Do Menopausal Women Need Estrogen Replacement to Avoid Osteoporosis?

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This paper considers the hypothesis that modern gynecological practices relating to sex-steroid hormones reflect modern sedentary lifeways, along with pharmaceutical commercial pressures, to produce a widespread medical perception that all postmenopausal women need estrogen replacement therapy to avoid osteoporosis (bone fracture risk resulting from low bone density). Like the concept of menopause itself, the concept of universal menopausal osteopenia (low bone density) is a modern medical construction. Numerous clinical trials have demonstrated that estrogen replacement therapies (ERT) help women to retain bone mass in ageing [33], but several trials have also shown that ERT is primarily effective in sedentary women who do not exercise [4; 5], Recent studies of ancient human bones suggest that bone-mass in women was higher in the pre-agricultural ancestral past due to greater physical activity demands and greater nutrient density than are common in modern corporeal lifeways [1; 23; 31]. From an evolutionary perspective, the metabolic nature of bone as a tissue that can be increased or reabsorbed in response not only to sex-steroid hormone levels but also to dietary mineral and protein status, vitamin D, and mechanical loading appears adapted to an environment that was abundant in nutritional micronutrients, sunlight exposure and regular, demanding physical activity [9; 18].

Bone is highly metabolic tissue that is continually ‘turning-over’: Osteoblasts build it and osteoclasts dissolve it according to mechanical stimulus and hormonal signals, and relative to available nutrients - particularly calcium, magnesium, protein and vitamin D [15]. Throughout youth, the ratio of growth to reabsorption is highest, with a period of peak bone-mass acquisition between ages 16-35 [15]. During pregnancy and lactation, women become more bone-catabolic in order to draw from the mineral reserves in bone to nourish infant development [18]. Bone loss then is not per se a pathological process. After age 50, the ratio of reabsorption to growth is generally higher in everyone, but if a healthy reserve has been amassed in youth, this is unlikely to result in old-age fractures [15; 18], However, there are stressors that can prohibit the

accumulation of a healthy bone reserve in youth, including severe malnutrition, specific deficiencies (such as calcium, magnesium, omega 3 fatty-acids, protein, vitamin D) [40; 49], numerous early pregnancies, major infectious diseases, lack of physical activity throughout the peak-bone accumulation period [1; 31], the surgical removal of gonadal organs that produce bone-protective hormones, and use of the contraceptive pill [1; 2Unfortunately, several of these very stressors – especially vitamin D deficiency, physically passive lifeways, women's reproductive surgeries, and use of the contraceptive pill - remain highly prevalent throughout the affluent world today [30; 49].

This paper forms part of an integrative biohumanistic research project on sex-differentiated ageing in the history of medicine, informed both by recent biomedical and anthropological evidence, and by an approach to the history of medical concepts that considers how past inheritances continue to shape research and clinical practices. Menopausal osteopenia is a disease category that appeared only in the second half of the twentieth century in the context of the postwar pharmaceutical investment in estrogen replacement therapies, as demonstrated by the late medical historian Gerald N. Grob in his 2014 monograph *Ageing Bones* [12]. Grob argued that the concept of menopausal osteopenia turns a process of normal ageing into a pathology, and presented a compelling case for this concept as an example of "disease mongering," referring to the new designation of pathologies beyond scientific evidential grounds, in the service of commercial interests in the therapies pertaining to treat them. Globally, numerous menopause and osteoporosis researchers and national medical associations continue to support the use of estrogen replacement as a universal preventative treatment for all women over the age of 50 on the basis of Dual-energy X-ray absorptiometry (DXA) data that have suggested an accelerated bone turnover after this age [13; 25]. The medical market for bisphosphonates (drugs that present loss of bone density) has also massively grown as a treatment for those deemed 'at risk' of the disease on the basis of low Bone Mineral Density scores. Imaging technology corporations, too, have gained from the emerging global obsession with scanning bodies to determine osteoporotic risk, in the view that this risk itself indicates a growing disease epidemic in the affluent world due to a rapidly ageing population [12].

In further support of Grob's skeptical account, several studies, both recent and historical, have demonstrated that bone turnover accelerates in women before the decline in estrogen associated with the end of menses, suggesting that it is not a product of menopause per se, but of the process of ageing more generally [11; 28]. Numerous studies funded by the pharmaceutical producers of estrogen-replacement products, examining the effect of estrogen replacement on bone density have certainly demonstrated their positive effect in preserving bone mass [33]. But other, publicly-funded, clinical trials comparing HRT with resistance training have shown that the bone protective effect of estrogen is most pronounced in sedentary women who do not exercise, in whom it also

increases fat mass, while resistance training without HRT increases bone density and muscle mass with congruent fat loss [5; 39].

In the early-twentieth-century discovery of the sex-steroid hormones, it was initially thought that testosterone was exclusively a male hormone and estrogen exclusively a female one. This over-simplification was quickly understood to be false when further enquiries revealed the presence of all the sex-steroid hormones in both men's and women's bodies [32]. Nonetheless, numerous researchers throughout the twentieth century, and even still today, casually refer to these hormones as if they are sex-specific. The view of estrogen as the hormone that regulates women's entire physiology which has characterized its twentieth-century history [46], continues to underly current misconceptions about osteoporosis as a female-specific disease of postmenopausal estrogen deficiency [12]. Certainly, the role of estrogen in fetal development and in puberty is important for female-specific sex-trait development, and its role in ovulation and conception is crucial for female reproductive function. But women are not only estrogenic and typically produce more testosterone than estradiol [8]. Importantly, both the androgens and estrogen have been found to have bone-protective effects both in men and women [21; 27; 44]. This is evident in several recent studies of transgender hormone-bone interactions: MTF (male-to-female) transgender women on long-term estrogen therapy show preservation of bone density in ageing, but so do FTM (male-to-female) transgender men taking exogenous testosterone [43; 51].

However, several modern pharmaceutical hormone practices specific to women in fact suppress women's natural testosterone: Both the estrogen-only contraceptive pill and the use of menopausal estrogen replacement. The mechanism of this suppression is well understood: Exogenous estrogenic compounds massively upregulate Sex-Hormone Binding Globulin (SHBG) and Cortisol-Binding Globulin (CBH) which preferentially bind and inactivate the androgens rather than the estrogens which trigger these proteins [20; 50]. Postmenopausal women on ERT thus acquire abnormally high estrogen (for their age) with abnormally low Free-Testosterone and DHEA [33]. The androgens, too, preserve bone density in men and women, having anabolic effects both directly on bone and indirectly via preserving muscle-mass and strength. [24; 26; 41] Thus, in supplementing one bone-protective and mildly anabolic hormone in exogenous estrogen replacement, ERT-using-women sacrifice other even more anabolic endogenous hormones that also protect bone.

Since the 1950s, most of the pharmaceutical research studies demonstrating a bone-protective effect of ERT have included women who have had hysterectomies and oophorectomies, often as a prophylactic measure against ovarian cancer, or as a treatment for gynecological disorders [46]. The loss of these organs, while producing minimal impact on endogenous estradiol levels, results in a precipitous decline in both testosterone and DHEA, producing a deficiency that is uncommon in women without surgery whose androgen levels remain relatively stable throughout menopausal transition and after (declining in a gradual, linear fashion with ageing, similarly to how they do in men) [6; 20]. Remember -

testosterone also preserves bone density! The use of hysterectomy, oophorectomy, and estrogen-based therapies to prevent osteoporosis have all been working together against the naturally bone-anabolic hormones that would otherwise be relatively abundant in postmenopausal women.

The estrogenic contraceptive pill used throughout the late twentieth century has similarly suppressed bioavailable testosterone and DHEA in women by stimulating SHBG and CBG [33; 53]. Specific contractive pill formulations have also been found to inhibit peak bone-reserve growth in young women, both by disrupting endogenous estrogen's anabolic effects on bone, and by suppressing the androgens' anabolic effects on both bone and muscle [2; 14; 48] Given the widespread prevalence both of various contraceptive-pill formulations and of hysterectomy and oophorectomy throughout the affluent world since the 1960s, it might be considered that these modern pharmaco-medical practices may themselves be among the novel pressures of modernity contributing to the increased prevalence of women's osteoporosis. The model then in which a woman who is predominantly sedentary and does no resistance exercise, lives primarily indoors, takes the contraceptive pill for several years in her twenties, then has her sex-hormone-producing organs surgically removed, then takes exogenous estrogen, conspires to produce an unusually androgen-deprived and osteopenic older woman, who is far more likely require estrogen (and/or bisphosphonates) as a protective measure against old-age fractures. Here it seems plausible that, at least to some degree, 'menopausal osteopenia' has been iatrogenically (i.e., unintentionally harmful) produced by the pharmaceutical industry to require the very drugs sold by the corporations that have funded much of the research on them.

However, there are also reasons to consider that changes in bodily lifeways in modern affluent cultures have also helped to produce the current epidemic of elderly osteoporosis. Osteoporosis is most common in some of the most affluent countries of Northern Europe and North America, but not in all those with higher life-expectancy [12]. One of the most likely reasons for the elevated osteoporotic risk from the postwar era onwards is the increase in largely sedentary indoor lifestyles, comprising jobs entailing all-day sitting, under artificial light, at a desk or in front of a computer, reliant on forms of transportation in which the passenger is physically passive, and on electronic household devices that spare the user any major physical effort, along with the increase in screen-based leisure activities that also entail sitting. Many modern technologies that only became widespread in the second half of the twentieth century have resulted in far less physically-active household labor and childcare: Consider the impact of the use of perambulators (wheeled baby carriages) and of mechanized devices for washing clothes, dishes and cleaning, as well as refrigeration and running water supplies that permit a massive reduction in walking and carrying for the daily provision of the necessities of life [29]. There has been a process of gradual load alleviation throughout human history, but which has been massively amplified and globalized since the end of World War Two [16]. To be free of physically-

taxing and time-consuming chores can undoubtedly be a good thing for creative and intellectual flourishing, but in their place we need to find other ways of regularly loading our bones if we wish to prevent their dissolution.

Numerous recent studies have shown that resistance training preserves bone mass in older adults, both in those who lifted heavy weights only in their youth, and in those who take up lifting weights as older adults [3; 17; 19; 46]. As several groups of researchers have recently shown, many earlier studies failed to confirm the bone-preserving effects of resistance training in older adults due to poor study-design with insufficient joint-reaction-force stimulus and too short duration to show meaningful changes in bone density and architecture [4; 52]. Perceptions that older women could not handle or would not comply with a program of lifting heavy weights appears to have informed many of these study-design practices. But recent research has shown properly-instructed compound and high-impact lifting to be well-received and have spectacular bone-preserving effects in postmenopausal women, particularly in the presence of osteopenia and osteoporosis [4; 17; 47].

In proclaiming menopausal osteopenia a universal human disease, some researchers have cited studies of historical skeletal remains showing osteoporotic fractures in past human societies, such as Ancient Egypt, the Roman Empire and medieval Europe, taking such examples as evidence against the role of physical activity in preserving bone since these historical populations engaged in regular manual labor and still appeared to have suffered osteopenia [37]. However, premodern agricultural women experienced their own set of negative pressures on bone mass, such as seasonal caloric undernutrition with resultant ovarian suppression [1; 18], widespread infectious diseases such as the bubonic plague and tuberculosis, 8-10 pregnancies per woman [9; 22], and mineral and protein deficiencies produced by diets focused heavily on cereal grains [23]. Given these factors, the high activity-levels of women in these post-agricultural historical societes alone could not be expected to compensate in preserving bone mass into old age. On the other hand, studies of the bones of hunter-gathers and of very early agriculturalist populations tell a rather different story: Stone-age skeletons typically show 15-20% higher bone mass than age-matched modern humans, with archeologists proposing the main causes being greater activity levels and greater nutrient density prior to the adoption of cereal-based agriculture [30; 31; 36; 40]. One recent study has shown prehistoric female forearm bones from Central Europe to have similar density and mass to those of present-day elite competitive rowers [23].

With optimal nutrition and physical activity - and in the absence of specific surgeries, medications, or diseases that increase bone turnover - it seems likely that most women could avoid osteoporotic fractures in old age without ever taking estrogen replacement [5]. Some forms of low-dose ERT, particularly transdermal, may be relatively safe based on recent research reviews, and the evidence of such therapies having benefit for reduction of hot-flush symptoms in menopausal transition appears robust [10; 42]. But estrogen’s prescription as a universal anti-osteoporotic

prophylactic is a symptom of a unique historic nexus of modern medical, pharmaceutical, and lifeway disservices to women's strength and resilience.

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