Hormone Replacement Therapy and the Cardiovascular System
Nonlipid Effects

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Summary

Coronary heart disease (CHD) is the leading cause of death in women, and the risk of this disease rises markedly after loss of ovarian function. Hormone replacement therapy (HRT) can reduce the incidence of CHD in postmenopausal women by 50%. HRT causes changes in lipids and lipoproteins, but it is now clear that many other effects of gonadal steroid hormones have important influences on the cardiovascular system. These nonlipid effects include a variety of changes in other metabolic risk factors for CHD, as well as direct arterial effects.

Insulin resistance and hyperinsulinaemia may be pivotal disturbances in the pathogenesis of CHD. Estradiol reverses the effects of menopause on glucose and insulin metabolism, resulting in an increase in pancreatic insulin secretion and a decrease in insulin resistance, although other types of estrogen may not do this. Androgenic progestogens may oppose this potentially beneficial effect on insulin resistance.

Central obesity is linked with many CHD risk factors, and HRT reverses the increased fat distribution that results from loss of ovarian function at the menopause. HRT may also improve the balance between coagulation and fibrinolysis, resulting in a reduction in arterial thrombosis.

Finally, estradiol acts directly on the arterial wall, modifying both endothelium-dependent and calcium-dependent processes. These actions result in improved blood flow and reduced blood pressure and, importantly, have the potential to reduce myocardial ischaemia.

The importance of coronary heart disease (CHD) in women is becoming increasingly recognised, as is the contribution of sex hormone deficiency and replacement (Manolio & Harlan 1993). The association between loss of ovarian function and increased CHD risk has been known for many years (Gordon et al. 1978; Oliver & Boyd 1959; Sznajderman & Oliver 1963), but the benefits of hormone replacement therapy (HRT) have been realised only more recently. Population studies have clearly shown a major benefit of postmenopausal estrogen replacement on the incidence of CHD (Knopp 1988). Therefore, it is important to understand how estrogen produces these effects on the cardiovascular system, both to extend our knowledge into the pathogenesis of CHD and to help optimise HRT regimens for the prevention and treatment of the disease.

Traditionally, HRT has been thought to benefit the cardiovascular system mainly through changes in lipids and lipoproteins (Bush et al. 1987). However, although both hormone deficiency and HRT
have clear effects on lipids and lipoproteins (Crook et al. 1992; Stevenson et al. 1993), the benefit of HRT to the cardiovascular system is only partly explained by these changes. This may be due to the fact that studies of HRT have not always measured the most important lipoproteins, but it has also become clear that other metabolic effects and direct arterial effects of HRT are of great importance; the purpose of this article is to review these nonlipid mechanisms.

1. Glucose and Insulin Metabolism

Disturbances of glucose and insulin metabolism are of major importance in the development of CHD. It is well known that diabetic women have a higher incidence of CHD than diabetic men (Abbot et al. 1987), which suggests that the sex hormone influences on glucose and insulin metabolism may be of particular significance with regard to the risk of CHD in such patients. Impaired glucose tolerance is predictive of subsequent CHD (Fuller et al. 1983; Jarrett et al. 1982), and this increased risk is likely to be mediated through insulin resistance and hyperinsulinaemia. Indeed, insulin resistance and hyperinsulinaemia have been proposed as pivotal disturbances in the constellation of metabolic factors that contribute to increased risk of CHD (Reaven 1988). Elevated insulin concentrations are frequently found in men and women with CHD (Ley et al. 1994; Rönnemaa et al. 1991), and we have demonstrated quantitatively increased insulin resistance in men with CHD (Ley et al. 1994). We have also found insulin resistance in male (Swan et al. 1994) and female (unpublished data) patients with syndrome X, a condition characterised by angina, and a positive ECG exercise test, but no demonstrable abnormality on coronary angiography.

Insulin resistance and hyperinsulinaemia are related not only to adverse changes in lipids and lipoproteins (Ley et al. 1994), including increased proportions of the small dense low density lipoprotein subtype B (Krauss 1991), but also to blood pressure, increased proportions of android (central or upper body) fat (Ley et al. 1994), and increased levels of plasminogen activator inhibitor-1 (Juhan-Vague et al. 1989). Hyperinsulinaemia may also increase CHD risk by directly promoting atherosclerosis (Stout 1990), and insulin propeptides may be important in this respect. Insulin propeptide concentrations are increased in non-insulin-dependent diabetes, but not in a variety of other conditions associated with insulin resistance (Proudler et al. 1994). However, we have found that they are increased in patients with premature CHD.

Few studies have examined the effect of loss of ovarian function on glucose and insulin metabolism, although we have reported a positive and independent relationship between circulating insulin concentrations and menopausal age in healthy women (Proudler et al. 1992). In addition, insulin resistance increases progressively with age in postmenopausal women (Walton et al. 1993). Postmenopausal women also have reduced pancreatic insulin secretion and reduced insulin elimination rates compared with premenopausal women (Walton et al. 1993).

Studies in vitro and in vivo have shown that estrogen administration increases pancreatic insulin secretion and improves insulin sensitivity. Clinical studies have also shown that estradiol-17β has this effect in hormone deficient women (Cagnacci et al. 1992; Notelovitz et al. 1987). However, different effects are seen with alkylated estrogens, which produce an increase in insulin levels and an impairment of glucose tolerance (Spellacy et al. 1972); conjugated equine estrogens may also have this effect. Progesterone increases pancreatic insulin secretion but, in contrast to estrogen, it increases insulin resistance. The effect of progestogens may partly depend on the androgenicity of the steroid used.

We have conducted a comparative study of oral and transdermal HRT regimens (fig. 1; Godsland et al. 1993). Healthy postmenopausal women were randomised to treatment with either continuous oral conjugated equine estrogens 0.625mg daily with cyclical addition of dl-norgestrel 0.15mg daily or continuous transdermal estradiol-17β 0.05mg daily with cyclical addition of transdermal norethisterone acetate 0.25mg daily. An untreated control