Hormone replacement therapy: what is the evidence today?

Summary Based on the most recent studies, it clearly appears that long-term hormone replacement therapy (HRT) prevents fractures but does not improve established coronary artery disease. In addition, HRT leads to a small increase in breast cancer incidence and to a decrease in colorectal cancer incidence. HRT increases the incidence of venous thrombosis, pulmonary embolisms and strokes. As a consequence, HRT can no longer be recommended for primary or secondary prevention of cardiovascular diseases. In addition, it was also demonstrated that HRT was not able to improve cognitive functions and prevent dementia. Therefore regarding daily clinical practice, HRT certainly remains useful to control the symptoms of oestrogen deficiency in recently menopausal patients, but it should definitively no longer be recommended for long-term treatment.


**Introduction**

The main indication of hormone replacement therapy (HRT) is to control postmenopausal symptoms related to oestrogen deficiency, such as hot flushes, and to improve health-related quality of life. Based on various observational studies, it was thought that HRT could be efficient in preventing chronic conditions related to age such as coronary heart disease, osteoporotic fractures, decline of cognitive functions and even delay the onset of Alzheimer disease. Two main clinical studies published in 1995 and 2002 failed to show significant improvements, respectively, in secondary and in primary cardiovascular prevention. The Heart and Oestrogen Replacement Study (HERS) was a randomised placebo-controlled trial of 4.1 years duration (HERS I) which included a total of 2763 postmenopausal women with coronary disease aged 67 years, followed by a 2.7-year (HERS II) open-label observational period including 2321 women. The main outcomes of HERS, which was designed as a secondary prevention study, were the incidence of thromboembolic events, biliary tract surgery, cancer, fracture and overall mortality rate [5]. The Women's Health Initiative (WHI) was a large randomised controlled trial with the aim in primary prevention to define the risks and benefits of oestrogen associated with progestin in 16,608 healthy postmenopausal women aged 50–79 years. The primary outcomes of WHI were the incidence of coronary heart diseases and invasive breast cancer, whereas the secondary outcomes were the incidence of stroke, pulmonary embolism, endometrial and colorectal cancers, hip fractures and overall mortality. The trial arm, including women with intact uterus and receiving a combination of oestrogen and progestin, was initially planned for 8.5 years but was stopped after 5.2 years of follow-up due to health risks significantly exceeding benefits [10]. A parallel trial arm performed in hysterectomized women receiving oestrogen alone is still being continued. The authors intend to briefly review the results of the main outcomes of both HERS and WHI clinical trials, which recently lead to the reconsideration of using of HRT in postmenopausal women.

**Skeletal effects**

HRT was recognized to prevent postmenopausal bone loss related to oestrogen deficiency and to decrease vertebral fracture by about 60% based on one short-term (one year) randomised controlled trial [8]. All previous randomised controlled trials consistently showed either a stabilisation or an improvement of bone mineral density (BMD) in women using HRT as reported in a recent meta-analysis [16] with an increase in BMD at the spine, hip and wrist. Numerous observational studies reported a reduction in fracture incidence associated with the use of HRT. A recent meta-analysis based on 13 randomised controlled trials, taking into account the number of women with an incident vertebral fracture rather than the number of fracture, confirmed a protective effect of HRT of 33% [13]. Originating from the same authors, another recent meta-analysis based on 22 randomised controlled trials reported a 27% reduction in the incidence of non-vertebral fractures in women using HRT [14].

Surprisingly in the HERS study, women randomised to HRT presented with more hip fractures than women randomised to placebo with a relative risk (RR) of 1.61 (CI: 0.98–2.66) during the 6.8 years of the study duration, corresponding to 40 versus 25 absolute number of cases. Considering any type of fracture (hip, wrist, vertebrae and others), the RR was close to unity (RR 1.04, CI: 0.87–1.25) with an absolute number of 230 events in the HRT group versus 222 in the placebo-treated group [6]. In the WHI study, the HRT group showed a significant decrease of both hip (44 versus 62) and clinical vertebral fracture (41 versus 60). Absolute rates showed a reduction of one third as compared to the placebo treated group. The reduction in both other osteoporotic fractures (23%) and total fractures (24%) was also statistically significant [10]. The WHI population was not selected based upon skeletal risk factors (no BMD data available) and therefore the absolute number of events was relatively low (106 hip fractures among 16,608 participants). Nevertheless, the WHI study is the first clinical trial with long-term data clearly supporting the efficacy of HRT to prevent fractures even at the hip site.

**Cancers**

The HERS study [6] showed a modest, but significant increase in breast cancer risk in the combined HRT users group as compared to the control group with a RR of 1.27 (0.84–1.94), corresponding to 59 versus 47 events/10,000 women/year. The WHI [10] study data demonstrated a small but significant increase in breast cancer risk with long-term use of combined HRT compared with the control group with a RR of 1.26 (1.00–1.59), corresponding to 38 versus 30 events/10,000 women/year. In these studies, there is no evidence for an increased mortality suggesting earlier detection and/or a better clinical follow-up and/or tumors having a better prognosis.