

Androgen effects on bone and muscle

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Bone health and strength are dependent on the coupling of bone resorption and bone formation. This process is governed by the interaction of osteoclasts and osteoblasts plus the modulating influence of the bone mechanosensory cells—the osteocytes. Both sex steroids—estrogen (E) and testosterone (T)—have receptors on all bone cells, with androgen dominance on osteoblasts and osteocytes. Specific receptors for the weaker androgens, such as DHEA have also been identified.

The activity of the sex steroids, influenced by various enzymes found in bone, is reflective of the hormone ligand before its binding to the bone cells. As a result, T acts both directly and via its aromatization to estradiol. The activity of the androgens also varies with the bone surface; periosteal cells, for example, do not have 5 α -reductase activity, indicating that T is the active metabolite at this clinically important site. Androgens influence bone cell function via local and systemic growth factors and cytokines. By enhancing osteoblast differentiation, androgens regulate bone matrix production, organization, and mineralization. Androgens also regulate osteoclast recruitment and activity.

Endogenous androgens increase bone mineral density (BMD) in both adolescent and adult premenopausal women. Women with excess endogenous androgen—for example, those with hirsutism and polycystic ovary syndrome (PCOS)—have increased BMD compared with normal young women. E and androgen therapy increases BMD to a greater degree than does E therapy alone. This is true for both oral combinations of esterified E and methyltestosterone and for subcutaneous T implants. Androgenic progestins have an additive effect on BMD when combined with E therapy and have the further advantage of being protective to the endometrium in E-treated women.

Androgens increase muscle mass and strength. The resulting improvement in physical activity leads to the activation of bone-forming sites and the stimulation of the bone formation—modulating cells, the osteocytes. Mechanical loading, when combined with hormone therapy, results in greater osteogenic response than does either alone. (Fertil Steril® 2002;77(Suppl 4):S34–41. ©2002 by American Society for Reproductive Medicine.)

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Androgens have a profound effect on the physiology of bone and muscle in women. By direct androgenic activity and transformation into estrogens (Es), androgens modulate the bone-remodeling cycle. Androgens also increase muscle mass and strength and induce mechanical factors that alter the balance between bone resorption and formation in favor of formation. The net result is increased bone mass and strength. Central to this issue is an understanding of the interplay between the various sex steroids—Es and androgens—and the cells involved in bone remodeling: osteoclasts, osteoblasts, and osteocytes (Fig. 1).

PHYSIOLOGY OF BONE REMODELING: A BRIEF OVERVIEW

The Bone-Remodeling Cycle

Bone remodeling is a continuous process that ensures bone strength by coupling the removal of

old bone (resorption) with the synthesis of new bone (formation) (1). There are four distinct steps in the bone-remodeling cycle that primarily involve two cell types: osteoclasts and osteoblasts.

In *activation*, preosteoclasts are stimulated and differentiated into mature osteoclasts by a variety of cytokines and growth factors. In *resorption*, an acidlike substance is secreted from the ruffled border of the osteoclasts, dissolving, digesting, and absorbing the organic matrix and minerals of old bone. In *reversal*, once the resorptive cavity reaches a predetermined depth, a cement surface, derived from monocytes, covers the defect and prevents further bone erosion. Finally, in *formation*, osteoblasts are attracted into the resorptive cavity and, under the influence of various hormones and growth factors, mature and refill the resorptive cavity with “new” bone. There are two interrelated stages to this last process. The first

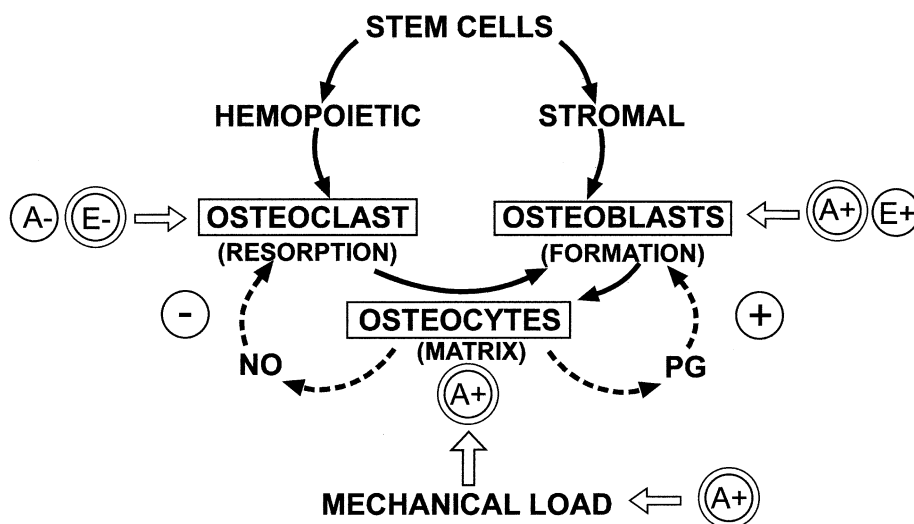
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FIGURE 1

Bone remodeling, sex steroids, and mechanical loading. E, Estrogen; A, Androgen; NO, nitric oxide; +, stimulatory; -, inhibitory; PG, prostaglandin; double circle, primary activity; single circle, secondary activity. (From Smit and Burger (1). Reprinted by permission of the publisher.)



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stage involves the synthesis of bone matrix, 90% of which is made up of type I collagen. The newly formed osteoid is then mineralized with calcium hydroxyapatite crystals. The latter also contain trace amounts of magnesium, potassium, sodium, and carbonate. Vitamin D₃ (1,25 hydroxy D₃) is essential for this process. In its absence, mineralization is defective, and osteomalacia may result.

Mechanical Loading and Bone Remodeling

Less well recognized in the bone-remodeling cycle is the role of mechanical strain and its effect on the modulating activity of osteocytes (3). The strength of the newly formed bone is in some measure determined by the arrangements of the triple-helix collagen fibrils within the matrix and by the attachment and orientation of the hydroxyapatite crystals to the collagen. The bone mineral has a relatively high stiffness (hardness) and low elasticity, whereas the protein matrix is highly elastic (4). This allows bone to absorb impacts without breaking. Mechanical loading—exercise and gravity—regulates the quality of bone via the stimulation of osteocytes (3). Osteocytes are derived from the osteoblast lineage and produce nitric oxide (NO) and prostaglandins (PG)E₂, both of which are responsible for osteogenesis by modifying the activity of osteoblasts and osteoclasts (5).

Negative Bone Balance

Bone mass is maintained when the resorption and formation phases are balanced (coupled), that is, the amount of bone removed is replaced with an equal amount of fresh bone. Negative bone balance results from one of the follow-

ing two situations: [1] high activity or turnover of osteoclasts and/or an increase in the number of resorptive sites or [2] low turnover or inadequate osteoblast function, with diminished osteoid secretion and an inability to fill a normal resorptive cavity (2).

Cancellous Vs. Cortical Bone

Cancellous and cortical bone have different anatomical features but identical cell types and a similar remodeling cycle.

Cortical bone is found primarily in the long bones of the arms and legs (appendicular skeleton) and as a “shell” surrounding the vertebrae. Cortical bone has three surfaces. The endosteal envelope is the surface facing the marrow cavity; the periosteal envelope is the outer surface of the bone; and the intracortical envelope is the bone tissue between the endosteum and periosteum. In addition to the quality of the bone, the strength of the appendicular skeleton is dependent on the diameter of the bone (cross-sectional moment of inertia) and the cortical width. Bone remodeling in children takes place on the periosteum (increasing the bone’s diameter). In adults, endosteal bone loss predominates, with a narrowing of the intracortical envelope (6). The degree to which this process occurs premenopausally will impact on subsequent strength of the long bones and—together with the degree of the physiologic loss of cortical bone postmenopausally—the eventual risk of fracture.

Cancellous (or trabecular) bone is found mainly in the

vertebrae and has a honeycomb-like arrangement of horizontal and vertical plates that are interconnected. This ensures its mechanical strength. Bone remodeling takes place on the inner and outer envelopes of each trabecular plate. Excess bone remodeling results in thinning of the plates, with eventual complete absorption of the trabecula, loss of mechanical strength, and liability to fracture. Acute loss of estrogen (with an increase in osteoclast activity) is more likely to result in trabecular perforation in women than in men (7). This may be due to the slower decline of androgens and their conversion to estrogen in men.

ANDROGENS: PHYSIOLOGY AND EFFECT ON BONE

Androgens and Estrogen Metabolism

As discussed in greater detail elsewhere (8), the primary metabolism of androgens and estrogens takes place in three sites: the ovary, adrenal cortex, and adipose tissue, with additional contributions from the metabolism of the sex steroids in muscle. The liver plays a significant role in at least two respects: the metabolism of endogenous estrogen into metabolites of varying degrees of estrogenicity and the synthesis of sex hormone-binding globulin. The former process is genetically determined and lifestyle modified. The latter process controls the bioavailability of both Estradiol (E_2) and T. The activity of the sex steroids is also determined by various enzymes, all of which are either found in bone or reflect the state of the hormone ligand before its binding to bone cells. These enzymes include aromatase activity (converting T to E_2); 17- β hydroxysteroid dehydrogenase (controlling the androstenedione to T and the estrone (E_1) to E_2 pathways); and sulfatase, the enzyme that regulates estrone sulfate to estrone interactions. Testosterone is further metabolized to dihydrotestosterone (DHT) by the 5 α -reductase enzymes. Periosteal cells do not have detectable 5 α -reductase activity, indicating that T may be the active metabolite at this clinically important site (9). The major androgens of the adrenal gland include DHEA S and androstenedione (A). The androgenic steroids—directly or by conversion to E_2 —mediate their physiologic function through binding to the androgen receptor. There is also a specific receptor for DHEA in osteoblasts.

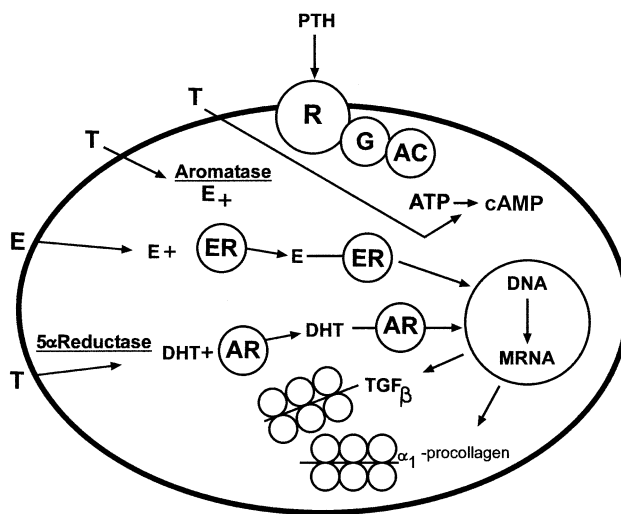
Androgen Receptors in Bone Cells

Androgen receptors (ARs) are found in all three bone cells: osteoblasts, osteoclasts, and osteocytes. The AR is similar to other steroid receptors (estrogen, progesterone, mineralocorticoid, and glucocorticoid) and is found primarily within the nucleus (10).

Androgen receptors are mainly expressed in osteoblasts and to a greater degree in cortical than in cancellous bone. Androgen receptor expression is greatest in osteoblast cultures from young bone when compared with senescent bone.

FIGURE 2

Putative mechanism of androgen action in the human female osteoblast. E, 17- β estradiol; ER, estrogen receptor; PTH, parathyroid hormone; R, pth receptor; G, G protein; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate. (From Gasperino (17). Reprinted by permission of the publisher.)



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Androgen receptors predominate in active osteoblasts at the site of bone formation (11).

Androgen receptors in the nucleus are responsible for the classic genomic transcription of the osteoblasts' mRNA (Fig. 2). Androgens diffuse freely through the plasma membrane and into the nucleus and bind to the ARs. Once the ligand-AR complex is activated, the protein moiety is released with the subsequent formation of a homodimer (or possibly a heterodimer, because there is a report of two isoforms of AR protein in osteoblast-like cells). Modulated by various coactivators and corepressors, the AR, bound to DNA, influences the transcription and translation of the genes that govern the osteoblasts' function (12). There is an abundance of both AR and estrogen receptors in osteoblasts, indicating the dual role of T and E_2 in normal bone physiology. Androgens may also regulate osteoblast activity via a more rapid, nongenomic mechanism through receptors on the osteoblast cell surface (13).

Androgen receptors are also found in bone marrow cells that regulate osteoclastogenesis (14). The sex steroid regulation of osteoclast function is controlled primarily by E_2 and the estrogen receptor. An indirect effect of T through its aromatization to E_2 is a possibility. ARs are found in osteocytes embedded in the bone matrix (10).

Specific binding receptors for the following androgens have also been identified: T, DHT (which have similar binding affinities), and DHEA (11). The extent to which T

acts directly or via its aromatization to E_2 is unclear and may vary with the polymorphism of the AR. The fact that men who have mutations in either their estrogen receptor or their aromatase gene develop osteoporosis is illustrative of the potential importance of the T to E_2 conversion in bone. Dihydrotestosterone is nonaromatizable. Other, weaker androgenic compounds may also have specific binding sites (15).

Factors Controlling Androgen Receptor Expression and Osteoblast Function

Osteoblast Proliferation

Androgen receptors are up-regulated by androgens in bone and also by exposure to glucocorticoids, estrogen, and 1,25 hydroxy D_3 (16). Androgens stimulate osteoblast proliferation, but under experimental conditions, prolonged exposure to androgens may inhibit osteoblast cell proliferation significantly. It is not known whether intermittent androgen therapy improves bone mineral density (BMD) in women to a greater degree than does continuous androgen therapy. The modulation of cell apoptosis by androgens has not been clearly established and is confounded by issues such as programmed cell death and the influence of other steroids and cell types. For example, apoptosis of osteocytes is closely linked to estrogen withdrawal and may be one reason that mechanical loading will not prevent bone loss in the presence of low E_2 levels (18).

Osteoblast Differentiation

Androgen exposure enhances osteoblast differentiation and the synthesis of extracellular matrix proteins, such as type $1\alpha 1$ collagen, osteocalcin, and osteonectin. This is reflected by a dose–response increase in bone-specific alkaline phosphatase activity. Androgens also stimulate mineralization (19). In short, androgens appear to have an important function in regulating bone matrix production and organization.

Bone Microenvironment

Androgens also influence bone cells' function through their effect on local and systemic factors that control the bone cells' microenvironment. Androgens have a profound effect on transforming growth factor (TGF) β , which is one of the more potent osteoblast mitogens. Dihydrotestosterone-mediated increases in TGF- β activity are via TGF- $\beta 2$, but other isoforms may be involved. Both DHT and T up-regulate TGF- β synthesis. In its latent form, TGF- β is stored in bone, where it functions as the body's main reservoir for this growth factor (20). Other growth factor systems that are positively influenced by androgens (DHT) include fibroblast growth factor and insulin-like growth factor (IGF) II. The latter effect is caused by an increase in the IGF-II binding affinity and not by an increase in the amount of the IGF-I or IGF-II in the osteoblasts' culture media (21). Androgens also

decrease osteoclast genesis by inhibiting the production of interleukin-6 in the stromal cells of the bone marrow. This results in diminished maturation and development of osteoclast precursors into osteoclasts (14). The effect of androgens on the reduction of interleukin-6 has been demonstrated for T, DHT, and the adrenal androgens, including A and DHEA. Testosterone and DHT also regulate osteoclast activity—and reduce bone turnover—by the inhibition of both parathyroid hormone- and IL-1-stimulated PGE_2 production (22).

ENDOGENOUS ANDROGENS AND BONE MASS

Age-Related BMD and Androgens

Cross-sectional epidemiologic studies have demonstrated a positive correlation between endogenous androgens and BMD in both adolescent females and in premenopausal adult women (23). The adolescent accrual of bone mass is probably influenced by both estrogens and androgens.

Studies in premenopausal women have shown an independent and possibly additive effect of androgens and estrogens on peak bone mass. Free T is the androgen that is most consistently associated with BMD at the lumbar spine, hip, and distal radius (24). There is also an inverse relationship between SHBG and BMD in menstruating premenopausal and perimenopausal women (ages 35 to 50 y). Lower SHBG was associated with higher BMD at all measured sites (25).

The situation in postmenopausal women is less clear. A significant association between total serum T and diminished vertebral bone mass has been shown by Davidson et al. (26). Lower androgen levels, reduced BMD in the hip, and an increase in hip fractures has also been noted. Lower bioavailable T levels have been correlated with loss of height. Height loss is a surrogate marker for vertebral deformation and osteoporotic fractures (27). Others have found no independent association of free T and vertebral fractures in older postmenopausal women, after correcting for $17-\beta E_2$ levels (28). The progressive decline in DHEA with increasing age (29) may contribute to senile osteoporosis. Variability in the degree and rate of the age-related decrease of androgen (and estrogen) synthesis could explain some of the discordance in the results to date and serves to illustrate the importance of individualizing androgen (and estrogen) therapy. Prescribed hormonal therapy is additive to the endogenous production of the sex and adrenal steroids.

Endogenous Androgen Excess

Women with hirsutism often have increased BMD. This may be due to increased sensitivity of the peripheral tissues—pilosebaceous unit and bone—to androgens, rather than to an absolute increase in androgen blood levels. A recent study (30), for example, evaluated a group of women diagnosed with idiopathic hirsuties (hirsutism in the presence of normal ovulatory cycles and serum androgen levels) and a matched nonhirsute control group of women. The

BMD of the lumbar vertebrae (L2 through L4) and the total-body BMD were significantly greater in the hirsute group. Young women with documented hyperandrogenism have also been shown to have increased BMD compared with normal young women.

In various studies, women with polycystic ovary syndrome (PCOS), have been shown to have a correlation between elevated T (total and bioavailable) and A and BMD (23). This has been observed for the radial BMD and upper body bone mass. The role of estrogen metabolism in PCOS subjects is a confounding variable. However, a direct effect of hyperandrogenism on bone mass was illustrated by a study that observed that nonobese, young, hirsute oligomenorrheic and amenorrheic subjects have higher BMD than nonhirsute oligomenorrheic and amenorrheic controls (31). In a subgroup of PCOS patients with amenorrhea, spine and femoral BMD values were comparable to control values but were lower than the BMD in women with idiopathic hirsutism and nonamenorrheic PCOS, despite comparable E_2 values (32). The importance of endogenous androgens and BMD is further illustrated by a decrease in BMD after the use of androgen antagonists both in eumenorrheic women with hyperandrogenemia and in women with PCOS (33).

ANDROGEN THERAPY AND BMD

Androgens

A number of clinical trials have shown that androgen therapy (T by subcutaneous pellet implantation or oral methyltestosterone) when combined with estrogen therapy, has an additive effect on BMD compared with estrogen-alone treatment. These studies were preceded by the earlier empiric use of combination estrogen and androgen therapy in clinical practice and by the observation in individual women of the anabolic effect on bone of combination estrogen and androgen therapy.

A recent study has advanced the rationale for knowing when to choose estrogen and androgen therapy in preference to estrogen-alone therapy when treating women with osteoporosis. Using clinically available bone marker tests (34), postmenopausal women were treated for 9 weeks with daily doses either of a combination of esterified estrogen (1.25 mg) and methyltestosterone (2.5 mg) or of 1.25 mg of conjugated equine estrogen. Similar decreases in the urinary excretion of the bone resorption markers (deoxypyridinoline, pyridinoline, and hydroxyproline) were noted in both groups. Subjects treated with conjugated equine estrogen showed decreased serum markers of bone formation (bone-specific alkaline phosphatase, osteocalcin, and C-terminal procollagen peptide). In contrast, the estrogen and androgen-treated women had significant increases in serum bone formation markers. Levels of SHBG increased with conjugated equine estrogen therapy, but significantly decreased after the estrogen and androgen regimen.

Nonresponse of BMD to adequate estrogen therapy may be indicative of low-turnover osteoporosis, especially when appropriate serum levels of estrogen have been achieved and the urinary excretion of the collagen cross-link peptides are appropriately suppressed. Under these circumstances—and possibly in most women with osteoporosis—the anabolic bone-building potential of androgens should be considered. One study that supports combined estrogen and androgen treatment separated women on oral therapy into two groups based on whether they were satisfied with their current hormone therapy. Group 1 (satisfied) remained on conjugated equine estrogen (1.25 mg) daily. Group 2 (dissatisfied) subjects were changed to subcutaneous hormone implants consisting of E_2 (75 mg) and T (100 mg) every 6 months. One year later, the BMD of women who continued with the oral therapy remained the same. In contrast, the BMD increased significantly in the women treated with pellets: 5.7% at the spine and 5.2% at the femoral neck (35).

The efficacy of estrogen and androgen treatment has been demonstrated in appropriately designed randomized blinded studies. Surgically menopausal women were treated for 2 years with daily doses either of esterified estrogen (1.25 mg), or of esterified estrogen (1.25 mg) and methyltestosterone (2.5 mg). Both treatment regimens prevented bone loss at the spine and the hip; only combined estrogen and androgen therapy was associated with a significant increase in spinal BMD as compared with baseline values (36). In a similar study, surgically menopausal women were randomized to one of the following treatments: daily conjugated equine estrogen (0.625 mg); conjugated equine estrogen (1.25 mg); esterified estrogen (0.625 mg) plus methyltestosterone (1.25 mg); or esterified estrogen (1.25 mg) plus methyltestosterone (2.5 mg). All treatments prevented bone loss in the spine and hip. The higher estrogen and androgen dose increased spine and hip BMD significantly more than did the other treatments (37).

The long-term effect of subcutaneous estrogen and androgen administration on BMD was evaluated in a 2-year single-blind trial. Patients received E_2 (50-mg pellets) or E_2 (50-mg pellet plus T 50-mg pellets), administered every 3 months for 2 years. Cyclic oral progestins were taken by women with intact uteri. The BMD increased in both treatment groups but increased earlier and to a greater degree in the estrogen and androgen group. This was noted for the BMD of the total body and of the vertebral and trochanteric sites. The total serum T remained within the normal physiologic range throughout the duration of the study (38). This result may reflect the importance of sustaining hormone levels by defining the interval between treatments. Women in another study were treated with 75-mg E_2 pellets every 6 months, alone or with added T (100 mg), every 6 months for 1 year. Both groups had an improvement in the BMD of the spine and hip, but there was no difference in BMD between the two treatment groups (39).

Androgenic Progestogens

Progesterone receptors have been identified in primary cultures of human osteoblasts and osteoclasts (40). Progesterone has been shown to stimulate the proliferation of osteoblasts and to increase the number of alkaline phosphatase-positive colonies from osteoprogenitor cells (41). Progesterone stimulates mineralization of newly formed bone and increases cortical bone formation. Progesterone also blocks the glucocorticoid receptor in bone. This experimental animal data is complementary to the observation that women with luteal phase defects (who are progesterone deficient) lose bone mass compared with women with normal menstrual cycles (42). The anovulatory women increased their bone mass when treated with medroxyprogesterone acetate during their luteal phase (43). These findings have not been confirmed.

Progesterone or progestins are prescribed for only one reason: to protect the endometrium in naturally menopausal women who are on estrogen therapy. Progesterone is available in the micronized form or as synthetic progestogens. The latter are divided into derivatives that are structurally related to progesterone and have minimal or no androgenic activity, such as medroxyprogesterone acetate (MPA) and megestrol acetate; and those that are related to T and do have variable androgenic activity, such as norethindrone (NET) and norethindrone acetate (NETA).

In clinical trials (44), micronized progesterone and medroxyprogesterone acetate (taken cyclically or continuously) did not contribute significantly to the bone-protective effects of estrogen-alone therapy (conjugated equine estrogen, 0.625 mg daily). In contrast, women receiving NETA, in a dose of 1 mg daily, when additionally given either 5 μ g or 10 μ g of ethinyl E₂ daily, displayed a significant increase in their BMD when compared with matched controls or with estrogen-alone treated patients (45). On the basis of the results of this and other studies, it may be concluded that NETA—by changing the bone remodeling cycle in favor of bone formation—has an additive effect on BMD when combined with estrogen therapy (46). Unopposed NETA, at doses higher than that needed for hormone therapy, has also been shown to increase BMD (47).

Progestins prevent estrogen-induced endometrial hyperplasia. Androgens do not. Natural-menopausal women who are osteopenic and require estrogen therapy may benefit from the use of an added androgenic progestin without the need for additional androgen therapy.

Other Androgen Compounds

Dehydroepiandrosterone, the anabolic steroids (i.e., nandrolone decanoate) and a unique tissue-specific compound, tibolone, have all been demonstrated to have bone-building potential. Dehydroepiandrosterone is a precursor for the synthesis of both androgens and estrogen (29). Treatment with 50 mg of DHEA daily increases total T into the low

normal range for women. However, variability in the amount of DHEA present in products currently available, concerns regarding the long-term safety of DHEA in this dose, and inadequate data of its effect on bone preclude DHEA from routine use until more data are available.

Nandrolone decanoate, especially when used together with hormone therapy (48), significantly increases BMD. It may be useful in the elderly, who may also benefit from its recognized anabolic effect on muscle.

Tibolone is a unique product that has mild estrogenic (1/10th the potency of ethinyl E₂), progestogenic (1/8th the potency of norethindrone), and androgenic (1/50th of 17- α methyltestosterone) effects (49). The biologic efficacy of tibolone is mediated through three of its metabolites that have weak affinity for the progesterone, estrogen, and androgen receptors and by tissue-specific stimulation of various enzyme systems. Clinical trials have shown that bone loss can be prevented in the spine and hip with doses ranging from 1.25–2.5 mg per day. In comparative studies, tibolone (2.5 mg) is as effective as traditional hormone replacement regimens (49). Tibolone significantly lowers high-density lipoprotein cholesterol.

ANDROGENS, MUSCLE, AND EXERCISE

There are clear associations among muscle mass, muscle strength, and bone density. Muscle exerts a greater load on bone than does weight-dependent gravity (50). In one study, >70% of the bending moments on bone were transmitted by muscle force rather than by body weight (51). This mechanical stimulation induces the activation of bone-forming sites on periosteal bone surfaces. This new bone formation is mediated through the synthesis and activity of both PG and NO (5); the latter is derived from bone surface osteocytes (3). Mechanical loading when combined with estrogen, results in a greater osteogenic response than either separately. This is probably the result of estrogen's antiresorptive effect and of the stimulation of bone formation with exercise. This is verified by a study conducted in young men, demonstrating an increase in markers of bone formation (serum bone-specific alkaline phosphatase; osteocalcin) after resistance training, with a transient suppression of bone resorption markers (urinary deoxypyridinoline) (52).

Approximately 4% of muscle mass is lost during the first 3 years after menopause (53). This is associated with a significant decline in muscle strength. In men, muscle strength is preserved until age 60 years and reaches levels found in menopausal women at about 75 years of age (54)—a factor that may explain the greater tendency for falls in older women. Muscle strength is first lost in the upper extremities (55). Because loss of muscle strength precedes the loss of bone mass, a grip strength test may be a good predictor of future lower extremity bone loss and of locomotor or balance problems.

TABLE 1

Change in lean tissue mass and strength after estrogen (E) or estrogen-androgen (E-A) therapy.

Variable	E pre	E post	E-A pre	E-A post	P
Lean tissue (kg)					
Upper	1.91	1.94	1.90	2.08	<.02
Trunk	20.58	20.61	20.48	21.29	<.001
Lower	6.85	6.91	6.77	7.01	<.04
Muscle strength (lb)					
Lower body press	232	257	235	286	<.002

From Dobbs et al. (56) Reprinted by permission of the publisher. E-A > in free T and > decrease in SHBG compared with E only. E, esterified estrogen (1.25 mg); E-A, esterified estrogen (1.25 mg), methyltestosterone (2.5 mg).

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Postmenopausal androgen therapy increases lean tissue mass and decreases fat mass. This is also noted in postmenopausal women treated with tibolone. A recent double-blind randomized study (56) evaluated the body composition (by total dual energy x-ray absorptiometry [DEXA] analysis) and muscle strength (by using the one-repetition maximum technique in separate leg and arm bench-press exercises) before and after 16 months of treatment either with esterified estrogen (1.25 mg daily) or with the same dose of estrogen plus methyltestosterone (2.5 mg per day). The following results are shown in Table 1: The estrogen and androgen group had a significant increase in their lean tissue mass and a comparable improvement in lower body muscle strength. The changes in the estrogen and androgen group were significantly greater than those in the estrogen-alone-treated group. The serum values of free T were significantly greater in the androgen-supplemented group compared with the estrogen-alone treatment group. SHBG values were significantly lower in the estrogen and androgen group compared with the estrogen-alone group.

CONCLUSION

As stated in a recent review of muscle strength, bone mass, and age-related bone loss (50), "both mechanical and non-mechanical factors are crucial to reverse bone loss, and it is the interaction between the two that needs to be understood and that holds the key to success." This interaction is summarized at a cellular level in Figure 1 and highlights the interrelationship of the various cell types involved in bone remodeling. Sex steroids are directly involved in modulating osteogenesis and muscle metabolism and function. In this context, it can be concluded that androgens—either directly or via aromatization to estrogen—have a profound influence on the preservation of bone and on muscle mass and strength. The scientific rationale for androgen therapy is well founded. Long-term clinical trials are needed to confirm clinical efficacy of E.A. therapy in osteoporosis prevention and treatment.

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