Hormones and Healthy Bones
Joint Project of
National Osteoporosis Foundation and Association of Reproductive Health Professionals

Literature Review (January 2009)
Testosterone for Women and Estrogen for Men

   Abstract: Complex changes occur within the endocrine system of ageing individuals. This article explores the changes that occur in the metabolism and production of various hormones and discusses the resulting clinical consequences. As individuals age there is a decline in the peripheral levels of oestrogen and testosterone, with an increase in luteinizing hormone, follicle-stimulating hormone and sex hormone-binding globulin. Additionally there is a decline in serum concentrations of growth hormone, insulin-like growth factor-I and dehydroepiandrosterone and its sulphate-bound form. Even though there are complex changes within the hypothalmo-pituitary-adrenal/thyroid axis, there is minimal change in adrenal and thyroid function with ageing. The clinical significance of these deficiencies with age are variable and include reduced protein synthesis, decrease in lean body mass and bone mass, increased fat mass, insulin resistance, higher cardiovascular disease risk, increase in vasomotor symptoms, fatigue, depression, anaemia, poor libido, erectile deficiency and a decline in immune function. For each endocrine system, studies have been carried out in an attempt to reverse the effects of ageing by altering the serum hormonal levels of older individuals. However, the real benefits of hormonal treatment in older individuals are still being evaluated.

   Abstract: Complex changes occur within the endocrine system of ageing individuals. This article explores the changes that occur in the metabolism and production of various hormones and discusses the resulting clinical consequences. As individuals age there is a decline in the peripheral levels of oestrogen and testosterone, with an increase in luteinizing hormone, follicle-stimulating hormone and sex hormone-binding globulin. Additionally there is a decline in serum concentrations of growth hormone, insulin-like growth factor-I and dehydroepiandrosterone and its sulphate-bound form. Even though there are complex changes within the hypothalmo-pituitary-adrenal/thyroid axis, there is minimal change in adrenal and thyroid function with ageing. The clinical significance of these deficiencies with age are variable and include reduced protein synthesis, decrease in lean body mass and bone mass, increased fat mass, insulin resistance, higher cardiovascular disease risk, increase in vasomotor symptoms, fatigue, depression, anaemia, poor libido, erectile deficiency and a decline in immune function. For each endocrine system, studies have been carried out in an attempt to reverse the effects of ageing by altering the serum hormonal levels of older individuals. However, the real benefits of hormonal treatment in older individuals are still being evaluated.

   Abstract: BACKGROUND: Although androgen withdrawal can control prostate cancer for long periods in many patients, controversy exists regarding management when the tumor becomes androgen independent. Several options are now available. METHODS: A review of the pertinent literature of the last 20 years was conducted to provide guidance in defining
and managing hormone-refractory prostate cancer. RESULTS: Stage D prostate cancer can be subclassified to correlate tumor biology with disease stage. Secondary hormone manipulations may induce responses in patients after failure of initial androgen suppression, and chemotherapy with docetaxel has prolonged survival in patients with androgen-independent prostate cancer (AIPC). The weight of evidence supports the maintenance of castrate levels of testosterone in metastatic AIPC. Bisphosphonates decrease skeletal complications. CONCLUSIONS: Secondary hormone therapy, chemotherapy, and bisphosphonate therapy may provide benefits for selected patients. Correlation of disease stage with biologic characteristics of the tumor and host facilitates proper choices of interventions. Docetaxel-based chemotherapy regimens should be considered for first-line treatment of patients with progressive metastatic AIPC.

Abstract: Osteoporosis is being recognized increasingly in men, and represents a substantial public health problem. As the male population ages and lives longer, the incidence of osteoporotic fractures is expected to increase. The current lifetime risk for a fragility fracture is approximately 27% in men aged 50 years or more, and will increase further over the next 20 years. A major problem with osteoporosis in men is that it continues to be unrecognized, and the majority of men with fragility fractures due to osteoporosis are not being treated. A higher level of awareness is required amongst both general practitioners and the general public that osteoporosis is a treatable condition that can affect men. Secondary causes for osteoporosis are more common in men than in women, and require rigorous exclusion and treatment. Undiagnosed clinical hypogonadism is a common cause of osteoporosis in men, and is readily treatable. The cause of primary osteoporosis in men is unknown, but it results in an osteoblast defect. Genetic factors are likely to be important. In some but not all men, relative estrogen deficiency contributes to rapid rates of age-related bone loss and fractures. An adequate calcium intake, regular weight-bearing exercise, and normal vitamin D status are all very important, particularly with increasing age. The role of testosterone in treating eugonadal men with osteoporosis is currently unclear, and larger prospective studies will be required to carefully evaluate the benefits and risks of therapy. First-line treatment of osteoporosis in hypogonadal or eugonadal men is with bisphosphonates. Alendronate increases bone density and reduces vertebral fractures measured using a semiquantitative method in eugonadal or hypogonadal men with osteoporosis. In the near future, it is likely that subcutaneous human parathyroid hormone (1-34) or teriparatide will also be available as an important new anabolic treatment for men with osteoporosis. Teriparatide treatment also increases bone density in men. Selective estrogen receptor modulating drugs require further evaluation in men, but would appear to theoretically benefit men, especially those with low estradiol levels. In the future, selective androgen receptor modulating drugs may be useful in the prevention and treatment of osteoporosis, and in increasing lean body mass in men, without having adverse effects on prostate and breast tissue.

Abstract: A new understanding of the endocrinology of menopause is that women, at menopause, are not only lacking estrogens resulting from cessation of ovarian activity but have also been progressively deprived for a few years of androgens and some estrogens
originating from adrenal DHEA and androstenedione (4-dione). In fact, serum DHEA decreases by about 60% between the maximal levels seen at 30 years of age to the age of menopause. This decreased secretion of DHEA and DHEA-S by the adrenals is responsible for a parallel decrease in androgen and estrogen formation in peripheral tissues by the steroidogenic enzymes specifically expressed in each cell type in individual target tissues. This new field of endocrinology, called intracrinology, describes the local synthesis of androgens and estrogens made locally in each cell of each peripheral tissue from the adrenal precursors DHEA and 4-dione. These androgens and estrogens exert their action in the same cells where their synthesis takes place and they are released from these target cells only after being inactivated. To further understand the effect of DHEA in women, DHEA has been administered in postmenopausal women for 12 months. Such treatment resulted in increased bone formation and higher bone mineral density accompanied by elevated levels of osteocalcin, a marker of bone formation. Vaginal maturation was stimulated, while no effect was observed on the endometrium. Preclinical studies, on the other hand, have shown that, due to its predominant conversion into androgens, DHEA prevents the development and inhibits the growth of dimethylbenz(a)anthracene-induced mammary carcinoma in the rat, a model of breast cancer. DHEA also inhibits the growth of human breast cancer ZR-75-1 xenografts in nude mice. The inhibitory effect of DHEA on breast cancer is due to an androgenic effect of testosterone and dihydrotestosterone made locally from DHEA. When used as replacement therapy, DHEA is free of the potential risk of breast and uterine cancer, while it stimulates bone formation and vaginal maturation and decreases insulin resistance. The combination of DHEA with a fourth generation SERM, such as EM-652 (SCH 57068), a compound having pure and potent antiestrogenic activity in the mammary gland and endometrium, could provide major benefits for women at menopause (inhibition of bone loss and serum cholesterol levels) with the associated major advantages of preventing breast and uterine cancer. A widely used application of intracrinology is the treatment of prostate cancer where the testicles are blocked by an LHRH agonist while the androgens made locally in the prostate from DHEA are blocked by a pure antiandrogen. Such treatment, called combined androgen blockade, has led to the first demonstration of a prolongation of life in prostate cancer.


Abstract: BACKGROUND: Although several agents are available to treat osteoporosis, the relative efficacy and toxicity of these agents when used to prevent fractures has not been well described. PURPOSE: To compare the benefits in fracture reduction and the harms from adverse events of various therapies for osteoporosis. DATA SOURCES: MEDLINE (1966 to November 2007) and other selected databases were searched for English-language studies. STUDY SELECTION: For the efficacy analysis, investigators selected studies that reported the rate of or risk for fractures. For the adverse event analysis, they selected studies that reported the relationship between an agent and cardiovascular, thromboembolic, or upper gastrointestinal events; malignant conditions; and osteonecrosis. DATA EXTRACTION: Using a standardized protocol, investigators abstracted data on fractures and adverse events, agents and comparators, study design, and variables of methodological quality. DATA SYNTHESIS: Good evidence suggests that alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, parathyroid hormone (1-34), and raloxifene prevent vertebral fractures more than placebo; the evidence for calcitonin was fair. Good evidence suggests that alendronate, risedronate, and estrogen prevent hip
fractures more than placebo; the evidence for zoledronic acid was fair. The effects of vitamin D varied with dose, analogue, and study population for both vertebral and hip fractures. Raloxifene, estrogen, and estrogen-progestin increased the risk for thromboembolic events, and etidronate increased the risk for esophageal ulcerations and gastrointestinal perforations, ulcerations, and bleeding. LIMITATION: Few studies have directly compared different agents or classes of agents used to treat osteoporosis.

CONCLUSION: Although good evidence suggests that many agents are effective in preventing osteoporotic fractures, the data are insufficient to determine the relative efficacy or safety of these agents.


Abstract: Prostate cancer is second only to lung and bronchial cancer as the leading cause of cancer death in men. Local treatment, surgery, and radiation remain the mainstay of treatment for early-stage disease. However, in locally advanced and advanced disease, there has been considerable evolution in the hormonal therapies. Suppression of testosterone production, the primary goal of hormonal therapy, may be accomplished with the use of estrogens, antiandrogens, and agonists and antagonists of luteinizing hormone-releasing hormone (LHRH). This article provides an overview of the primary hormonal therapies currently used in prostate cancer. Estrogen therapy was initially the predominant medical form of hormone manipulation and an alternative to orchiectomy. However, serious thrombogenic side effects were associated with its use, which decreased after the introduction of LHRH agonists in the 1980s. Many of the side effects occurring with oral estrogen therapy may be modulated by parenteral administration, and thus estrogen use is being revisited. LHRH agonists effectively reduce testosterone levels to castration levels (<50 ng/mL) within 2 to 4 weeks, although their use is associated with tumor flare.

Antiandrogen monotherapy may offer quality-of-life benefits over treatment with androgen deprivation. The additive benefit of combined androgen blockade is yet to be determined. Recent evidence suggests that hormonal therapy may offer a survival benefit when initiated in earlier stages of prostate cancer. Future investigations will be directed to determining the most efficacious regimens.


Abstract: BACKGROUND: Dehydroepiandrosterone (DHEA) and testosterone are widely promoted as antiaging supplements, but the long-term benefits, as compared with potential harm, are unknown. METHODS: We performed a 2-year, placebo-controlled, randomized, double-blind study involving 87 elderly men with low levels of the sulfated form of DHEA and bioavailable testosterone and 57 elderly women with low levels of sulfated DHEA. Among the men, 29 received DHEA, 27 received testosterone, and 31 received placebo. Among the women, 27 received DHEA and 30 received placebo. Outcome measures included physical performance, body composition, bone mineral density (BMD), glucose tolerance, and quality of life. RESULTS: As compared with the change from baseline to 24 months in the placebo group, subjects who received DHEA for 2 years had an increase in plasma levels of sulfated DHEA by a median of 3.4 microg per milliliter (9.2 micromol per liter) in men and by 3.8 microg per milliliter (10.3 micromol per liter) in women. Among men who received testosterone, the level of bioavailable testosterone increased by a median of 30.4 ng per deciliter (1.1 nmol per liter), as compared with the change in the placebo group. A separate analysis of men and women showed no significant effect of DHEA on

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body-composition measurements. Neither hormone altered the peak volume of oxygen consumed per minute, muscle strength, or insulin sensitivity. Men who received testosterone had a slight increase in fat-free mass, and men in both treatment groups had an increase in BMD at the femoral neck. Women who received DHEA had an increase in BMD at the ultradistal radius. Neither treatment improved the quality of life or had major adverse effects. CONCLUSIONS: Neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life. (ClinicalTrials.gov number, NCT00254371 [ClinicalTrials.gov]).

9. Pinkerton JV, Dalkin AC. Combination therapy for treatment of osteoporosis: A review. Am J Obstet Gynecol. 2007;197:559-65. Abstract: Combination therapy for osteoporosis has been tested in small trials of short duration with various combinations. Pertinent human and animal randomized clinical trial data were identified through Medline and reviewed with a focus on the risks and benefits of different types of combination therapies. Improvements in bone density were found in some, but not all, combinations. There are no large trials of adequate length or numbers to determine fracture efficacy. Consider combination therapy if monotherapy is unsuccessful, if there is an added nonskeletal benefit to the proposed combination or as sequential treatment with an anabolic agent followed by an antiresorptive agent. Although combination therapy, in general, has limitations based on cost, concern about potential oversuppression of bone, and lack of long-term safety and fracture efficacy, selected patients may benefit.

10. Simpson ER. Sources of estrogen and their importance. J Steroid Biochem Mol Biol. 2003;86:225-30. Abstract: In premenopausal women, the ovaries are the principle source of estradiol, which functions as a circulating hormone to act on distal target tissues. However, in postmenopausal women when the ovaries cease to produce estrogen, and in men, this is no longer the case, because estradiol is no longer solely an endocrine factor. Instead, it is produced in a number of extragonadal sites and acts locally at these sites as a paracrine or even intracrine factor. These sites include the mesenchymal cells of adipose tissue including that of the breast, osteoblasts and chondrocytes of bone, the vascular endothelium and aortic smooth muscle cells, and numerous sites in the brain. Thus, circulating levels of estrogens in postmenopausal women and in men are not the drivers of estrogen action, they are reactive rather than proactive. This is because in these cases circulating estrogen originates in the extragonadal sites where it acts locally, and if it escapes local metabolism then it enters the circulation. Therefore, circulating levels reflect rather than direct estrogen action in postmenopausal women and in men. Tissue-specific regulation of CYP19 expression is achieved through the use of distinct promoters, each of which is regulated by different hormonal factors and second messenger signaling pathways. Thus, in the ovary, CYP19 expression is regulated by FSH which acts through cyclic AMP via the proximal promoter II, whereas in placenta the distal promoter I.1 regulates CYP19 expression in response to retinoids. In adipose tissue and bone by contrast, another distal promoter--promoter I.4--drives CYP19 expression under the control of glucocorticoids, class 1 cytokines and TNFalpha. The importance of this unique aspect of the tissue-specific regulation of aromatase expression lies in the fact that the low circulating levels of estrogens which are observed in postmenopausal women have little bearing on the concentrations of estrogen in, for example, a breast tumor, which can reach levels at least
one order of magnitude greater than those present in the circulation, due to local synthesis
within the breast. Thus, the estrogen which is responsible for breast cancer development,
for the maintenance of bone mineralization and for the maintenance of cognitive function is
not circulating estrogen but rather that which is produced locally at these specific sites
within the breast, bone and brain. In breast adipose of breast cancer patients, aromatase
activity and CYP19 expression are elevated. This occurs in response to tumor-derived
factors such as prostaglandin E2 produced by breast tumor fibroblasts and epithelium as
well as infiltrating macrophages. This increased CYP19 expression is associated with a
switch in promoter usage from the normal adipose-specific promoter I.4 to the cyclic AMP
responsive promoter, promoter II. Since these two promoters are regulated by different
cohorts of transcription factors and coactivators, it follows that the differential regulation of
CYP19 expression via alternative promoters in disease-free and cancerous breast adipose
tissue may permit the development of selective aromatase modulators (SAMs) that target
the aberrant overexpression of aromatase in cancerous breast, whilst sparing estrogen
synthesis in other sites such as normal adipose tissue, bone and brain.

11. Valverde P. Pharmacotherapies to manage bone loss-associated diseases: a quest for the
Abstract: In this review, benefits and side-effects of current and emerging therapies to treat
and prevent pathological bone loss are described. Bisphosphonates are the antiresorptive
compounds most widely used in the treatment of bone-loss associated diseases. They are
generally well-tolerated although have recently been associated with osteonecrosis of the
jaw and other complications. Therapies modulating estrogen receptor activation are
indicated in the prevention and treatment of either breast cancer or osteoporosis in
postmenopausal women. Thus, hormone replacement therapy is effective in prevention of
osteoporosis, but its long-term use can increase the risk of breast cancer, stroke and
embolism. Tamoxifen benefits all stages of breast cancer, but its use may lead to uterine
cancer and thromboembolism. Raloxifene is approved in prevention of breast cancer and
treatment of postmenopausal osteoporosis, but its use can increase the risk of fatal stroke.
Aromatase inhibitors are superior to tamoxifen at advanced stages of disease and as
adjuvants, but their use increase fracture incidence. Fulvestrant is as effective as aromatase
inhibitors in the treatment of advanced breast cancer and does not cause bone fractures.
Another antiresorptive available for the treatment of postmenopausal osteoporosis, Paget's
disease and hypercalcaemia is calcitonin, which also exhibits analgesic effects. A promising
antiresorptive agent currently in clinical trials is denosumab. Additional therapies for
osteoporosis that decrease fracture risk consist of PTH-like anabolic agents and the dual
action bone agent strontium ranelate. Antiseptics and antibiotics are used extensively in
periodontal disease intervention to target bacterial biofilm, although host-directed therapies
are also being developed.