Use of hormone replacement therapy in women with diabetes

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Introduction

Coronary heart disease (CHD) is the major cause of mortality in women with type 2 (non-insulin-dependent) diabetes mellitus. Hormone replacement therapy (HRT) has generally favourable effects on cardiovascular risk factors. In this article, the known benefits of HRT in non-diabetic women and the potential benefits in women with diabetes mellitus are discussed. The results of a questionnaire study conducted among postmenopausal women attending a diabetes clinic to ascertain the prescription rates of HRT in diabetic women are presented.

The average age of the menopause in women is 50.8 years. Classically the diagnosis is made retrospectively following 12 months of amenorrhoea, although many women seek medical advice before this time because of the onset of menopausal symptoms. Eighty per cent of women experience vasomotor symptoms, which can be distressing and embarrassing.

Several studies have demonstrated an increased usage of hormone replacement therapy (HRT) in the past 10 years, although uptake of HRT remains less than 15% in women aged 40–65 years (Wilkes at al, 1991).

Ryan et al (1992) studied compliance with HRT in a group of women attending for bone mineral densitometry. They found a compliance rate of 74% following medical advice to continue therapy which fell to 61% at 12 months. Fear of cancer often deterred patients from starting treatment, and bleeding and weight gain were the main reasons for discontinuing therapy.

The immediate benefit gained by the patient is symptomatic relief. Hot flushing is the most commonly reported menopausal symptom and these vasomotor symptoms respond particularly well to HRT. Longer-term benefits are seen on the skeletal and cardiovascular systems.

Osteoporosis

Osteoporosis is defined by the World Health Organization (WHO) as 'a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk' (Report of a WHO Study Group, 1994). It is therefore an important health hazard in menopausal women. Bone loss occurs at a rate of up to 4% per year for the first 8 years after the menopause, therefore fractures are an increasingly common source of morbidity in this group of patients.

The bone-sparing properties of oestrogens have been recognised for decades. Most studies indicate that fracture rates may be halved in current or recent past users of oestrogens.

Cardiovascular system

The incidence of cardiovascular disease in women rises steadily following the menopause, approaching that of men by age 70. Coronary heart disease (CHD) remains the leading cause of death in women over 65 years of age.

There is evidence that HRT can reduce death and disability from CHD; however, it is important to stress that CHD is multifactorial in causation, and overall risk factor modification remains the cornerstone of primary and secondary prevention. Epidemiological studies suggest that cardiovascular morbidity and mortality may be reduced by as much as 50% in postmenopausal women taking unopposed oestrogen therapy.

ARTICLE POINTS

1 Hormone replacement therapy (HRT) is underprescribed in the UK.

2 HRT can have major beneficial effects on the skeletal and cardiovascular systems.

3 Women with diabetes mellitus have an increased mortality from cardiovascular disease

4 HRT appears to have a favourable effect on cardiovascular risk factors.

5 More research on HRT and diabetic women is needed.

KEY WORDS

- **Diabetes mellitus**
- **Menopausal women**
- **Hormone replacement therapy**
- **Cardiovascular disease**

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PAGE POINTS

1 Postmenopausal diabetic women have a much greater risk of developing cardiovascular disease than non-diabetic women.

2 Several cardiovascular risk factors may coexist in postmenopausal diabetic women.

3 HRT has been shown to improve glycaemic control as measured by HbA_{1c} levels.

4 HRT has had favourable effects on lipid profiles in both non-diabetic and diabetic women.

Although there are limited data on the use of oestrogen and progesterone combinations, the findings so far are encouraging.

Type 2 diabetes and risk of cardiovascular disease

Postmenopausal women with type 2 diabetes have a much greater risk of developing cardiovascular disease than non-diabetic women. The potential benefits of HRT in this group can only be extrapolated from results of studies in non-diabetic women as there is currently a paucity of research on HRT in women with diabetes mellitus. HRT has a favourable influence on several cardiovascular risk factors.

Insulin resistance

Reduced insulin sensitivity is a key factor in the clustering of cardiovascular risk factors observed in postmenopausal women with type 2 diabetes. Hyperlipidaemia, glucose intolerance, hypertension, impaired fibrinolysis and abdominal obesity often coexist in these individuals.

The PEPI trial was the first major, randomised, placebo-controlled trial examining the effects of HRT on heart disease risk factors in non-diabetic women (The Writing Group for the PEPI Trial, 1995). This trial demonstrated that patients receiving active treatment had slightly lower fasting insulin and glucose levels, although their 2-hour post-challenge glucose levels were slightly increased relative to the placebo group.

Brussard et al (1995) examined the effects of HRT in women with type 2 (non-insulin-dependent) diabetes mellitus. They employed the euglycaemic hyperinsulinaemic glucose clamp technique and demonstrated that HRT significantly reduced hepatic glucose production and improved glycaemic control as measured by the glycated haemoglobin (HbA_{1c}) level. It is possible that some of this beneficial effect may be offset by the addition of progestogens, although further studies are required to evaluate the effects of different HRT preparations upon insulin sensitivity in women with type 2 diabetes.

Dyslipidaemia

Patients with type 2 diabetes, particularly females, have elevated plasma triglyceride levels and lower high-density lipoprotein (HDL) cholesterol concentrations, both of which are independent risk factors for CHD. Most studies examining the effects of HRT on lipid profiles have been undertaken in non-diabetic women, and have demonstrated favourable changes, i.e. a rise in HDL cholesterol concentration and a fall in low-density lipoprotein (LDL) cholesterol concentration.

Brussard et al (1995) demonstrated this rise in HDL cholesterol in a group of women with type 2 diabetes treated with oral oestradiol. The PEPI trial, however, found that unopposed oestrogen had a more favourable effect on HDL cholesterol than oestrogen given with continuous or cyclic synthetic progestogen. There were also differences depending on the progestogen: women treated with oestrogen and micronised progestogen had significantly higher cholesterol levels than women treated with oestrogen and medroxyprogesterone acetate.

Risks of treatment

Breast cancer

Fear of breast cancer is one of the main reasons women choose never to start HRT. The greatest risk factors for developing breast cancer are a strong family history of breast cancer and a biopsy indicating pre-malignant change. Breast cancer kills more young women than CHD, although women are five times more likely to die of an ischaemic cardiac event.

A large number of case-control and cohort studies have studied HRT use and breast cancer risk. These have produced conflicting results. There have been several meta-analyses of these studies which were largely biased towards oestrogen-only HRT, although more recent reviews have included combined preparations.

Hunt et al (1987) compared long-term oestrogen-only HRT and oestrogen–progestogen combinations and found a similar risk of breast cancer with the two preparations.

The meta-analysis by Colditz et al (1993) found that use of a combined preparation was associated with a relative risk of 1.2 at 5 years, which rose to 1.46 after 5–10

years of use. There would therefore appear to be a small but gradual increase in breast cancer risk of 30–50% with over 10 years of HRT use.

Women using HRT in the long term need to weigh up the risks and potential benefits from prolonged use of HRT.

Endometrial cancer

It is well recognised that unopposed oestrogens increase the risk of endometrial cancer, so it is current practice to add a progestogen to HRT in women with an intact uterus (Voight et al, 1991). This is supported by epidemiological data showing no excess risk of endometrial cancer with long-term combined therapy.

The pathological change in the endometrium associated with an increased risk of cancer is complex or atypical hyperplasia. The UK Continuous Combined HRT Study (Sturdee et al, 1994) identified complex hyperplasia in 2.7% of women on sequential HRT before transfer to a continuous preparation. Evidence exists that continuous combined oestradiol can reverse endometrial hyperplasia, therefore withdrawal bleeding is avoided without risk to the endometrium. Until recently the timing of the withdrawal bleed was used as an indicator of a healthy endometrium; however, this study has demonstrated no correlation between endometrial histology and the onset of bleeding.

Venous thromboembolism

The risk of venous thromboembolism in women on HRT is thought to be small: approximately one in 5,000 users per year. It would appear to be greatest in the early years of use and in patients with predisposing factors such as a personal or family history of venous thromboembolism, recent surgery or trauma, obesity, severe varicose veins or prolonged immobilisation. These factors should be borne in mind when decisions on treatment are being discussed with patients.

Prescription of HRT in women with diabetes mellitus

The overwhelming impression from current literature was that HRT is underprescribed in women with diabetes mellitus (Feher et al, 1996). In order to ascertain the local usage of HRT in diabetic women attending a diabetes clinic, a questionnaire survey was performed (Bal et al, 1997). The questionnaire (*Figure 1*) was completed by the doctor at the patient's routine clinic visit. Data were gathered on 89 consecutive women aged between 36 and 65 years, who had been amenorrhoeic for more than one year.

Of the 89 women, 25 (28%) had type 1

PREVALENCE OF HRT IN WOMEN WITH DIABETES MELLITUS

Name .....

Age ..... years

DOPD No. .....

Diabetes type: 1 2 3

Year of diagnosis .....

Treatment: Diet OHA Insulin

Diabetic complications:

Ischaemic heart disease		Hypertension	
Cerebrovascular disease		Nephropathy	
PVD		Renal repl Rx	
*Hyperlipidaemia		Hypo. unaware	
Retinopathy		Neuropathy	
Cataract		Foot ulcer	
Blind		Amputation	

Family history of ischaemic heart disease: Yes/No

Smoker
Ex-smoker
Non-smoker

Years post menopause .....years

On HRT? Yes: Duration of treatment ..... years

No: Ever discussed Yes/No
**Contraindicated (true) Yes/No
Contraindicated (diabetes) Yes/No
Declined Yes/No

* Cholesterol >6.0 mmol/l, Tg >3.0 mmol/l or on Rx

**Thromboembolic disease; ovarian carcinoma; breast carcinoma; liver disease; severe cardiac impairment; severe renal impairment.

Figure 1. Questionnaire administered to women who had been amenorrhoeic for more than one year and were aged <65 years, attending a diabetes clinic. DOPD = diabetes outpatient department number; HRT = hormone replacement therapy; OHA = oral hypoglycaemic agents; PVD = peripheral vascular disease; Renal repl RX = renal replacement therapy; Tg = triglycerides.

Table 1. Reasons why patients were not receiving HRT (n = 65)

	Number	%
Never discussed treatment	50	77
Declined treatment	8	12
Valid contraindication	5	8
Diabetes deemed a contraindication	2	3

diabetes and 64 (72%) had type 2 diabetes. Overall, 24 (27%) were receiving HRT: 11 of the 25 patients (44%) with type 1 diabetes but only 13 of the 64 (20%) with type 2 diabetes. Sixty-five (73%) were not taking HRT, for a variety of reasons (*Table 1*). Significantly, 77% of patients had never discussed this form of treatment with a health-care professional.

The cardiovascular risk profiles of our cohort were examined. Fifty-one (57%) had documented coronary heart disease (CHD) or more than one risk factor for CHD in addition to diabetes, namely hyperlipidaemia (cholesterol >6.0 mmol/litre, triglycerides >3.0 mmol/litre, or on lipid-lowering therapy), hypertension, a history of smoking, or a family history of CHD. Only 25% of patients in this group were receiving treatment, although a small number (8%) had been offered treatment and declined.

Although this is a small survey, the results are interesting. The overall prescription rate of HRT was found to be almost double that in the general population. This difference may be explained partly by our very active local menopause clinic and heightened awareness of local GPs. We are currently planning to extend this survey to other diabetes clinics throughout the West of Scotland in order to increase the sample size and to assess geographical differences in prescription rates.

Conclusion

There is considerable evidence to suggest that the prescription of HRT can improve mortality in non-diabetic women. It should also reduce the burden of CHD in women with type 2 diabetes through a favourable effect on cardiovascular risk factors. Unless specific contraindications exist, these women may achieve even greater benefits from treatment than their non-diabetic counterparts.

There is, however, a paucity of research on this topic. Further studies on the effects of the various forms of HRT in women with diabetes mellitus, who are a very high risk population with respect to vascular disease, are needed urgently. ■

PAGE POINTS

1 HRT is generally considered to be grossly underprescribed in diabetic women.

2 However, the HRT prescription rate in this small study of diabetic women was double that in the general population.

3 Three-quarters of women in the study had never discussed HRT with a health professional.

4 Although more than half had CHD or more than one risk factor in addition to their diabetes, only a quarter were receiving treatment.

5 Diabetic women may achieve even greater benefits from HRT than non-diabetic women.

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