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ABSTRACT

Estradiol (E2) is women's dominant 'bone hormone' since it is essential for development of adolescent peak bone mineral density (BMD) and physiological levels prevent the rapid (3-week) bone resorption that causes most adult BMD loss. However, deceasing E2 levels trigger bone resorption/loss. Progesterone (P4) is E2's physiological partner, collaborating with E2 in every cell/tissue; its bone 'job' is to increase P4-receptor-mediated, slow (3–4 months) osteoblastic new bone formation. When menstrual cycles are normal length and normally ovulatory, E2 and P4 are balanced and BMD is stable. However, clinically normal cycles commonly have ovulatory disturbances (anovulation, short luteal phases) and low P4 levels; these are more frequent in teen and perimenopausal women and increased by everyday stressors: energy insufficiency, emotional/social/economic threats and illness. Meta-analysis shows that almost 1%/year spinal BMD loss occurs in those with greater than median (~31%) of ovulatory disturbed cycles. Prevention of osteoporosis and fragility fractures requires the reversal of stressors, detection and treatment of teen-to-perimenopausal recurrent cycle/ovulatory disturbances with cyclic oral micronized progesterone. Low 'Peak Perimenopausal BMD' is likely the primary risk for fragility fractures in later life. Progesterone plus estradiol or other antiresorptive therapies adds 0.68%/year and may be a highly effective osteoporosis treatment. Randomized controlled trials are still needed to confirm progesterone's important role in women's bone formation.

Introduction

Bone is a complex, adaptable tissue with a protein 'matrix' that becomes strong with mineralization. Each bone, of over 200 in our bodies[1], grows to its particular size, shape and structure for its role(s) in mobility, protection of vital organs and emergency calcium availability. The two main types of bone – cancellous and cortical – have different roles and rates of turnover. The calcium stored in cancellous bone (honeycomb-like bone in the center of vertebrae and long bones) is essential to catalyze heart, nerve, brain, and muscle functions. Dense outer cortical bone of limbs and others is necessary for strength.

Bone tissues renew/renovate through a complex 'remodeling' process across the lifespan. Bone adaptably responds to nutritional inputs, gravity, exercise and hormonal signals; its bone-negative responses to illness, pain and weight loss emergencies are kept short. The overall lifecycle *bone health goal* is to build a large, well-mineralized and strong skeleton (bone mineral density, BMD), so age-related normal losses will not cause osteoporosis, manifest by fragility fractures (bone breaks with ≤ force of a fall from a standing height).

Both estradiol (E2, 'women's hormone') and progesterone (P4), E2's ovarian partner hormone, play essential roles in bone balance. E2 slows bone resorption and P4 stimulates bone formation[2]. That P4 is important for bone is controversial. One reason is that E2 prevents bone resorption, the primary reason for BMD loss[3] (Box 1). But bone remodeling/renovation is a two-part, balanced process; bone resorption is fast while formation is slow. The balance in bone remodeling during the menstruating years likely determines lifelong bone health (Box 1).

The purposes of this review are to describe the E2–P4 partnership in normal bone, review P4's practical and clinical roles in osteoporosis *prevention* and added to antiresorptive therapies for *treatment* of increased fragility fracture risk. To understand P4 and bone health, we need to understand women's 'bone renovation', *remodeling*, system (Box 1). It is also initially necessary to appreciate bone's changes across the reproductive phases of women's life cycle (Figure 1).

Integrating women's reproduction with the bone life cycle

Figure 1 shows idealized spinal BMD changes over time and will serve as a guide through the description of women's reproductive lifespan. Since ovarian hormone patterns vary across menstrual cycles and across life phases, and E2 and P4
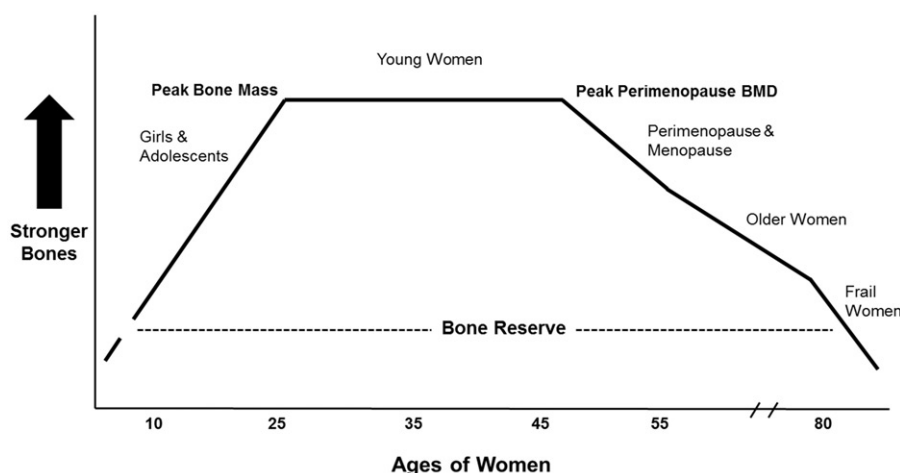
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Figure 1. This theoretical diagram describes the ideal 'life cycle' of lumbar spine (L1–4) areal bone mineral density (BMD). It initially shows bone modeling-related gains through childhood and adolescence[10]; following peak BMD during the menstruating (premenopausal) years, remodeling ideally has a balance of resorption and formation[17,21]; during perimenopause following a skipped period, bone resorption overbalances bone formation with life's most rapid normal bone loss[26]; menopause (starting 1 year after last menstruation) initially has rapid BMD loss that becomes more gradual with healthy aging[32]; when frailty begins in older ages, rapid bone loss again occurs[32] and fragility fractures increase[35].

strongly influence bone health, it is necessary to understand how key hormones relate to bone remodeling (Box 2).

Box 1. Bone renovation.

1. The five main phases of women's life cycle (adolescence, premenopause, perimenopause, menopause, frail aging, Figure 1) differ in normal rates of bone change due to differences in women's 'bone renovation system'.

2. Adult bone is renovated (within small packets of bone throughout the body called 'bone mineralization units', BMU) through a two-phase, unidirectional process of initial removal of old bone called *bone resorption*; this is followed by replacement with new osteoid (bone matrix) in *bone formation* followed by its mineralization.

3. Women's bone grows to 'peak bone mass' in adolescence through 'modeling' in which biomarkers for both resorption and formation are elevated but formation is not preceded by resorption.

4. The two phases of bone renovation differ in timing and cellular actors. Resorption is quick (over 3 weeks) and accomplished by bone marrow *osteoclast* cells. Formation is slow (over 3–4 months) achieved by bone marrow derived *osteoblast* cells.

5. The two phases of bone renovation, resorption and formation, are linked together (called 'coupling') so when resorption increases, formation also increases. Bone mineral density is neither lost nor gained when resorption and formation are in balance.

Peak bone mineral density

Bones need to grow to the optimal size, shape and strength – this is called 'modeling'; unlike *re*modeling in adult bone, modeling does not start with resorption[1]. Before birth, in infancy, during childhood and in adolescence, bone grows to optimally suit its skeletal roles. 'Peak BMD' that differs by the particular bone as well as by sex and age[4], is key to understanding prevention of fragility fractures. Peak BMD is the densest and strongest bone we ever achieve. For women, peak total hip and femoral neck BMDs accrue during ages 16–19 years in prospective random population data[5]; lumbar spine peak BMD accrues during ages 30–40[5,6].

Many variables are associated with higher peak BMD. These include genetics[7], age at menarche[8,9], more physical activity/less sedentary time[7], higher calcium/vitamin D3 intakes and less intense eating 'restraint' attitudes[10], and likely how soon following menarche ovulation and P4 production are established[11]. Evidence is growing that use of combined hormonal contraception (CHC) during adolescence[12,13] and young adulthood[11,14] may interfere with optimal peak BMD accrual, perhaps by suppressing necessary bone turnover.

Box 2. Hormonal roles in the bone remodeling cycle.

1. Estradiol is the most important hormone for the bone of women since, when it is in moderate or high physiological levels, its role is to decrease bone resorption[3] (through osteoprotegerin osteoblast production, increased intestinal calcium absorption and other mechanisms) and thus to prevent bone loss.

2. When estradiol levels drop, this triggers a cascade of cytokines (most important being RANK-L) that stimulates a rapid increase in bone resorption.

3. Progesterone sits on specific osteoblast receptors[41,42] and stimulates new osteoblasts to be made from mesenchymal stem cells (instead of into adipocytes) and also stimulates osteoblasts to create more bone matrix[2]. It is women's bone formation-stimulating hormone.

4. Testosterone is metabolized into dihydrotestosterone in osteoblasts and stimulates bone formation but it is also metabolized into estradiol. It is men's primary bone formation-stimulating hormone.

5. Cortisol, the adrenal stress hormone present in both men and women, although absolutely essential for human life, in high levels both increases bone resorption (through inhibiting calcium absorption and central suppression of gonadal steroid production causing declining estradiol levels) and paralyzes bone formation by inhibiting osteoblast progesterone and testosterone effects.

Premenopause

During the primary menstruating years, BMD is ideally *maintained* (Figure 1). To understand why and appreciate P4's role in women's bone health, we must take a closer look at the normal menstrual cycle. The idealized cycle (Figure 2(A))

shows that, during flow, both E2 and P4 levels are low. However, E2 levels then gradually rise to a mid-cycle peak about 240% higher[15] that suppresses bone resorption (Box 2). However, E2 then declines, increasing bone resorption. The E2 peak stimulates the luteinizing hormone (LH) peak that triggers ovulation/egg release and luteal onset. With ovulation, the ovarian follicle cells that initially made E2 are transformed to also make P4. Unlike our 'cultural picture' based on the unit-less diagrams in Google, P4 rises to a high peak that is 1400% above its flow nadir[15] (Figure 2(B)). E2 is in pmol/l and P4 in the *1000-fold higher* nmol/l units.

The normally ovulatory cycle provides bone balance because, as E2 levels rise, bone resorption is inhibited (Box 2). This is followed by a P4 peak that stimulates bone formation. Although the decreasing E2 levels from peak to menstrual flow trigger a small increase in bone resorption (Box 2)[16], P4's bone formation–stimulation counter-balances that to result in a net, stable BMD[17,18]. For optimal P4-related bone formation, however, the ovulatory cycle appears to need a luteal phase length of 10–14 days by quantitative basal temperature[19,20] or 12–16 days by LH peak[21].

That silent ovulatory disturbances occurring within clinically normal cycles are related to BMD loss was first shown in a prospective, observational 1-year study in 66 women. These women were pre-screened for normal cycle/luteal phase lengths in two consecutive cycles (Figure 3); in addition, the women were of normal/stable weight, non-smokers and aged 20–42 years[17]. Those who continued to be normally ovulatory or experienced only one short luteal cycle per year maintained cancellous BMD. However, those with one or more short luteal phases or any anovulatory cycles significantly lost BMD at rates of 4–6%/year[17].

Premenopausal cycles in population-based women older than 25 years are usually predictable, about 3–5 weeks apart[22]; ovulatory characteristics are not so stable. A prospective 2-year study in 123 healthy, regularly cycling, young adult women showed that an average of 39% of their cycles in 1 year were ovulatory-disturbed[21]. Examined by higher vs. lower proportion of ovulatory disturbances, spine and hip BMD changes differed significantly (Figure 4). A population-based study that measured P4 and E2 on a single day in a random cycle showed these cycle-timed values indicated *anovulation* over one-third of the time in more than 3000 women aged 20–49 years (mean 42 years)[23].
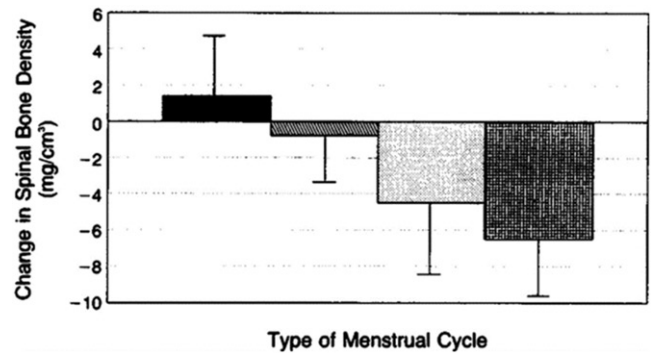

Figure 3. Cancellous spinal bone mineral density (BMD) changes over 1 year by year-long ovulatory characteristics within regular, normal-length menstrual cycles in 66 weight-stable, healthy, initially normally cycling and ovulatory premenopausal women. BMD change in the solid bar ($n = 13$) includes women with all normally ovulatory cycles; the slant-hatched bar ($n = 12$) includes women with one short luteal phase/year; the stippled bar ($n = 28$) includes women with two or more short luteal phase cycles/year; the cross-hatched bar ($n = 13$) shows women with any anovulatory cycles. Reprinted with permission from the *New England Journal of Medicine*[17].
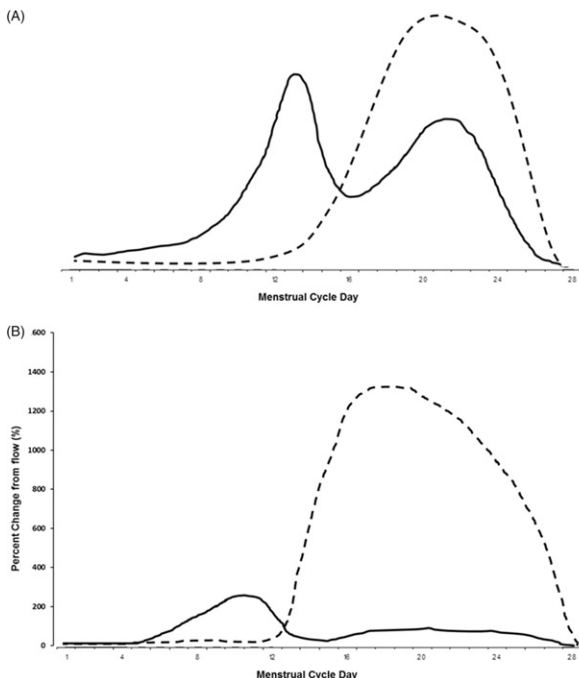

Figure 2. (A) A simple, idealized depiction of estradiol (solid line) and progesterone (dashed line) changes occurring across the normal menstrual cycle as depicted by the common unit-less diagrams that are readily available. (B) The percentage changes from follicular-phase low levels in estradiol and in progesterone that illustrate their relative changes across the normally ovulatory menstrual cycle. Redrawn from a diagram by Nielsen[15].
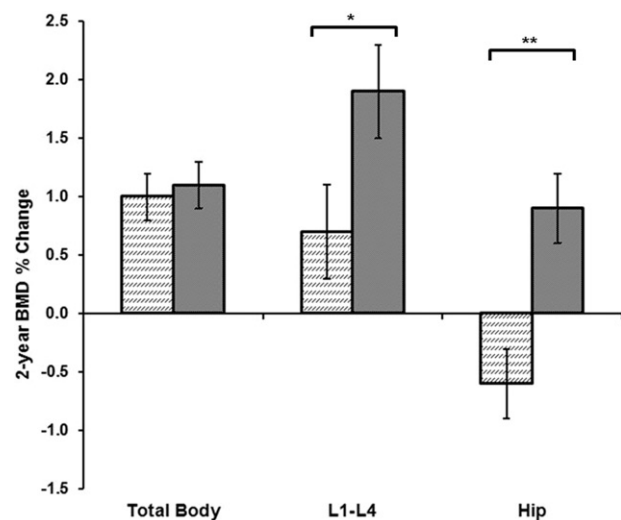
Figure 4. Mean 2-year areal bone mineral density (BMD) changes (dual-energy X-ray absorptiometry) by whether women had higher (striped bars) or lower (solid bars) experiences of subclinical ovulatory disturbances, based on a median split (39% of all cycles), within regular menstrual cycles (~30 days) in 123 women ages 20–35 (average 22 years). BMD % change data shown as mean ± SEM adjusted for: change in lean body mass in kg, baseline gynecological age and body mass index (kg/m^2)[21]. Significant differences: $^*p = 0.034$; $^{**}p = 0.001$. Drawn from data in this publication[21].

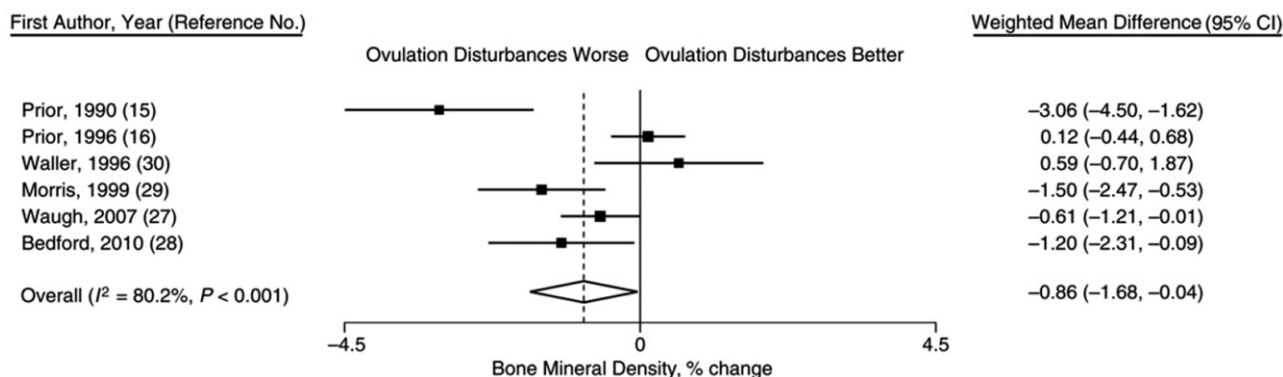**Figure 5.** Forest plot from a meta-analysis of six prospective, observational studies in 436 premenopausal women tracking 1-year menstrual cycles, ovulatory characteristics and percentage changes in bone mineral density (BMD). Results show a highly heterogeneous ($I^2 = 80.2\%$) random effects model with -0.86%/year more spinal BMD loss in those with worse ovulatory disturbances[24]. Reprinted with permission of *Epidemiologic Reviews*[24].

Finally, a meta-analysis of spinal BMD change that monitored 436 women aged 18–422 years for cycles and ovulation, showed that, within each study, those with less than a median proportion of normally ovulatory cycles were losing almost 1% (−0.86%) of spinal BMD/year[24] (Figure 5). Therefore, over the 30–45 years of menstruating life, if an ideal peak BMD is not gained[4,6,11] or if BMD is lost at −0.86%/year, a woman may reach the time of rapid bone loss in late perimenopause ('Peak Perimenopausal BMD') thinking she has strong bones but having already lost more than 10–20% (Figure 5).

Perimenopause

Perimenopause, a long transitional between premenopause and menopause, is characterized by major hormonal changes: (1) higher, erratic E2 levels[25] and decreasing ovulatory P4 levels[26] with increased ovulatory disturbances[27,28]; (2) hypothalamic–pituitary–ovary hormonal feedback disturbances[26,28]; and (3) increased inflammatory marker[29] and stress hormone levels[30]. All of these changes (Box 2) are negative for bone balance. In perimenopause (Figure 1), rapid bone loss begins[26] in the late menopausal transition[31] (with the first skipped cycle). Perimenopausal spinal BMD loss rates exceed those in early menopause (−1.83 ± 4.49% vs. −1.22 ± 3.14%; $p = 0.005$)[26,32], as confirmed in prospective, population data[32]. Given that perimenopausal E2 levels are significantly higher[26], high bone resorption must relate to repeatedly declining E2 levels[25] plus disturbed ovulation[28] and decreased bone formation[33] (Box 2)[26,32,34].

Menopause

The former belief that rapid bone loss was due to menopause-related 'estrogen deficiency' explained women's greater fragility fracture rates versus men[35]. As already discussed, peak BMD levels[4], young adulthood[24] and perimenopausal[32] rates of BMD change all contribute to BMD/bone strength at 'Peak Perimenopausal BMD' (Figure 1). The influence of these earlier life bone factors on incident menopausal fragility fractures is not yet known. The rate of menopausal bone loss slows gradually (Figure 1) until it averages about −0.5%/year while women remain healthy, mobile and without quality-of-life-altering diseases[32]. Note, this slowed BMD loss rate occurs despite years of low E2 and P4 levels.

Rapid menopausal bone loss begins again[32], however, and increased fractures occur when women become frail in older adulthood[36]; frailty and rapid bone loss are often triggered by a critical illness[37]. We also know that major osteoporotic fractures (fragility fractures of hip, clinical spine, forearm and humerus) are associated with increased rates of bone loss[38]. Again, according to Figure 1, the level of BMD/bone strength at onset of frailty in elderly women is related to preceding peak BMD and subsequent losses prior to menopause onset.

Progesterone for prevention of bone loss in adolescent, pre- and perimenopause

Oral micronized progesterone (progesterone) that is identical to ovarian luteal-phase P4 production is now available for cyclic therapy[39]. However, progesterone therapy only became available in France in the 1980s[39] and North America in the mid-1990s. Before that time, synthetic progestins were used in lieu of progesterone. However, progestins have varying chemical structures and such heterogeneous effects on other tissues that they have no non-reproductive class effects[40]. Since progestins only need to transform a proliferative to secretory endometrium and preserve a pregnancy to be so classified, before using them in lieu of progesterone we must ensure that they act like progesterone in bone. It has been proven that medroxyprogesterone acetate (MPA) *in vitro* activated the osteoblast P4 receptor causing increased osteoblast cell maturation from mesenchymal stem cells[41]. MPA also, especially in estrogen-co-therapy (or likely with a longer cell culture exposure) increased the differentiation of osteoblast cells into those making alkaline phosphatase[41] associated with bone matrix formation. Only osteoblasts from female rats, however, were P4-responsive[42].

Although cyclic progesterone may be appropriate therapy, in every situation a woman needs to be holistically assessed for the other important general and bone health variables such as overall nutrition[43], body mass index (BMI, kg/m^2),

adequacy of energy intake for energy expenditure[44], protein[45], calcium and vitamin D[46] intakes, sedentary behavior[47] or physical activity[9], adequacy of sleep and circadian rhythm[48], and the psychosocial environment to rule out stress, threat, abuse, depression[49] and cognitive dietary restraint[21] (Figure 4). This section will discuss life phases before menopause during which cyclic progesterone may prevent osteoporosis.

Adolescent women at risk for osteoporosis

The years from menarche to 20 years (adolescence) include both a reproductive transition (from childhood to reproductive status)[50] and a bone health transition to achieve the majority of peak BMD[4–6]. Early menarche (age ≤11 years) in the population is associated with a higher adult weight/obesity[51], a normal adult BMD, and with increased mortality[52]. It is likely that maturation to ovarian E2 production exceeds the development of ovulation and P4 release for those with early menarche[53].

If an adolescent experiences hypothalamic oligo- or amenorrhea, as 1–4% in the population may[54,55], then cyclic progesterone (in a luteal-phase equivalent dose[56] of 300 mg at bedtime for 14 days) is an ideal therapy. In amenorrhea, it is given 14 days on and 14 days off. In regular cycles, it is best on cycle days 14–27. Although no data on oligo-/amenorrhea, long-term, cyclic progesterone treatment are available in adolescents, a cyclic MPA randomized controlled trial (RCT) (discussed below) showed 50% 1-year menstrual cycle/ovulatory recovery[57]. Cyclic progesterone information for women/healthcare providers is available (http://www.cemcor.ca/resources/cyclic-progesterone-therapy). If an adolescent with early menarche is overweight, taking cyclic progesterone may assist in weight normalization because weight-stable women eat an additional ∼300 kilocalories/day during the luteal phase[58]; P4 requires energy for its temperature-increasing action.

Although secondary amenorrhea is rare in the population[55], oligomenorrhea is not uncommon[54] and both are associated with bone loss during a time of expected bone gain[16,59] or with increased fracture risk[60]. Increasingly we understand that hypothalamic reproductive disturbances relate to one or more 'threats' and central stress responses[61]. They may involve loss of menstrual cycles (amenorrhea) or longer than 35-day cycle intervals (oligomenorrhea), and these are associated with lower E2 and P4 productions[62]. Short luteal phases and anovulation within regular, normal-length cycles (called 'subclinical ovulatory disturbances') involve low P4 but normal E2 levels; they are also usually hypothalamic stress-related and reversible[62,63]. Although one might think, as clinicians often do[64], that those with hypothalamic cycle/ovulatory disturbances require estradiol 'replacement', those adolescent/young women treated with supraphysiological estrogen with progestin in CHC experienced half the rate of cycle recovery as those who were untreated or prescribed menopausal-like hormone therapy[65].

Premenopausal women at risk for negative bone changes

Subclinical ovulatory disturbances are common in the population, are reversible[63] and related to negative BMD effects[17,21,23,24]. In confirmation, a cross-sectional, population-based study in over 500 premenopausal women found that those with BMD values in the lowest 10th percentile had significantly lower P4 and occasional subnormal E2 levels versus those with normal BMD levels[66]. Therefore, it is logical to provide cyclic progesterone 'replacement' therapy for women with hypothalamic cycle/ovulatory disturbances.

In the 1990s, we recruited a cohort of 73 healthy, non-smoking, normal-weight women aged 21–45 years (mean 32 years) with hypothalamic disturbances of cycle length (amenorrhea, oligomenorrhea) or ovulation (anovulation and recurrent short luteal phases) to a 1-year randomized, double-blind, placebo-controlled 2×2 factorial trial of cyclic MPA (prior to oral micronized progesterone availability) and/or supplemental calcium[57]. Sixty-one women completed the study; there were no serious adverse effects[57]. Women were stratified by reproductive disturbances into four groups treated with cyclic MPA (10 mg for 10 days/month or cycle) and calcium carbonate (500 mg twice daily) or their respective placebos (Figure 6) with 14–16 women/group[57]. The primary outcome of spinal BMD change showed significant +2–3% annual mean gains in cyclic MPA groups, no change on calcium alone and a significant −2% loss on double placebo; 2×2 analysis of variance, MPA: $F = 19.43$, $p = 0.0001$; calcium: $F = 3.34$, $p = 0.073$ without significant interaction (Figure 6)[57]. Thus MPA acting through the P4 osteoblast receptor caused a significant annual gain in spinal BMD in active women with hypothalamic disturbances, ranging from amenorrhea to regular cycles with repeated short luteal phases. During the cycle following experimental treatment, almost half had recovered perfectly normal cycle and luteal-phase lengths[57]. Note that this study used 10 mg of MPA cyclically which, unlike Depo-MPA (150 mg intramuscularly
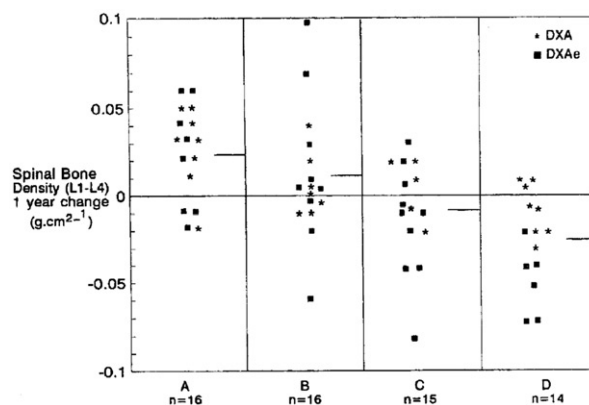
Figure 6. This dot-plot depicts individual spinal bone mineral density BMD changes/year in 61 healthy, normal-weight, active, non-smoking women ages 21–45 stratified by their hypothalamic menstrual cycle (amenorrhea, oligomenorrhea) or ovulatory disturbances within normal cycles (anovulation, short luteal phases) into a randomized, double-blind, placebo-controlled 2×2 factorial design trial of cyclic medroxyprogesterone (MPA, 10 mg/day, 10 days/month or cycle) or supplemental calcium (500 mg twice/day). Groups by therapy: A = cyclic MPA, calcium; B = cyclic MPA, calcium placebo; C = MPA placebo, calcium; D = placebos for MPA, calcium. The short horizontal line is the group mean. With permission from the American Journal of Medicine[57].

Study or Subgroup	EPT Mean	SD	Total	ET Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
PEPI	3.62	3	169	3.11	3.16	168	12.1%	0.51 [-0.15, 1.17]
Mizunuma	6.13	7.67	14	5.42	2.93	10	0.4%	0.71 [-3.70, 5.12]
LIU	2.46	3.03	21	1.24	1.53	23	3.6%	1.22 [-0.22, 2.66]
LINDSAY 0.625	3.45	0.35	81	2.43	0.33	84	30.3%	1.02 [0.92, 1.12]
LINDSAY 0.45	3.01	0.34	87	2.09	0.33	91	30.4%	0.92 [0.82, 1.02]
LINDSAY 0.3	1.07	1.18	91	1.21	1.33	87	20.9%	-0.14 [-0.51, 0.23]
ADACHI 20	1.76	5.69	31	1.87	4.94	34	1.2%	-0.11 [-2.71, 2.49]
ADACHI 10	2.72	6.74	33	1.87	4.94	34	1.0%	0.85 [-1.99, 3.69]
Total (95% CI)			527			531	100.0%	0.68 [0.38, 0.97]

Heterogeneity: Tau² = 0.07; Chi² = 37.36, df = 7 (P < 0.00001); I² = 81%
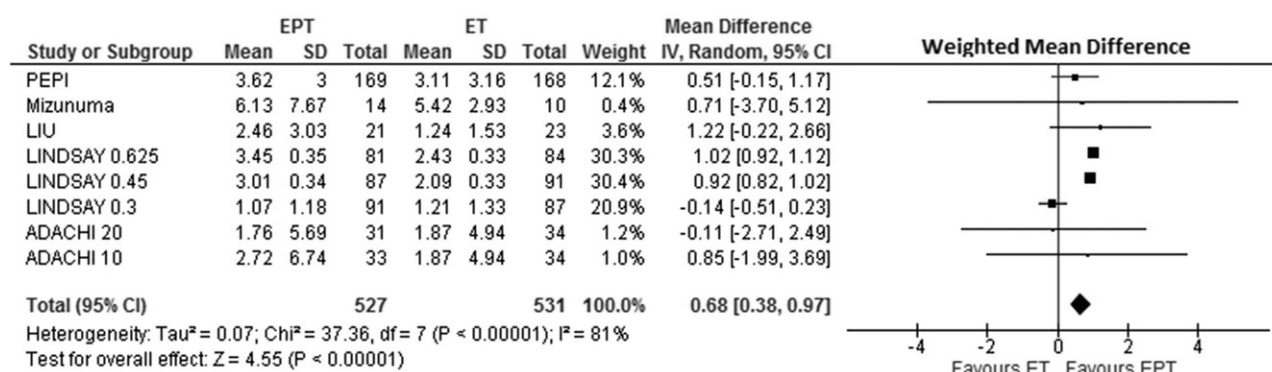Test for overall effect: Z = 4.55 (P < 0.00001)

Figure 7. Meta-analysis of spinal areal spinal bone mineral density (BMD) changes in five controlled comparative trials that randomized more than 1000 menopausal women directly to estrogen therapy alone (ET) or estrogen–progestin therapy (EPT) without regard to hysterectomy status. The weighted mean difference in a random effects model of BMD change is reported as g/cm^2 over 1 year[72]. Reprinted with permission from the *Journal of Musculoskeletal and Neuronal Interactions*[72].

every 3 months), is not high enough to either suppress endogenous E2 levels (causing increased bone resorption, Box 2) or to act negatively on bone formation through the glucocorticoid receptor.

Perimenopausal women at risk for osteoporosis

Almost no bone-therapy studies are available in perimenopause. There is some observational evidence that CHC use may prevent femoral BMD loss; weekly nitrogen bisphosphonate (alendronate 70 mg/week) plus vitamin D may prevent spine and femoral neck but not total hip BMD losses[67]. Neither of these therapies is proven safe in perimenopause since perimenopausal CHC risks for thromboembolic disease are at least tripled and bisphosphonates are contraindicated in potentially fertile women. To our knowledge, cyclic or daily progesterone therapy has not been tested in perimenopausal women at risk for osteoporosis.

Progesterone for osteoporosis treatment in menopausal women

Following our understanding of bone remodeling (Box 1) and the complementary bone roles played by E2 and P4 (Box 2), to increase BMD and prevent fracture it is likely that co-treatment would be optimal[68]. A comparative 1-year RCT tested daily conjugated equine estrogen (CEE, 0.6 mg/day) vs. MPA (10 mg/day) in 41 women randomized at hospital discharge (~1 week) after premenopausal surgical menopause[69]. At study onset, the N-telopeptide (bone resorption marker) was already ≥2 standard deviations above premenopausal norms[69]. Significant cancellous spinal BMD loss occurred on CEE and MPA and was marginally greater on MPA ($p = 0.04$)[69]. CEE, however, prevented significant BMD loss at the whole body and femoral neck sites but MPA did not[69]. Thus the formation effects of MPA or progesterone can increase BMD only when resorption levels are normal; they do not suppress the resorption 'driver' of bone loss (Box 1).

Menopausal hormone therapy (MHT) is estrogen-based; current guidelines instruct that only menopausal women without a hysterectomy be treated with added progestin/progesterone[70]. Estrogen alone, estrogen with progestin, and MPA/progesterone alone all effectively improve hot flushes and night sweats[71]. Therefore we need to know: does BMD change differ during treatment with estrogen alone or estrogen–progestin/progesterone? Our recent meta-analysis of RCTs that directly randomized more than 1000 menopausal women (mean age 55 years) to estrogen alone or estrogen–progestin/progesterone, while measuring 1-year spinal BMD change says it does (Figure 7)[72]. CEE (0.625 mg/day) was the usual estrogen and MPA (2.5 mg/day) the progestin. Of the five RCTs, eight dose-paired comparisons were analyzed by weighted mean percent BMD difference in a random effects model[72]. Results showed a significantly greater BMD gain (+0.68%/year; 95% CI 0.38–0.97) ($p = 0.00001$) on CEE plus MPA[72]. Thus MPA added to the BMD and likely bone strength gains from estrogen alone.

The next logical question is whether progesterone adds to BMD gains when combined with non-estrogen antiresorptive agents. MHT's risks may outweigh its benefits[73] and estrogen plus MPA (but not estradiol plus progesterone) is associated with significantly increased breast cancer risk, as indicated by the longitudinal observational studies in menopausal women in the French E3N study[74]. The only available data on this question are from a random sample of 19 clinical charts of women with osteoporosis treated with a non-nitrogen bisphosphonate plus MPA/progesterone[75]. Over 2% annual spinal BMD gain on etidronate plus MPA/progesterone (+2.57; 95% CI 1.85–3.54) was higher than with etidronate alone from an RCT meta-analysis (+1.42; 95% CI 0.89–1.32)%/year[75]; comparative results for femoral neck BMD on etidronate–MPA (+1.83; 95% CI 0.89–3.56) vs. etidronate alone (+0.73; 95% CI 0.14–1.32)[75,76] suggest progesterone would add important BMD benefits to stronger antiresorptive osteoporosis therapies.

RCTs of CEE alone[73] and CEE/MPA[77] showed fracture prevention in the Women's Health Initiative hormone therapy trials. However, there are no head-to-head fracture prevention trials of estrogen alone vs. estrogen plus MPA/progesterone or of antiresorptives alone vs. antiresorptives plus bone formation stimulators[78]. Based on the results of a network meta-analysis, parathyroid hormone (PTH, teriparatide) acting primarily as a bone-formation stimulating agent, was more effective at fracture prevention than the strong antiresorptives[78]. Increasingly, agents acting on bone formation and

resorption are combined[68] since antiresorptives alone suppress bone formation through coupling (Box 1) and are associated with significant long-term risks[79].

Treatment for symptomatic menopause with hot flushes is significantly more effective with estrogen–progestin than estrogen alone[80]; RCT evidence suggests that progesterone alone will be effective and safe[81]. Since many menopausal women will have both hot flushes and fracture risks requiring treatment, combined antiresorptive plus progesterone therapy may yield amplified benefits[71].

Conclusion

Progesterone is estradiol's partner hormone in bone. P4 appears to play important roles in achievement of an ideal *peak* bone mineral density (BMD) in adolescence and young adulthood and in the prevention of bone loss during pre- and likely perimenopausal life phases, leading to a normal *peak perimenopausal BMD*. For women with hypothalamic disturbances of cycles and ovulation, cyclic progesterone therapy (based on RCT data with cyclic MPA) is an effective BMD-increasing therapy and may also facilitate reproductive recovery. P4 will likely safely add BMD/strength gains to antiresorptive therapy in menopausal and frail elderly women at increased fracture risk.

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