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Review

A woman's journey through the reproductive, transitional and postmenopausal periods of life: Impact on cardiovascular and musculo-skeletal risk and the role of estrogen replacement

John C. Stevenson*

National Heart & Lung Institute, Imperial College London, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

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ABSTRACT

Sex hormones are fundamental for female development and they are important physiologically to maintain the health and normal functioning of several organs such as the brain, heart and bone. It is now clear that the hormonal changes that occur during a woman's life, particularly her estrogen status, can modulate disease activity. This is especially true for cardiovascular and musculo-skeletal diseases, which are two leading causes of morbidity and mortality in women. With the general aging of the population they represent a serious and growing public health concern.

Estrogen synthesis and blood levels fluctuate during a woman's life and in this review three broad periods will be considered: reproductive phase, transition and postmenopausal phase. Generally speaking, women in the reproductive phase of their life are at low risk of cardiovascular and musculo-skeletal disorders. However, the onset of menopause and the loss of ovarian function is associated with a significant increase in the prevalence of diseases such as coronary heart disease, osteoarthritis and osteoporosis. The prevalence of these debilitating diseases continues to increase through the postmenopausal period. Estrogen replacement is an obvious treatment approach to counter the problems associated with the loss of ovarian function and subsequent estrogen deficiency. Overall, oral and transdermal estrogen replacement are similarly effective in relieving menopausal symptoms and disorders that manifest during this period of a woman's life. Transdermal estrogen may be preferable in older women because of its lower thrombogenic potential.

In this journey through a woman's life current best evidence relating to cardiovascular and musculoskeletal risk will be reviewed in line with well documented management strategies.

Contents

* Tel.: +44 20 7351 8112; fax: +44 20 7351 8771.
E-mail address: j.stevenson@imperial.ac.uk

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1. Introduction

Estrogens are a group of sex hormones which play a pivotal role in the sexual development of women. The amount of estrogen synthesised is dependent upon the reproductive status of the individual and is highest during the reproductive years, and declines during transition and the postmenopausal period. Estrogen acts physiologically to maintain the health and normal functioning of several organs such as the brain, heart and bone [1]. As a consequence, changes in the level of circulating sex hormones such as estrogen can have a profound effect on the health status of women, and there is no doubt that the hormonal changes that occur during a woman's life can modulate disease activity [1]. This is highlighted in US data from the 1990s which determined the annual incidence of chronic diseases in relation to a woman's age (from 30 to 80 years) [2]. What is interesting from these findings is the significant age-related burden accounted for by cardiovascular (CV), and bone disorders (Fig. 1). In this article recent evidence relating to the impact of CV and musculo-skeletal diseases will be reviewed in relation to 3 phases of a woman's life:

- Reproductive phase (approximate age range 20–45 years).
- Transition (approximate age range 40–60 years).
- Postmenopausal phase (approximate age 60 years and upwards).

In addition, the role of estrogen replacement therapy will be assessed as part of this review given its pivotal role in the management of these disorders. Estrogen replacement can be administered by various routes and in this article the relative merits of oral and transdermal therapy will be evaluated based upon currently available evidence.

2. Cardiovascular risk

CV disease is the leading cause of death in men and women worldwide, and the greatest contributor to this adverse statistic is atherosclerotic coronary heart disease (CHD) resulting in myocardial infarction (MI) [3]. Risk factors for CHD include hypertension, cigarette smoking, hypercholesterolaemia, obesity, inactivity and diabetes [4]. The prevalence of CHD and hypertension, two of the main causes of CV death, rises exponentially with age in women (Table 1). It is interesting to note that women of reproductive age have a 3–5-fold lower rate of MI mortality than men, but this differential reduces with age [3]. Indeed, data from the USA showed that 1 in 8 or 9 women aged 45–64 years had clinical evidence of CHD and this number increased to about 1 in 3 in women aged over 65 years [2]. The authors noted that CHD is now the leading cause of death in women in the United States and with the aging of the population more women than men die from CHD.

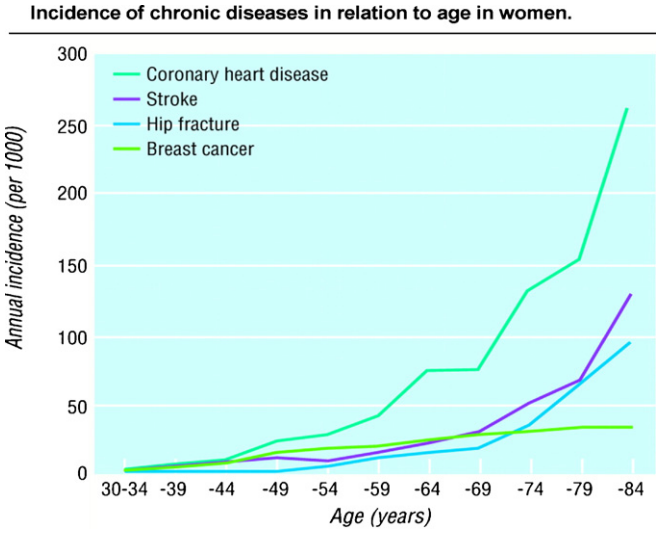

Fig. 1. Incidence of chronic diseases in relation to age in women in the USA [2].

Table 1
The rate of coronary heart disease and hypertension in UK women in 1998 (data from the Office of National Statistics for England and Wales) [5].

Parameter	Women's age group (years)						
	0–34	35–44	45–54	55–64	65–74	75–84	85–
Coronary heart disease							
Rate/1000	0.1	1.7	13.0	49.3	111.5	166.6	180.0
Hypertension							
Rate/1000	1.8	13.0	43.3	93.2	142.6	170.2	99.5

2.1. Reproductive years

As clearly highlighted in Table 1, women up to the age of 34 years generally have good cardiovascular health and low prevalence rates for CHD and hypertension [5]. This is reinforced by mortality data which show that up to the age of 45–50 years women are at relatively low risk of coronary death and there is an apparent 10-year gap between men and women in terms of when coronary manifestations first occur [2,6]. This 10-year difference appears to remain relatively constant up to the age of 70 years for women (80 for men) and then declines to about a 5-year differential (Fig. 2) [6].

An intriguing question arising from these findings is whether the difference in CV risk between the sexes relates to the positive effects of estrogen or negative effects of testosterone? While we are not currently in a position to answer this question, there is accumulating evidence of the CV protective effects of estrogens. For example, in the 1980s it was reported that estrogens appeared to protect women from cardiovascular disease through beneficial effects on lipid metabolism, as well as more direct effects on arterial walls via inhibition of atherosclerotic plaque formation [7,8]. Since then there has been accumulating evidence of potentially positive properties of estrogen which can benefit the CV system, such as effects on endothelium, vascular smooth muscle and autonomic nervous function [9,10], prostacyclin and nitric oxide [9,11], the renin–angiotensin system [12] and possibly calcium channels (acting as a calcium antagonist) [13]. Although the use of early high dose oral contraceptives raised concerns regarding thromboembolic risk with synthetic estrogen [8], analysis of a Framingham cohort reported a positive association between high estrogen status (premenopausal women and postmenopausal women on hormone replacement therapy (HRT)), increased fibrinolytic activity and cardioprotective properties which was not observed in individuals with low estrogen status (men and untreated post-

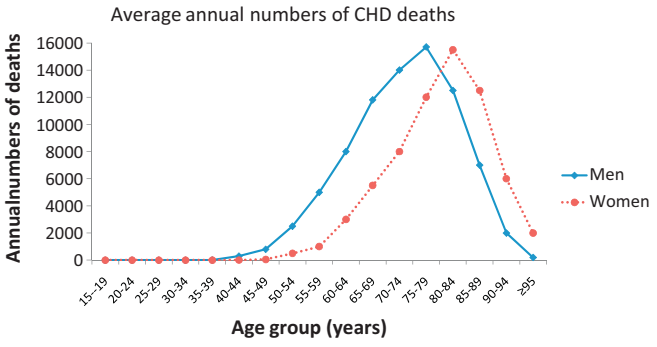

Fig. 2. Number of deaths due to CHD by age group and gender in the UK for the 5-year period 1989–1993 [6].

menopausal women) [14]. The authors concluded that estrogen status might explain the protection against CV disease experienced by premenopausal women and the loss of this protection following menopause.

Despite the overall positive influence of endogenous estrogen, a very small number of younger women do suffer from CHD and are at CV risk. In this age group, improving diet and lifestyle measures can substantially reduce long-term CV risk and the recommendations of the American Heart Association are clearly appropriate: eat a healthy diet, drink alcohol in moderation, avoid smoking, and exercise to achieve a healthy body weight [15]. Cigarette smoking deserves special mention since it is unquestionably the main risk factor in women of reproductive age, and with a prevalence of 22% in developed countries and 9% in developing nations, rates which are forecast to rise, tobacco usage remains a major health concern to society [16].

Oral contraception is an important consideration in this age group and generally speaking it does not increase CV risk, even in those individuals with hypertension, provided blood pressure (BP) is well controlled. If BP control is inadequate, then the physician should consider a progestogen-only product or some other means of contraception. In a large population-based case–control study women who were current smokers and who used oral contraceptives had an 8.8-fold increased risk of venous thrombosis compared with non-smoking women who did not use oral contraceptives [17]. Based upon these findings it would be wise for women who smoke regularly to use some other form of contraception.

2.2. Transition

During the transition there is a reduction in ovarian function and a precipitous loss of estrogen as well as alterations in progesterone secretion [1]. This leads to changes in the vasculature (impaired endothelial function) and altered body fat distribution, both of which potentially increase CV risk. This is highlighted in the data presented in Table 1 and Fig. 2 which documented almost an 8-fold increased prevalence of CHD between women aged 45–54 years compared with those aged 35–44 years (13.0 versus 1.7 cases per 1000 women).

There is some evidence that women who develop hot flushes during the menopause may be at increased CV risk as a result of impaired endothelial function, increased carotid intima-media thickness, adverse lipid profile and elevated BP [18]. Furthermore, it has been reported that hot flushes occur more frequently in smokers versus non-smokers (adjusted OR for moderate to severe hot flushes 1.9, 95% CI 1.3–2.9) and in women with high BMI (>30 kg/m^2) versus low BMI (<24.9 kg/m^2) (adjusted OR for moderate to severe hot flushes 2.1, 95% CI 1.5–3.0) [19]. Gerber and colleagues documented significantly elevated daytime ($p < 0.004$) and sleeping ($p = 0.007$) systolic BPs in women experiencing hot flushes compared with women who did not report them [20].

The role of HRT has been the subject of much debate and many reviews in the last decade. Much of this has centred around the early reporting and (mis)interpretation of very large studies such as the Women's Health Initiative study in the USA (for reviews see [21,22]). The findings of the First International Menopause Society Global Summit pertaining to CHD are summarised in Table 2. HRT can have profound effects on the CV system [23]. There are plausible biological mechanisms explaining both benefits (estrogen effects on lipid and carbohydrate metabolism, as well as direct arterial effects and an overall reduction in atherogenesis) and potential harm (high starting doses causing transient increases in coagulation activation and adverse vascular remodelling). Observational studies with HRT have provided some evidence of a beneficial effect on the incidence of CHD and controlled clinical trials have shown that the greatest benefit is achieved in women who initiate

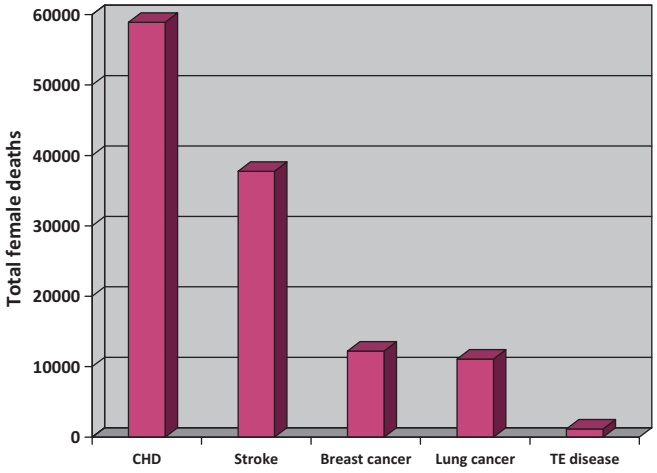

Fig. 3. Causes of death in England and Wales (1996) in women aged ≥50 years [5].

HRT early in the postmenopause. Reinforcing these conclusions, Salpeter et al. [24] reported findings from a meta-analysis involving 39,049 participants followed for 191,340 patient-years which showed that HRT reduced CHD events in younger postmenopausal women, indicating that it may have a primary preventive effect if started at an appropriate age.

2.3. Postmenopausal period

The data presented in Table 1 and Fig. 2 highlight the age-related increase in prevalence of CHD and hypertension. The magnitude of these findings is reinforced by causes of death data from England and Wales, which clearly demonstrates the relative risk of CV and cerebrovascular factors in women aged 50 years and over (Fig. 3) [5]. Similar findings have been reported in the USA [4]. While adverse atherosclerotic changes in the blood vessel wall are most evident in symptomatic disease after the age of 40 years, there is convincing evidence that the seeds of the disease are sown much earlier (Fig. 4) [26]. This is borne out by findings from young patients undergoing heart transplantation; 136 of 262 patients had atherosclerotic lesions and the prevalence was 17% in those aged < 20 years, 37% in 20–29-year-olds, and 60% in those aged 30–39 years (Fig. 4). For all age groups intimal wall thickness was greater in men than women, although the prevalence of atherosclerosis was similar (52% in both groups) [25].

2.4. Estrogen replacement treatment: oral versus transdermal formulations

HRT can be administered orally or non-orally (most commonly by percutaneous gel, transdermal patch or subcutaneous implant). Providing equivalent dosages are administered, all forms of estrogen replacement can relieve menopausal symptoms to a similar degree [26]. However, the route of administration can have a marked impact on the metabolic and hemostatic effects of the various estrogen replacement formulations. Orally administered estrogen induces extensive first-pass hepatic metabolism, and relatively large amounts of hormone are available to interact with hepatocytes and hepatic metabolic enzymes [26,27]. In contrast, transdermal delivery avoids gastro-intestinal absorption and a significant first-pass effect. This difference in pharmacokinetic properties between the oral and transdermal formulations of estrogen has been speculated to account for lipid and hemostatic changes which can impact relative cardiovascular risk [26,28]. As a result of its first-pass effect, oral estrogen has been shown to have more beneficial effects on cholesterol metabolism than transder-

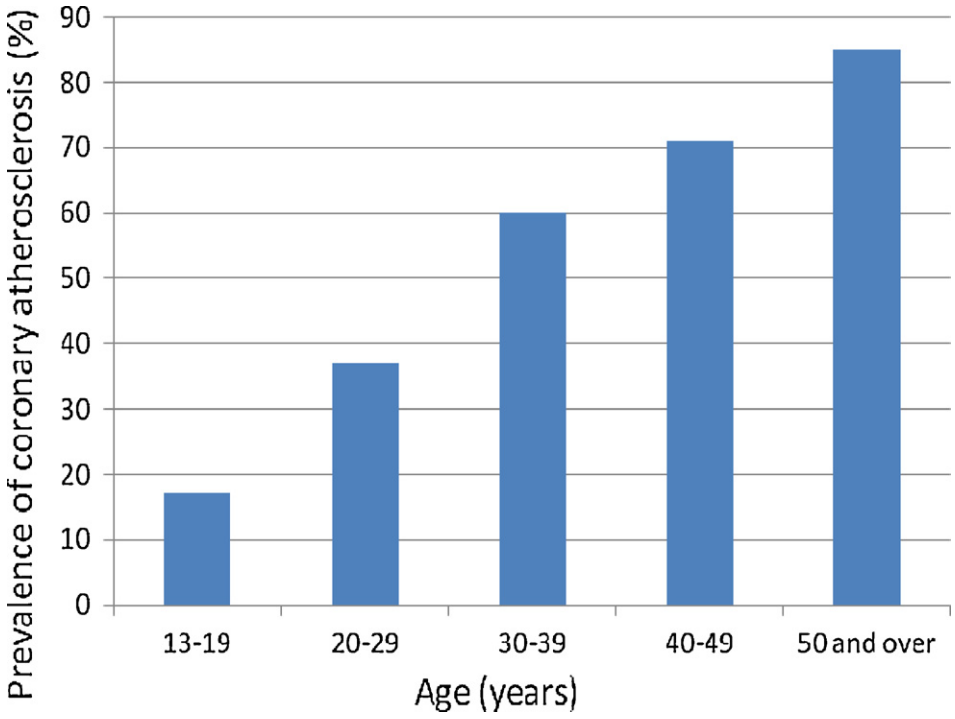

Fig. 4. Prevalence of atherosclerosis (%), defined as intimal wall thickness ≥0.5 mm, by age group in 262 heart transplant donors [25].

Table 2
A summary of the main findings related to the cardiovascular risk of hormone replacement therapy (HRT) administered in the early menopause from the First International Menopause Society Global Summit on menopause-related issues [21].

Risk-benefit parameters	Perception	Scientific evidence
Coronary heart disease (CHD), stroke, thromboembolism	HRT increases the risk of CHD and coronary events	HRT in women aged 50–59 years does not increase CV risk and may actually decrease it in this age group. Estrogen alone in women of this age was associated with significantly lower coronary calcification. No increase in coronary events occurs in the early postmenopausal period and the number of CHD events decreases with duration of HRT.
	HRT increases the risk of stroke	Evidence is unclear. Some large studies have shown no increase in risk whereas others have shown an increase. The overall low prevalence in the 50–59 age group means the overall risk is very small.
	HRT increases the risk of thromboembolism	The risk of venous thromboembolism is about 2× higher with standard doses of oral HRT. However, it is such a rare event in women aged < 60 years, the relative risk is low and may be further reduced by using a transdermal estrogen patch.

Table 3
Change in serum lipid levels in surgically menopausal women treated with oral conjugated estrogen ($n = 35$) or percutaneous gel estrogen ($n = 32$) for 12 months and a non-treated group ($n = 32$) [29].

Lipid parameters (mmol/L)	Control group		Oral group		Percutaneous gel group	
	Baseline	12 months	Baseline	12 months	Baseline	12 months
Total-C	4.84 ± 0.49	4.91 ± 0.39	4.86 ± 0.47	4.37 ± 0.34	4.81 ± 0.47	4.47 ± 0.42
LDL-C	3.35 ± 0.47	3.38 ± 0.34	3.33 ± 0.39	2.44 ± 0.26	3.30 ± 0.34	2.76 ± 0.36
VLDL-C	0.66 ± 0.17	0.68 ± 0.14	0.68 ± 0.17	0.70 ± 0.16	0.67 ± 0.12	0.62 ± 0.09
HDL-C	0.80 ± 0.18	0.85 ± 0.19	0.85 ± 0.21	1.14 ± 0.49	0.86 ± 0.24	1.08 ± 0.27
Triglycerides	1.49 ± 0.46	1.47 ± 0.43	1.53 ± 0.46	1.67 ± 0.45	1.50 ± 0.47	1.41 ± 0.46

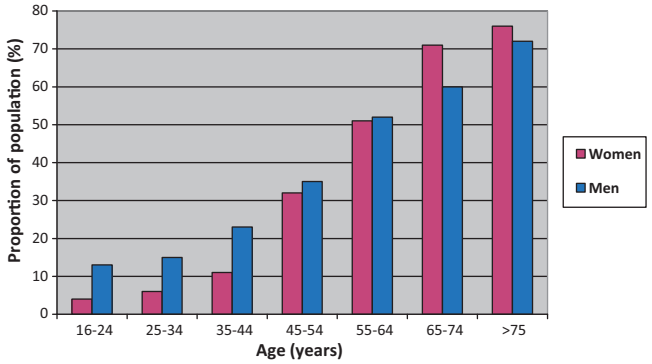

Fig. 5. Prevalence of hypertension in the UK (2002) [32].

mal estrogen in terms of lowering LDL-C and increasing HDL-C. However, transdermal delivery produces a favourable reduction of triglycerides, in contrast to oral estrogen [29,30] (Table 3). Overall, there does not appear to be a significant difference in CHD outcomes in women treated with oral estrogen compared with transdermal estrogen. However, certain trends have been observed which may influence a decision regarding which HRT to prescribe [26,28]:

- Oral therapy may be preferred in women with evidence of insulin resistance (obesity, metabolic syndrome or diabetes).
- Transdermal therapy may be preferred in women with hemostatic abnormalities and at risk of venous thrombosis because of its lower thrombogenic potential.

Overall, with regards to CV risk the route of administration of estrogen probably has less impact than the dose administered. Small subgroups of women may obtain benefit from one formulation over another, but in the majority of cases it may well come down to personal preference [26]. These findings are reinforced by a recent case-control study which determined the rate of stroke associated with oral and transdermal administration of HRT in women aged 50–79 years included on the UK general Practice Research database [31]. The risk of stroke was not increased with the use of low dose estrogen patches [rate ratio 0.81 (95% CI 0.62–1.05)] compared with no use, and was lower than the rate documented for low dose oral HRT [1.25 (1.12–1.40)]. The rate of stroke for current users of low and high dose oral HRT was higher than that for non-users [31].

2.5. Risk factors

Hypertension is one of the key treatable risk factors for secondary CV events, and in both men and women its prevalence markedly increases with age (Fig. 5) [32]. The interesting finding from these data is the overall trend showing that, compared with men, women have a reduced risk premenopause, but postmenopause the prevalence increases sharply and by the age of 65 years and older hypertension is reported more frequently in women. Perhaps what is most important about these statistics is how common hypertension remains; this is despite the introduction of many new classes of antihypertensive medications and clinical guidelines aimed at successful BP management. Data presented almost 20 years ago clearly showed that reducing diastolic BP by as little as 5 mmHg significantly lowered the risk of stroke by 40% and CHD by 25% [33]. The fact that probably less than half of treated hypertensive patients achieve optimal BP control emphasises the greater importance that the medical community needs to commit to this risk factor.

Other risk factors in women who transition through the menopause relate to the metabolic syndrome-diabetes continuum. This largely results from a lack of endogenous estrogen which is paralleled by a redistribution of fat from the gynoid to the more harmful android fat distribution pattern. The android distribution is more commonly seen in men, and also postmenopausal women, and is associated with insulin resistance [34]. Interestingly, HRT has been found to reduce the change to android fat distribution, and presumably lower CV risk, in early postmenopausal women [35]. In women with diabetes, there is a substantial increase in the prevalence of CHD events compared with the rate in diabetic males (HR 14.4, 95% CI 8.4–24.5 versus 2.9, 95% CI 2.2–3.9). The authors attributed this to a higher risk factor burden and a greater impact of BP and atherogenic dyslipidaemia in women with diabetes [36].

3. Musculo-skeletal system

While musculo-skeletal disorders are uncommon during the early years of a woman's life, hormonal changes that occur during the menopause can modulate diseases of the joints (most notably inflammatory arthritis and osteoarthritis) as well as bone metabolism (osteoporosis). Joint problems become more of a concern during the transition to a point where they have been reported to occur in up to 50% of women experiencing menopausal symptoms [37]. Two of the more common causes of inflammatory arthritis are rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The prevalence of osteoporosis increases with age and this is thought to be related to a steady age-related reduction in bone density, which is markedly exacerbated by the menopause [38].

3.1. Reproductive years

During the reproductive period women are generally healthy and inflammatory arthritis is very uncommon. Both RA and SLE appear to be modulated by sex hormones, although the precise role of estrogen remains poorly understood [37]. For example, RA disease activity has long been recognised to remit during pregnancy [39]. Furthermore, the severity has also been shown to fluctuate during the menstrual cycle, getting worse during the luteal phase and better during the early follicular phase when estrogen levels increase [40]. Additional evidence for a role of estrogen in RA comes from experimental studies which have shown that oophorectomy exacerbates the disease while administration of estrogens suppresses disease activity [37]. SLE is far more common in women than men and its incidence is highest in premenopausal women and the incidence increases following the onset of puberty. There are a number of lines of evidence which suggest that SLE disease status is influenced by hormonal status [37,41]:

- SLE fluctuates with sex hormone levels (menstrual cycle), but in a completely opposite fashion to RA.
- SLE symptoms have been reported to worsen in some pregnant women.
- Cyclophosphamide-induced ovarian failure and hypoestrogenism is associated with a reduction in disease flares.
- Estrogen has been shown to modulate components of the immune system including cytokine levels, immune cell function, and antibody binding and production, and these effects are thought to influence SLE disease activity.

Osteoarthritis is the most common form of arthritis and is an age-dependent progressive disease which is very rare in younger women. The incidence of osteoarthritis increases markedly during the menopausal years and continues to rise in postmenopausal women [37,42,43].

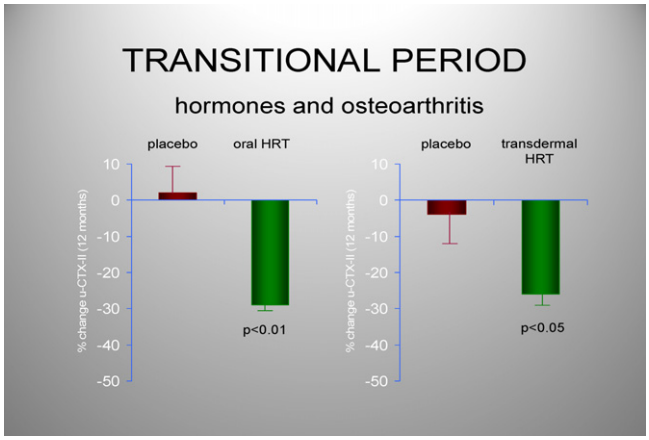

Fig. 6. Assessment of cartilage degradation by measurement of urinary C-telopeptides of type II collagen (uCTX-II) in women aged 45–65 years [52].

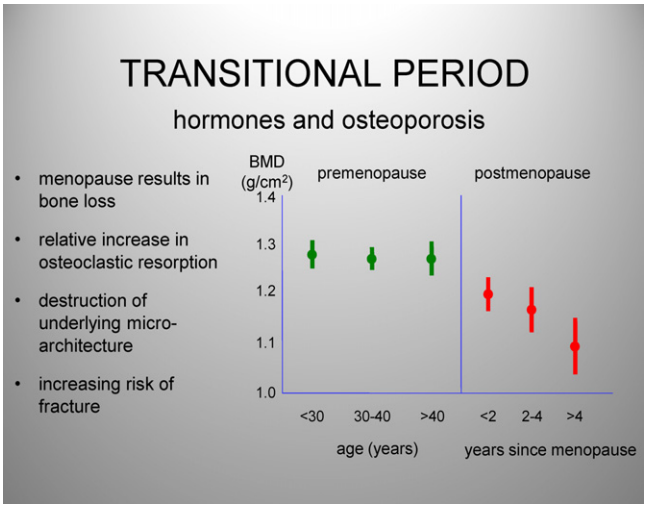

Fig. 7. Change in bone mineral density in women pre- and post-menopause [38].

Osteoporosis is also an uncommon disease in women of reproductive age, and when it does occur there is usually a secondary cause such as anorexia nervosa, cystic fibrosis, celiac disease, premature menopause, post-pregnancy osteoporosis or oral corticosteroid use (particularly in asthmatics) [44]. The obvious treatment in cases where endogenous steroid levels are decreased (anorexia and premature menopause for example) is hormone replacement, and this may best be achieved using a suitable oral contraceptive in this younger age group [44]. Calcium/vitamin D may be useful in girls with cystic fibrosis, celiac disease or those taking oral corticosteroids. Bisphosphonates are probably best avoided in this younger age group given that they are taken up by the bone and have exceptionally long biological half-lives and remain in the body for extended periods. Calcitonin may be clinically beneficial for treating osteoporosis in some younger patients but it is very expensive [44].

3.2. Transition

In women between the ages of about 45 and 60 years ovarian function declines and this transitional phase may be associated with the onset of menopausal symptoms. This period of a woman's life coincides with the appearance of many common arthritic conditions and the apparent reduction of others such as SLE [37].

RA is more common in women than men with a peak incidence occurring at the age of 40–44 years, and the median age of first symptoms occurring about 5 years earlier in women (approximately 45 versus 50 years). Many women develop RA symptoms during the transition following their last menstrual period [37]. Interestingly, epidemiological findings suggest a decreased risk of developing RA in women who had previously used oral contraceptives [45]. In combination, the above findings support a link between hormonal status and RA. However, the majority of studies assessing the impact of HRT on RA have reported little effect on its incidence or severity [37]. HRT may still be a reasonable choice in perimenopausal women, not only for managing menopausal symptoms but also as a preventative medicine in those at risk of developing osteoporosis.

There is weak evidence that HRT slightly increases the risk of developing SLE, but does not significantly affect disease activity [37]. The authors concluded that HRT is useful and safe in patients with SLE, but they did suggest close follow-up during the first 6 months of therapy. To avoid the possible small increased risk of venous thromboembolism associated with HRT it may be prudent to use a transdermal HRT formulation rather than an oral preparation. The effect of oral estrogen on hemostatic variables is generally not observed for transdermal preparations [28,46]. Clinical evidence suggest a 2–3-fold increased risk of venous thromboembolism with oral estrogen replacement, which is not seen in women treated with transdermal preparations [46–48].

Osteoarthritis is more prevalent in postmenopausal versus premenopausal women, and the increase is more than would be expected when age is taken into consideration. Additionally, up to the age of 50 years the prevalence of osteoarthritis is similar in men and women, but thereafter the disease is much more common, severe and generalised in women [37]. This apparent increase in osteoarthritis prevalence and severity in middle age suggests that there may be a relationship between the onset of osteoarthritis and the menopause [49]. Further support for a hormonal effect in osteoarthritis comes from the finding that the disease is more common in hysterectomised women [37]. Likewise, in a sheep model of osteoarthritis ovariectomised animals developed knee cartilage changes which were not evident in non-ovariectomised animals or in those that received estrogen replacement therapy following surgery [50].

What is the possible hormonal link between estrogen and osteoarthritis? It has been reported that estrogen has direct effects on collagen, cytokines and matrix metalloproteinases, and at low doses it may be beneficial by improving tissue remodelling (bone, articular tissue and joints) [37]. A number of studies have examined the effects of HRT on hip and knee osteoarthritis, and most reported a positive protective effect on overall prevalence rates [37]. For example, a pooled analysis of 4 studies which used a combined endpoint of knee and hip osteoarthritis demonstrated a reduction in prevalence in the HRT group with an odds ratio of 0.76 (95% CI 0.63–0.91) [51]. Various studies have reported reductions in the severity of osteoarthritis associated with HRT, and some observed a dose-response effect [37]. Ravn et al. (2007) presented evidence of the potential benefits of HRT in women aged 45–65 years by measuring the effects on urinary C-telopeptides of type II collagen (uCTX-II) [52]. Both oral and transdermal estrogen significantly reduced cartilage degradation as evidenced by 19–30% reductions in uCTX-II ($p = 0.02$ and $p = 0.003$, respectively) (Fig. 6). Despite the clear benefits of HRT in women suffering from osteoarthritis during the transition and postmenopause, very few physicians seem to prescribe it for this indication.

It is well-established that transition through the menopause can result in bone loss in many women (Fig. 7) [38]. Overall, there is a relative increase in osteoclastic resorption and the underlying microarchitecture of the bone is compromised, and this increases the risk of fractures [38,44]. The prevailing view is that

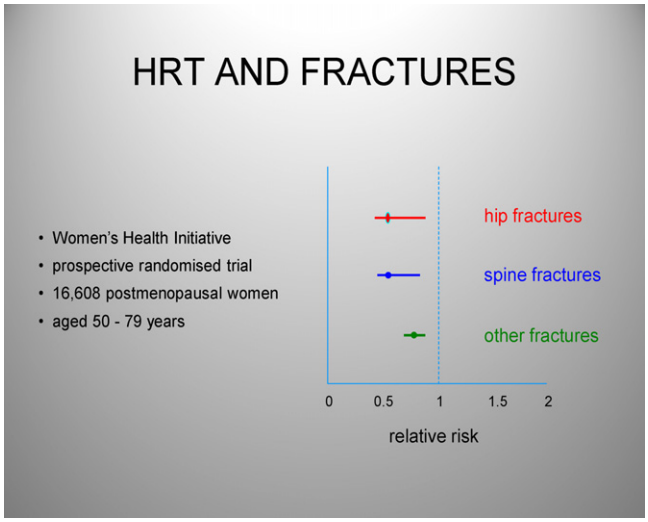

Fig. 8. The relative risk of bone fractures in women aged 50–79 years receiving HRT ($n = 8506$) or placebo ($n = 8102$) in the Women's Health Initiative trial [55].

this increased risk of osteoporotic fracture is confined to the very old; however, while osteoporosis is clearly age-related and fractures are commonest in the elderly, the transition does impart increased risk in younger women. For example, in the UK there are about 100,000 osteoporotic fractures per annum in women aged 50–65 years and this includes approximately 9000 hip fractures [53]. There is clear evidence that a large proportion of these women and their physicians are unaware of the increased risk posed by previously undetected low bone mineral density and in some cases undiagnosed osteoporosis. Thus, the National Osteoporosis Risk Assessment (NORA) longitudinal, observational study involving >200,000 ambulatory postmenopausal women aged 50 years and over with no previous diagnosis of osteoporosis, determined the occurrence of low bone mineral density and osteoporosis in this large US cohort which included 18,000 from minority groups [54]. Using WHO criteria, 39.6% had osteopenia and 7.2% osteoporosis. With regards the total number of fractures, it was greatest in osteopenic patients and this reflects the much greater number of patients with just low bone mineral density compared with the number with confirmed osteoporosis.

These data demonstrate that the greatest number of fractures occur in women who have not yet developed osteoporosis (i.e. they are osteopenic), and they therefore highlight the importance of primary preventive strategies in this high risk group. It is important to recognise that such strategies should prevent all fractures, including hip fractures, and that there should be strong evidence-based support for approved treatments. Findings from the Women's Health Initiative involving >16,000 postmenopausal women highlighted the benefits of HRT in terms of preventing osteoporotic fractures, including hip and spine fractures (Fig. 8) [55]. Despite these positive results, regulatory authorities (European Agency for the Evaluation of Medicinal Products and the UK Committee on Safety of Medicines) have discouraged the use of HRT as a preventive treatment for osteoporosis/fractures and recommend it as a second-line treatment. An International Consensus Group on HRT and Regulatory Issues reviewed the available evidence and concluded that HRT was the only treatment which had been clearly demonstrated to prevent hip fractures [53]. Moreover, since no new safety concerns had been raised, they recommended that HRT should be a first-line option for the primary prevention of osteoporosis-related fractures in postmenopausal women at increased risk. Recently, the Endocrine Society in the USA published a scientific statement on this topic and acknowledged the limitations of the data from the various Women's Health Initiative studies, which involved women of average age 63 years. These data cannot be applied to calculate risk-benefit of HRT for younger women who are perimenopausal. Based upon the available evidence they concluded that HRT afforded benefit for symptoms such as hot flushes and urogenital atrophy, and was also associated with the lowest rates of hip and vertebral fractures [56].

Interesting data were presented by Bagger et al. [57] in Denmark from a follow-up study involving 347 healthy postmenopausal women with normal bone mass who had received HRT or placebo for 2–3 years in a controlled clinical trial. Re-examination of these women 5, 11, and 15 years after stopping HRT demonstrated some long-lasting benefits of HRT administered during the early postmenopausal period in terms of increased bone mineral density and bone mineral content, and also a reduced risk of osteoporotic fractures compared with placebo (OR = 0.49; 95% CI 0.26–0.88). These findings highlight the intriguing possibility that HRT during the early postmenopausal period may provide long-term benefits for the prevention of postmenopausal bone loss and fractures. Unlike bisphosphonates, HRT is not associated with spontaneous fracture of the femoral shaft [58].

3.3. Postmenopausal period

In terms of joint disorders inflammatory processes have generally run their course in older women and new cases of rheumatoid arthritis are rare. The patient still suffers from the ravages of previous disease, but the main problem in this age group is osteoarthritis. The incidence of osteoarthritis increases with age, especially after the age 50 years, and it occurs more frequently in women than men [43]. From a societal perspective it places a huge burden on healthcare systems and costs since it is the most common cause for the patient requiring assistance with lower extremity tasks such as walking, stair climbing, etc. [43]. NSAIDs can be very effective in relieving the symptoms associated with osteoarthritis, but it is prudent to remember that there appears to be increased CV risk with these agents, particularly the COX-2 inhibitors, when used for long periods [59]. For the older woman who is on HRT it may be beneficial for this treatment to be continued since there is some evidence of a protective effect [60].

As noted earlier, osteoporosis is more common in women and the prevalence increases with age and it is therefore a major concern in older individuals. It is associated with low bone mass, microarchitectural disruption of the bone, bone tissue fragility which deteriorates with aging, and an increased risk of fractures. Some clinically important facts and figures relating to osteoporosis are highlighted in Box 1 [51,61–63]. Pelvic fractures usually result from low energy trauma and are associated with appreciable morbidity and mortality [64]. For example in a study involving 148 patients admitted to medical and geriatric wards with pelvic fracture 85% occurred in women and 83% resulted from low energy trauma. 93% were considered to be due to osteoporosis, and in-patient mortality was 7.6% and 1-year mortality 27%. There was a marked impact on mobility and 51.1% required mobility assistance [64].

Optimal management of osteoporosis in postmenopausal women is aimed at primary prevention in those at increased risk of developing the disease. The benefits of estrogen have been scientifically validated and it has been shown to produce a predictable dose- and duration-dependent increase in bone density, and it is also effective in preventing osteoporotic fractures at all relevant skeletal sites [53]. In women aged 60 years or less the benefits of estrogen, not only in terms of reduced osteoporotic fractures but also decreased risk of heart attacks and mortality, are persuasive arguments for its use as first-line therapy in the primary prevention of osteoporosis in this age group [53]. Trans-

Box 1: Facts and figures relating to osteoporosis and osteoporotic fracture [53,61–63].

- Osteoporosis costs the European Union Euros 31.78 billion per year.
- In 2000 there were 3.79 million cases of osteoporotic fracture, including approximately 900,000 hip fractures.
- Lifetime risk of any osteoporotic fracture is "very high" and lies within the range of 40–50% for women and 13–22% for men.
- There are geographic and ethnic variances in osteoporotic fracture rates.
- Fracture incidence is increasing in women in line with the increase in longevity.
- In women 80 years or older with a fracture, 70% are osteoporotic and 27% osteopenic.
- In the UK the remaining lifetime risk rates for different types of fracture in men and women at 50 years have been calculated as:

Fracture type	Women	Men
Hip	11.4%	3.1%
Vertebral	3.1%	1.2%
Distal forearm	16.6%	2.9%
Total	53.2%	20.7%

- Hip fractures are considered the most severe: only 50% of patients regain their prefracture status in terms of ability to walk and the need for aids at home, and up to 20–30% of patients die within 12 months of their hip fracture and it is calculated half of these deaths are due to the hip fracture *per se*.
- Hip fracture in women is more common than any form of female cancer.
- 50% of hip fracture patients eventually require institutionalized care.
- Vertebral fractures are associated with 20–30% mortality after 5 years.
- Distal forearm fractures are much more common in women than men and are usually associated with falls, and they are therefore more common in winter. There is no excess mortality with wrist fractures, but functional outcomes are impaired in about 50% of women for about 6 months.

dermal preparations which lack the thrombogenic potential of higher dose oral formulations may be optimal in older women since venous thromboembolism has been shown to increase with age [28,48]. The currently approved alternatives to HRT for the secondary prevention of osteoporosis include bisphosphonates, tibolone, raloxifene, teriparatide, strontium ranelate, calcitonin and denosumab. Of these, only the bisphosphonates have been shown to prevent hip fracture and that was in older women with a mean age over 65 years [53].

4. Conclusions

Cardiovascular and musculo-skeletal diseases are leading causes of morbidity and mortality during a woman's lifetime. With the general aging of the population they represent a serious and growing public health problem, and place an enormous burden on global healthcare systems and resources.

CV disease is generally rare in younger women and this has been attributed, at least in part, to the protective vascular effects of endogenous estrogen. However, there is evidence to show that the seeds of future CHD problems (atherosclerosis) are sown early in a woman's life and there are strong arguments for promoting well-established lifestyle approaches (cease smoking, eat healthily, drink moderately and exercise regularly) to minimise future risk. During the transition, the protective effects of estrogen are reduced or lost and CV risk is increased. Consequently it is important to monitor and manage risk factors such as hypertension, hyperlipidaemia, obesity and hyperglycaemia. In symptomatic perimenopausal women aged 60 years and younger, HRT has been shown to provide significant benefit (reduction in hot flushes and urogenital symptoms) and it has also been shown to reduce the risk of CHD.

Overall, there does not appear to be a significant difference in CHD outcomes in women treated with oral estrogen compared with transdermal estrogen. However, transdermal therapy may be preferred in older women (a few years after the onset of the menopause) with hemostatic abnormalities and at risk of thromboembolism because of its lower thrombogenic potential. This is based upon the fact that the risk of venous thrombosis increases with age.

Musculo-skeletal disorders are also generally very rare in younger women, but become more common and more severe with age. Indeed, the menopause coincides with the appearance of a number of arthritic conditions including RA and osteoarthritis, as well as osteoporosis. Osteoarthritis and osteoporosis are common debilitating diseases in postmenopausal women and they both appear to be hormonally sensitive. Early diagnosis and identification of individuals at risk is important so as to initiate appropriate management programmes.

There is evidence to support the use of HRT for the prevention of osteoarthritis and osteoporosis in high risk women going through the transition. Indeed, HRT has been shown to be the most effective primary preventative for osteoporosis, and it is associated with the lowest rates of hip and vertebral fractures. Many medicines are available to treat established osteoarthritis and osteoporosis, and in such cases it is important to tailor treatment to the individual based upon a full understanding of risk as well as benefit. Again, transdermal estrogen may be preferable in older women because of the age-related increased risk of thrombotic events.

Contributors

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