Novel paradigm on the effect of estrogen on bone

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Abstract

According to prevailing unitary model of involutional osteoporosis, female postmenopausal bone loss can be divided into two separate phases: the accelerated, transient phase, which is most distinct over the subsequent decade after the menopause and accounts for 20-30% of the cancellous bone loss and 5-10% of the cortical bone loss (type I osteoporosis), and the following gradual, continuous bone loss (type II osteoporosis). Estrogen deficiency is currently quite unanimously accepted as the primary cause of type I osteoporosis, as well as also a major determinant of type II osteoporosis, and quite plausibly, the quest to uncover the origin of type I (and II) osteoporosis has focused on the estrogen withdrawal-related skeletal changes at and around the menopause. However, given that the cyclical secretion of estrogen begins normally in early adolescence and continues over the entire fertile period (excluding the potential periods of pregnancy) until the eventual cessation of female reproductive capability, one could argue that this menopause-oriented approach is limited in scope. In this review, some classic findings of the pubertal effects of estrogen on female bones are presented, findings that were paramount to Fuller Albright when he first described the disease called postmenopausal osteoporosis in 1940, but studies/findings that have failed to attract the attention they deserve. When these findings are incorporated with the primary function of the axial skeleton and long bones, the locomotion, an alternative, novel explanation for the function of estrogen and accordingly, the origin of the accelerated phase of postmenopausal bone loss, is proposed: estrogen packs mechanically excess bone/mineral into the female skeleton at puberty, a bone stock that later serves as the origin of the type I postmenopausal osteoporosis.

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Estrogen and postmenopausal osteoporosis

Since Fuller Albright introduced his classic concept on postmenopausal osteoporosis, the role of estrogen has been the question of paramount interest among skeletal researchers. The cyclical secretion of estrogen normally begins in early adolescence and continues throughout the entire fertile period (excluding periods of pregnancy) until the eventual cessation of female reproductive capability. The principal target organs of estrogen include the breast, uterus, fallopian tubes, ovaries, vagina, vulva, terminal portion of the urethra, and the skeleton. Common to tissues of these organs is that they contain estrogen receptors and the organs themselves increase in size in response to estrogen stimulation and atrophy in the absence of estrogen stimulation.

The extraskeletal effects of estrogen, such as the hypertrophy of the reproductive organs at puberty following the onset of estrogen secretion and the disappearance of these changes at menopause as a consequence of estrogen withdrawal, are a virtual biological axiom. However, somewhat paradoxically, the skeletal effects of estrogen at menarche and menopause (particularly concerning mineral mass) do not seem to obey this "ON-OFF" –relation, although our skeletons have been as much a part of biology as the rest of us. Rather, according to prevailing views on postmenopausal osteoporosis, the female skeletal mass (bone stock) that exists before menopause under normal secretion of estrogen represents an appropriate baseline. As the withdrawal of estrogen is quite unambiguously accepted as the root cause of the accelerated phase of bone loss, it inherently leads that the type I postmenopausal bone loss has to be an estrogen withdrawal-triggered failure in the delicate bone balance (homeostasis) that exists before menopause.
Estrogen-driven pubertal packing of the skeleton - experimental evidence

Fuller Albright actually proposed that estrogen triggers the build-up of calcium reserves in bone, from which calcium can be released into the bloodstream during pregnancy and lactation to serve the needs of the fetus and newborn. He based this proposal primarily on two studies in which the skeletal effects of estrogen were explored in pigeons. However, the reproductive function of estrogen is very distinct in birds: prior to egg laying, the marrow cavities of certain bones are invaded by a complex network of cancellous bone, called medullary bone. This extra stock of bone serves no mechanical role but functions as a mineral reservoir for eggshell calcification and quickly disappears after the final egg has been laid. Quite plausibly, findings in birds may not necessarily apply directly to other species (particularly humans), but a similar mechanism of the female skeleton having significantly higher bone mass relative to the body and lean (muscle) mass than male skeleton seems to apply, at least to rats.

Structural and locomotive perspective

Considering that most of the above noted fundamental discoveries on the skeletal effects of estrogen were initially proposed over a half a century ago, one may wonder how is it possible that the concept of packing of mechanically-excess bone into female skeleton at puberty has eluded the attention of the present-day researchers? In an attempt to provide a plausible explanation, a reference to a Perspective article of Michael Parfitt is warranted:

"The primary function of the bones is to resist the mechanical forces applied to them by muscle contraction and gravity, so that the parts of the body can move without breaking. To carry out this function, each bone has a species-specific size, shape, and internal structure, the outcome of both evolutionary adaptation in the population and physiologic adaptation in the individual during growth. The precise three-dimensional location of each element of a bone is critical to its mechanical function, but much less important for subsidiary functions such as support of hematopoiesis and participation in mineral homeostasis. Endocrinologists and nephrologists have always been more interested in such non-mechanical functions and so have paid more attention to bone as a tissue than to bones as organs."

Accordingly, the tissue-level effects of estrogen and other systemic (hormonal) factors on bone have been characterized in detail, as summarized for example in a beautiful, comprehensive review by Riggs et al. However, despite being advocated by some of the most prestigious people in osteoporosis research, the structural (e.g., organ-level) approach is still scarcely used. In fact, the classic studies by Garn, suggesting that estrogen primarily deposits the mineral on the endocortical surface of female bones, are among the very few evaluating the possible effect of estrogen on bones from the structural point of view. An obvious limitation of even this structural approach is that bones are still considered "bare" structures, not an integral part of the mechanical environment they act upon. In this context, considering on one hand that the primary function of the skeleton is locomotion and on the other that principal loading on the bones comes from the muscle-contraction engendered loading, the most appropriate approach in assessing bone quality might actually be the so-called locomotive perspective – the evaluation of bone strength (the bottom line) in relation to the loading subjected on them.

Estrogen-driven pubertal packing of the skeleton - human evidence

To the best of my knowledge, Profs. Schiessl, Frost and Jee were the first to employ the locomotive perspective on humans by comparing the total body bone mineral content (a surrogate of the strength of the skeleton) to lean body mass (a surrogate of muscle strength) derived from the bone densitometric data of growing males and females of a study by Zanchetta et al. They showed the existence of the puberty-associated disproportionate packing of mechanically-excess bone into the skeletons of girls in comparison to boys. In essence, it was shown that relative to the lean/muscle mass (mechanical demands placed on bones) - the primary regulator of their mass, size and shape - girls have substantially heavier (stronger) bones than boys at the corresponding age.

To either corroborate or refute the above noted finding, a German research team specifically carried out an extensive characterization of the interaction between bone and muscle in healthy children using pQCT. By determining the cross-sectional areas of cortical bone and muscle of radial midshafts (representing bone and muscle strength, respectively) on 318 healthy children (159 boys and girls) aged 6-22 years and 336 adults (parents of these children) using pQCT, Schönaus et al. were able to show that the "bone strength–to-muscle strength" relation, which was identical in boys and girls before puberty, began to increase in girls at pubertal stage 3. This higher growth rate of the female bones resulted in significantly greater bone cortical cross-sectional area (stronger bones) relative to the incident loading in comparison to boys at pubertal stage 5, confirming the preliminary findings on the disproportionate increase in the strength of female bones at puberty.

Considering that estrogen is generally considered a predominantly female sex hormone, it could be regarded as somewhat unprecedented that another corroborative piece in this estrogen-bone puzzle, specifically regarding the causality between pubertal bone-packing and estrogen, has actually been provided by studies in men. However, men with syndromes of congenital estrogen deficiency or resistance due to rare genetic defects in estrogen receptor sensi-
Skeletal effects of estrogen

Using pQCT, Schönau and his colleagues have reported data suggesting that estrogen brings about an actual "condensation" of bones. Using the material described above (a study of 185 females and 177 males aged 6-23 years of age), they showed that the vBMD of the cortical compartment of the proximal radial diaphysis was similar in prepubertal girls and boys, but significantly higher (+3-4%) in females after pubertal stage 3, even after correction for the potential bias attributable to partial volume effect or difference in developmental stage. There also appears the acquisition of two types of calcium stores in cortical bone around female puberty, the first being attributable to the apposition of bone on the endocortical surfaces, and the second resulting from increased true mineral density in the cortical compartment. Comparison of the existing literature shows that the apparent cortical volumetric BMD in women is indeed slightly higher (+1% to +4%) also in the other sites of the appendicular skeleton in comparison to men. The increased vBMD of the cortical bone makes very much sense mechanism-wise, as according to the prevailing view, estrogen primarily controls bone turnover: As the vBMD of the cortical bone, an integrated measure of both cortical porosity and mean material density of cortical bone, is considered to reflect the metabolic activity of cortical bone (intracortical modelling), these findings actually suggest that intracortical remodelling is indeed lower in postpubertal females than in males, an apparent estrogen effect.

Estrogen and skeletal responsiveness to loading

In our recently published study, we initially set out to explore the possible role of gender on the skeletal responsiveness to increased loading. However, due to the somewhat unexpected results, we ended up extending far beyond the initial objective in the subsequent two experiments - to the skeletal effects of estrogen. Briefly, it was not that peculiar that we observed a substantially lower responsiveness to external loading in the female than male rats, but we were somewhat surprised to notice that relative to body size and muscle weight (incident loading), the female bones were considerably stronger (and also had higher bone mass) than
those of the males. At first, we simply decided to corroborate/refute the results of the first experiment (on 5-week-old rats) with 33-week-old female and male rats. However, after obtaining virtually identical responses using these mature rats, we hypothesized that if the apparent extra stock of mineral in female bones and the concomitant lower responsiveness to mechanical loading were truly attributable to estrogen, then withdrawal of estrogen should not only reduce bone strength (through reduced bone mass and/or density), but also lead to an increased response to loading. Accordingly, in the third experiment, 60 littermates of 3-week-old female rats were first subjected to either ovariectomy or sham-operation and then randomly assigned to treadmill training and control groups. At the end of a 16-week intervention, comprehensive densitometric and mechanical data confirmed both that bone strength was reduced in the ovariectomized rats and that these estrogen-depleted rats also displayed a better responsiveness to mechanical loading.

Our findings, suggesting that estrogen packs mechanically-excess mineral into the female skeleton at puberty, actually provided a credible mechanism for the previous studies concerning the timing of the most responsive period of female bones to mechanical loading. The racquet-sports-induced benefit in bone mass has been shown to be about two times greater if women had started playing at or before menarche (the beginning of the cyclic secretion of estrogen) rather than after it, indicating that the time immediately before and around the menarche is the most osteogenic period of growing female bones to increased loading. The hypothesis is also in perfect agreement with the fact that in growing girls the benefit of mechanical loading on mineral mass and strength of bone is better before than after the menarche. Finally, the observation of better skeletal response to increased loading in estrogen-depleted than estrogen-replete bone seems to concern the other end of the female reproductive life, the menopause (postmenopause), too. By performing a proper "skeletal responsiveness analysis", an analysis in which the actual response to exercise (change in BMD controls vs. exercise) is determined within the HRT and estrogen-depleted groups, to the data of the three studies exploring the effect of hormone replacement therapy (HRT) and exercise in postmenopausal women with the appropriate 2 x 2 factorial study design, we observed a statistically significant BMD response in the hip region of the estrogen-depleted women in all three studies, but no response in the estrogen-replete (HRT) women.

Pubertal packing - reproduction-related safety deposit?

Once mechanical loading (locomotion) is acknowledged as the major determinant of bone strength and one determines the strength of pubertal bone of girls (females) in comparison to boys (males), it becomes readily evident that there must be a distinct, additional determinant of bone strength in the female population. Considering the above reviewed evidence, this determinant seems to be estrogen (changes related to the female puberty/secretion of estrogen). This inherently leads to two questions:

1) Why would puberty/estrogen make the bones "too strong" relative to incident loading?

2) What might be the evolutionary benefit for a link between this pubertal bone packing and female biology?

Turner suggested that in mammals, increasing estrogen secretion during adolescence leads to increased cancellous bone volume, a stock of bone that can then be mobilized during pregnancy and lactation. Consistent with this notion, a number of recent experiments provide evidence on the accumulation of excess mineral (mass) in the developing female skeleton. This extra stock of bone seems to facilitate the first reproductive cycle, which is considered to be metabolically inefficient compared with subsequent reproductive cycles, after which a new skeletal steady state is established. It appears that the mechanism for that additional bone strength is indeed estrogen-related and we argue that the additional bone mass provides a reservoir for reproduction.

Although our hypothesis regarding the effects of estrogen (estrogen-driven extra packing of bone mineral into female bones in puberty) "violates" one of the fundamental principles of musculoskeletal biology, Wolff's law, it simultaneously highlights the overwhelming influence of estrogen and reproductive needs on the female skeleton. During the entire female reproductive life, estrogen simply overrides the loading-driven functional control of the skeleton, the primary regulator of bone size, shape and architecture in men. Thus, there seems to be an actual dimorphism in the skeletal control of bone strength: while the bones of men seem to be under constant control of incident loading, the female skeleton is apparently thrust into a higher (less responsive) level for the reproductive period. Accordingly, estrogen does not de-sensitize the bones to strain detection, as presumed today, but rather, the female bones simply have excess strength due to estrogen-induced packing. As a consequence, the previously effective loading is reduced ("damped") to levels not requiring an adaptive response.

Unpacking - the origin of type I osteoporosis

If estrogen secretion indeed results in packing of mechanically-excess mineral into the female skeleton, which seems obvious based on the above noted studies, then the prevailing view on pathogenesis of postmenopausal bone loss warrants reconsideration. Rather than trying to provide a complex pathogenetic mechanism for the accelerated phase of postmenopausal bone loss (type I osteoporosis), such as an estrogen withdrawal-triggered failure in the control of bone homeostasis/the function of any of the relevant bone cells, one is tempted to extend these findings concerning pubertal skeletal action of estrogen to apply to menopause, too.
Accordingly, a simple, evolution-based and biology-oriented explanation is proposed: the accelerated phase of bone loss at menopause simply results from the shedding of an evolutionary "safety deposit" of bone mineral when the female reproductive function ceases.

Although direct (longitudinal) data on the causative interplay between pubertal-packing and estrogen withdrawal-related menopausal loss of bone naturally cannot be found, the existing literature actually provides rather convincing proof for the concept. Soon after Schiessl et al. introduced their hypothesis on the disproportionate packing of mechanically-excess bone into the female skeleton at puberty24, Ferretti et al.53 added the data of 672 age-matched men and women, aged 20-87 years, to their previous study,24 and as a consequence, were able to cover changes in the whole-body bone mineral content and lean body mass in females and males through virtually the entire lifespan (from 2 to 87 years of age). Using this data from the age range from childhood up to old age in both sexes, the authors showed that in females, the pubertal packing of excess mineral and the accelerated phase of bone loss that follows the menopause appear to be "mirror images" of the same phenomenon. Unaware of the above noted study, we55 came to the same conclusion by pooling the total bone mineral content and body composition human data from studies of Zanchetta et al.24 and Rico et al.54 (Figure 1).

Our hypothesis on the skeletal function of estrogen is not only applicable to "hormone free, hormone replete, hormone deplete"-state (pubertal packing and then subsequent unpacking at menopause), but also to "hormone deplete, then replete"-state (repacking of postmenopausal bones by hormone replacement therapy, HRT). In a study evaluating the effects of HRT and exercise on postmenopausal women using CT scanning, Cheng et al.38 observed that in comparison to the placebo group, the women on 1-year HRT displayed a significant gain (increase) in volumetric BMD of both the proximal femur (containing mostly trabecular bone) and tibial shaft (containing mostly cortical bone). By analysing the average bone mass/density distribution across the bone cross-sections (using radial distribution of bone density as a function of the distance from the center of the bone mass through the diaphyseal wall), the authors could further pinpoint the positive HRT response of the tibial and femoral midshaft (cortical sites) to be predominantly located on the endocortical region56. In agreement with these findings, Uusi-Rasi et al. showed in their pQCT analysis that users of HRT have significantly higher volumetric BMD in the cortices of the tibial midshaft than the non-users, the difference being about 1.5-3%. In the distal tibia containing both trabecular and cortical bone, in turn, the HRT-related effect was less distinct and also seemed to be mediated through change in the geometry of the cortical component and not an increase in trabecular density57,58.

Summary

Estrogen, the principal reproductive hormone, seems to pack mechanically-excess bone into the female skeleton at puberty and take part in the development of gender differences in bone architecture (sexual dimorphism). The mineral storage function, apparently a safety deposit for the increased demands of pregnancy and lactation, provides a plausible and likely origin for the accelerated bone loss (type I osteoporosis) occurring at menopause.

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