERS trial enrolled 2763 women with a prior history of cardiovascular disease who were randomised to receive either conjugated equine oestrogens with medroxyprogesterone acetate or placebo. After a mean of four years of follow-up, there was no significant difference in the outcome of non-fatal myocardial infarction or cardiac death. However, the interpretation of these results is not as clear as it may seem superficially. For example, in the first year after randomisation, patients in the HRT group had a higher-than-expected event-rate that decreased in the subsequent years. In the placebo group, the event-rate was lower than expected in the first year, with higher rates during further follow-up. It remains unknown if these observations reflect a true pattern of events, or whether the variations may be due to chance. Other concerns about this study include the dosage of oestrogen used and the type of progestogen. Further studies are clearly needed to establish the optimal doses, types and routes of administration of HRT for CHD.

4. Metabolic actions of HRT

There are a number of metabolic mechanisms through which HRT benefits the cardiovascular system. HRT affects lipids and lipoproteins, which are important in the development of atheromatous disease. These effects vary according to the type of oestrogen or progestogen used and their route of administration. Oestrogen lowers total cholesterol, irrespective of type of steroid or route of administration, and this effect is maintained in the long term whilst on treatment [21]. This lowering of cholesterol results primarily from a decrease in LDL cholesterol concentrations due to an up-regulation of $apoB_{100}$ receptors. Oestrogen also lowers the levels of lipoprotein (a), a possible independent lipoprotein risk marker for CHD. Lipoprotein (a) is atherogenic largely because of its propensity for retention in the arterial wall [22]. High levels of lipoprotein (a) are associated with increased risk for CHD in some populations. However, in other populations where LDL levels are low, there does not appear to be an increased risk for CHD in the presence of raised lipoprotein (a) levels [23]. It may therefore be that high lipoprotein (a) concentrations signify increased CHD risk only when LDL levels are also raised. It is also not known whether changing lipoprotein (a) levels have any clinical impact on CHD risk.

Qualitative changes in LDL induced by HRT may also be important. Although HRT appears to increase the proportion of small dense LDL particles [24], it actually increases their clearance from the circulation [25]. Thus, their shortened residence time in the circulation could reduce the likelihood of their retention in the arterial wall. Oestrogen also improves the postprandial clearance of potentially atherogenic lipoprotein remnants [26], again with potential benefits for the prevention of atheroma. Finally, oestrogen protects LDL against oxidative damage [27] — another key step in the generation of atheromatous lesions.

Orally administered oestrogen increases HDL cholesterol, and particularly the HDL_2 which is thought to confer a protective effect against atherosclerosis development, by inhibiting hepatic lipase activity and by increasing the hepatic synthesis of apolipoprotein AI. Transdermal oestradiol appears to have a less marked effect on HDL cholesterol [28]. However, although it may cause little increase in HDL_2, it does cause a reduction in HDL_3 which could be a theoretically beneficial effect for CHD risk [13].

The type and route of administration of oestrogen determines its effects on triglycerides. Since triglycerides may be a particular risk factor for CHD in women [29], this is of potential importance. Conjugated equine oestrogens cause an increase in triglycerides [28], an effect which is pharmacological resulting from the hepatic first-pass effect of this steroid. Orally administered oestradiol has perhaps a smaller effect on raising triglycerides [30], but transdermal oestradiol causes a reduction in triglycerides [28] which is the physiological effect of oestrogen.

Progestogens have differing effects on lipids and lipoproteins, depending on their androgenicity and perhaps on their overall dosage. The addition of progestogens to oestrogen therapy has no adverse effect in terms of lowering of LDL. Androgenic progestogens, such as norgestrel, reverse the HDL-raising effect of oestrogen [28] because they increase hepatic lipase activity. Since it is not known whether the reduction in HDL reflects any impairment in remnant clearance, the clinical significance of lowering HDL remains to be determined. In contrast, certain non-androgenic progestogens, such as dydrogesterone, have little negative impact on oestrogen-induced increases in HDL and HDL_2 [30]. When all these changes in lipids and lipoproteins are considered together, the various changes seen with most HRT combinations are likely to be beneficial overall (Fig. 1).

Oestrogen also affects glucose and insulin metabolism. Insulin resistance is a pivotal metabolic disturbance underlying CHD development. The effects of administration of oestradiol 17β to postmenopausal women on glucose and insulin concentrations suggest an improvement in insulin resistance [31,32]. In contrast, alkylated oestrogens such as ethinyl oestradiol and conjugated equine oestrogens may raise insulin levels and impair glucose tolerance [33].

Progestogen addition may produce certain adverse effects on glucose and insulin metabolism, again depending on the type of progestogen used. Androgenic progestogens, such as norgestrel, may increase insulin resistance [34] whereas non-androgenic progestogens, such as dydrogesterone, have little adverse impact [30] (Fig. 2).

Oestrogen affects coagulation and fibrinolysis, increasing both procoagulant and fibrinolytic activity. The effects of HRT on haemostasis are somewhat complex [35]. There is usually a reduction in certain procoagulant factors linked with atheroma development, but oral oestrogen also increases thrombogenesis. This is compatible with the fact that HRT reduces the incidence of arterial thromboembolism [36], but may increase the risk of venous thromboembolism [37]. It is likely that the initiation of oestrogen therapy causes a transient imbalance between coagulation and fibrinolysis processes, thereby causing a short-term increase in venous thromboembolism risk. The effect of non-oral oestrogen administration may limit or even avoid this adverse effect. A detailed study showed no significant change in any haemostatic parameter with transdermal estradiol [38]. No data are available on HRT effects in patients with coagulopathies, but it seems likely that the use of transdermal oestradiol would be advisable, irrespective of the progestogen used, should such patients require HRT.

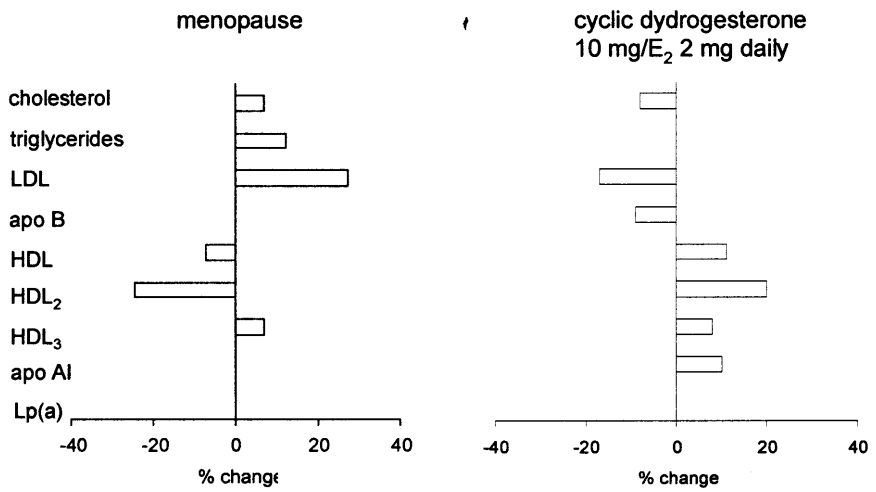

Fig. 1. Changes in lipids and lipoproteins seen with menopause [9] and with HRT (oral oestradiol 17β 2 mg daily and dydrogesterone 10 mg daily) [30].

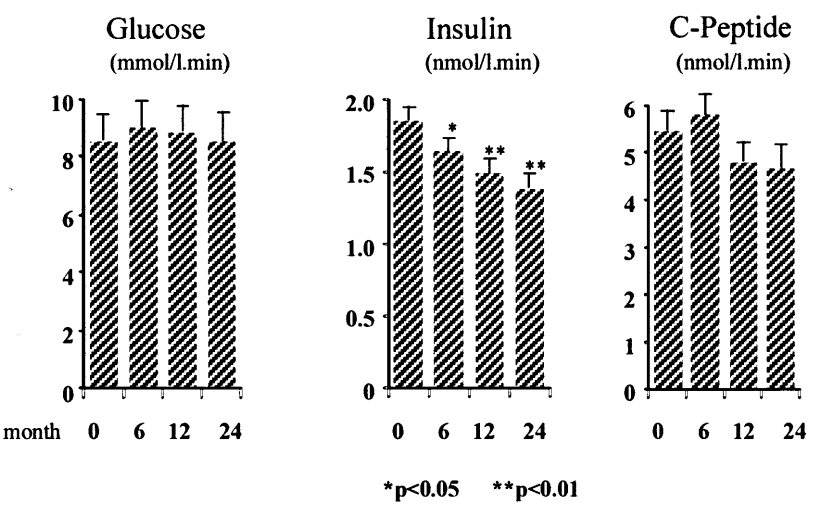

Fig. 2. Changes in glucose, insulin and C-peptide responses to an oral glucose challenge before and during HRT with oral oestradiol 17β 2 mg daily and dydrogesterone 10 mg daily [30].

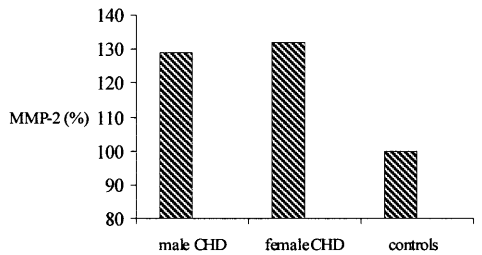

Fig. 3. Circulating MMP-2 activity in patients with CHD and healthy age- and gender-matched controls [65].

5. Vascular effects of HRT

Its overall effect on arteries is beneficial, in contrast to its effects on the venous system. In postmenopausal women, the menopause results in an increase in arterial waveform pulsatility index, an index reflecting reduced arterial compliance, in the carotid artery during the first few years [39]. The administration of oestradiol 17β reverses this increase, and this effect is not abolished by progestogen administration [40].

Oestrogen has direct effects on arteries through various genomic and non-genomic mechanisms. Oestradiol and certain other oestrogens stimulate synthesis of the potent vasodilator, nitric oxide (NO), by increasing levels of endothelial NO synthase (eNOS) [41,42]. Physiological doses of oestrogen infused directly into the coronary arteries of female patients with coronary atherosclerosis and angina restored acetylcholine-induced vasodilatation of these diseased coronary arteries and increased the blood flow [43]. This effect is mediated through endothelial NO. NO is involved in regulation of blood pressure, platelet function, inhibition of vascular smooth muscle proliferation and expression of adhesion molecules [44]. Previously published work has suggested that circulating plasminogen activator inhibitor-1 (PAI-1) [45], von Willebrand factor (vWf) [46,47] and thrombomodulin [47] concentrations may be elevated in CHD, as can those of various cell adhesion molecules (ICAM, VCAM-1, E-selectin) [47–49]. Postmenopausal oestrogen replacement has been reported to result in a lowering of PAI-1 and E-selectin in hypercholesterolaemic women [50]. We have recently shown in a randomised double-blind study [51] that concentrations of E-selectin and VCAM-1 are lowered by HRT given over 6 months in healthy postmenopausal women (-10 and -3%, respectively), in good agreement with previously published findings [52]. We have also shown that oestrogens reduce endothelin-1 release by vascular endothelial cells [42,53]. Endothelin-1 is the most potent naturally occurring vasoconstrictor thus far discovered [54] and is also a powerful mitogen for vascular smooth muscle cells [55]. Evidence from a study of postmenopausal women showed a significant 15–20% reduction in their plasma endothelin-1 levels in response to HRT [56].

Oestrogen affects vascular ion channels. Oestradiol acts through calcium-dependent mechanisms. In studies of isolated arterial rings, an increase in the calcium concentration of the medium resulted in contraction of the arterial rings but this effect was inhibited in a dose-dependent manner by the addition of oestradiol 17β [57]. Oestradiol also inhibits inward calcium currents and reduces intracellular free calcium in isolated cardiac myocytes [57]. In addition, oestrogen activates BKCa channels to cause coronary artery relaxation [58].

Oestrogens may also affect arterial function through changes in the renin–angiotensin system. Enhanced angiotensin-1 conversion is found in patients with the deletion allele of the angiotensin-1 converting enzyme (ACE) gene polymorphism, and such patients show impaired NO release from vascular endothelium [59]. An association of the ACE gene deletion allele and CHD has been shown particularly in women [60]. We have shown that HRT given to postmenopausal women reduces circulating ACE activity [61].

6. Vascular remodelling

Abnormal deposition and remodelling of vascular extracellular matrix is an important process involved in the pathogenesis and progression of atheroma, and restoration of the regulation of these processes may inhibit atherogenesis. A key group of enzymes involved in these processes are the MMPs and their tissue inhibitors (TIMPs). MMPs are zinc-dependent enzymes responsible for the degradation of extracellular matrix components such as collagen and proteoglycans, and have been implicated in the development of cardiovascular disease [62]. There is some evidence that they may contribute significantly to atheromatous plaque rupture [63], and may well be involved with plaque progression and regression. Their production is regulated by a variety of factors including growth factors such as interleukin-1 (IL-1), tumour necrosis factor, α (TNF-α) and interferons [64]. As well as the TIMPs, there are other circulating inhibitors of MMPs, including α2-macroglobulin, transforming growth factor-β (TGF-β), glucocorticoids and gonadal steroids [63]. We have found [65] that patients with CHD have significantly increased circulating levels of MMP-2 compared with normal individuals (males $P < 0.01$, females $P < 0.001$) (Fig. 3). Furthermore, we have shown in cultures of human vascular smooth muscle cells that oestradiol increases MMP release in a dose-dependent manner [66] (Fig. 4). It is therefore possible that modest increases in MMPs may counteract increased vascular collagen deposition, whereas high levels of MMPs will promote

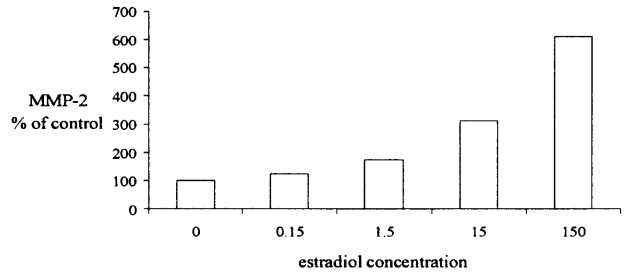

Fig. 4. MMP-2 activity in vascular smooth muscle cells exposed to different oestradiol doses [66].

atheromatous lesions. Thus, modest doses of oestrogen may be beneficial for atheromatous lesions, but too high doses may have deleterious effects in CHD.

7. Conclusions

It is clear that there is a very sound biological plausibility for the beneficial effects of HRT on the cardiovascular system. Epidemiological studies of the cardiovascular effects of HRT in postmenopausal women are very concordant in indicating a major benefit, particularly for CHD, and these findings are supported by small clinical studies using various surrogate endpoints. One randomised clinical trial did not demonstrate an overall benefit, but it is clear that other such studies are urgently needed. Overall, there is sufficient evidence to suggest that the use of HRT should be considered for protection against CHD in postmenopausal women with evidence of increased risk.

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