Chapter 9

Vitamin D Endocrinology and Calcium Homeostasis Disorders

Introduction

A vitamin is a compound required in the diet because it cannot be synthesized in the body. By this definition, Vitamin D is not a true vitamin. Vitamin D is normally produced in the body, requiring only exposure to sunlight. Vitamin D acts as a pro-hormone – a hormone precursor – that is converted to the active hormone by a regulated process; it was called a vitamin because of its discovery as a nutritional factor that would prevent the bone formation disorder Rickets'.

It could also be said that Vitamin D became a vitamin as a result of the Industrial Revolution. Beginning around 1700 as the Industrial Revolution started, the population began a shift from the countryside into the city. This had three effects that decreased Vitamin D synthesis: 1) the city buildings blocked the sunlight; 2) smog, largely produced by the use of coal for building heat and power generation, attenuated the available sunlight; and 3) many individuals (including children before the advent of child labor laws) worked indoors during the entire daylight period. In addition, the Industrial Revolution occurred primarily in northern countries, which experience very short days during the winter months. Autopsies reveal that >80% of the city-dwelling children showed some indications of Rickets'.

The cause was not understood until the 1920's, when it was discovered that the effects could be reversed by exposure to near-ultraviolet light or to sunlight. Relatively brief exposure to sunlight is sufficient to allow synthesis of Vitamin D; exposure of the hands, arms, and face to the sun about 15 minutes a day three times a week is enough.

Synthesis of Vitamin D

Vitamin D_3 is a secosteroid derivative of cholesterol. The 9-10 bond of 7-dehydrocholesterol is cleaved upon exposure to ultraviolet light (290-300 nm) to form pre-Vitamin D; pre-Vitamin D_3 isomerizes to Vitamin D_3 by rotation around the 6-7 bond (converting the 5-6 and 7-8 double bonds from *cis* to *trans*). Continued exposure to sunlight results in the conversion of pre-Vitamin D to lumisterol and tachysterol, which are inactive (although conversion to lumisterol is reversible), thereby preventing Vitamin D toxicity following extended sun exposure. The production of Vitamin D_3 is inhibited by sunscreen and by melanin, both of which absorb the wavelengths of light required for the cleavage of the 9-10 bond.
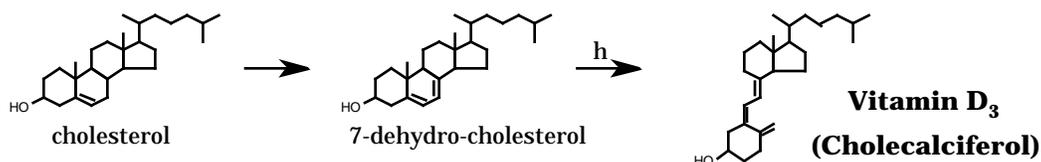

Figure 1. The biosynthesis of vitamin D_3.

Ultraviolet irradiation of milk converts ergosterol, a plant compound found in milk (cows are vegetarians!) to Vitamin D_2 (Figure 2), which is similar in action to Vitamin D_3. In the United States, however, milk is no longer irradiated, but instead is supplemented with 10 µg/liter of either Vitamin D_2 or Vitamin D_3. This prevents calcium uptake deficiencies in individuals who drink milk.
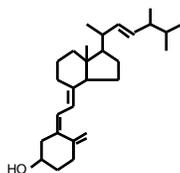

Figure 2. The structure of ergocalciferol (Vitamin D_2).

Activation of Vitamin D

Vitamin D is not in itself a hormone, but rather is a *hormone precursor*. Conversion of Vitamin D to the active form is a regulated process that occurs sequentially in the liver and kidney. Note that the process of conversion is identical for Vitamin D_3 and Vitamin D_2; the diagrams will use Vitamin D_3.

Vitamin D is converted to 25-hydroxy-Vitamin D in the liver by 25-hydroxylase, a mitochondrial cytochrome P450 (Figure 3). 25-Hydroxy-Vitamin D is released into the blood stream. In the kidney, 1 -hydroxylase (also a mitochondrial cytochrome P450), hydroxylates 25-hydroxy-Vitamin D at the 1 -position to form the active hormone. **1α-Hydroxylase catalyzes the rate limiting step for 1α,25-dihydroxy-Vitamin D formation**. All known effects of Vitamin D are mediated by 1 ,25-dihydroxy-Vitamin D. The placenta also contains 1 -hydroxylase, probably to ensure increased calcium uptake during pregnancy.
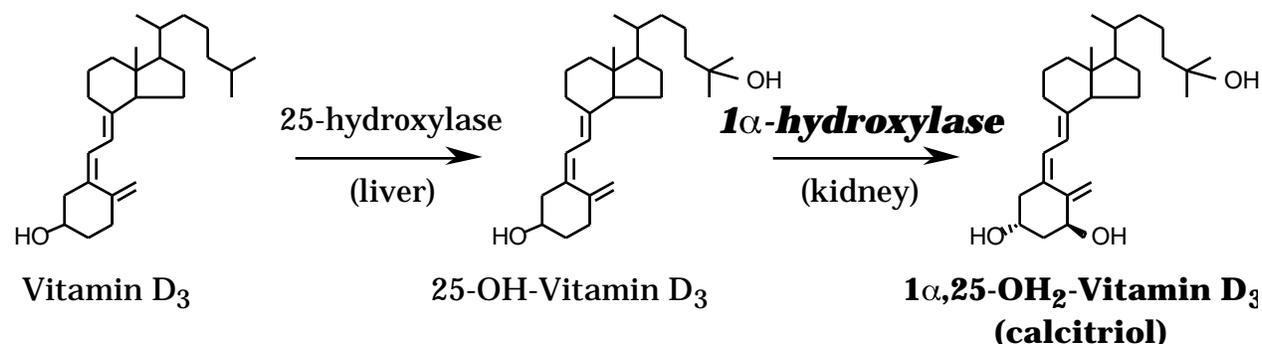

Figure 3. The activation of Vitamin D.

There is a relatively large amount of Vitamin D in the body (about 1000 µg), most of which is stored in the liver. This material has a half-life of about 30 days. About 200 µg of 25-hydroxy-Vitamin D is also stored in the liver, with a half-life of about 15 days. Neither of these compounds is active, and they are therefore not heavily regulated; their storage is logical, since the individual may not be exposed to

sunlight for a long period of time, especially in winter. In contrast, only about 0.5 μg of 1 ,25-dihydroxy-Vitamin D is present at one time, and it has a half-life of about 4 hours.

1 ,25-Dihydroxy-Vitamin D and its precursors have a serum Vitamin D Binding Globulin. As with the other steroid hormones, 1 ,25-dihydroxy-Vitamin D activity is proportional to the levels of free (rather than total) hormone present in serum. Vitamin D Binding Globulin has the highest affinity for 25-hydroxy-Vitamin D, with lower affinities for Vitamin D or 1 ,25-dihydroxy-Vitamin D.

A number of other metabolites of Vitamin D have been described; the function of these compounds is unclear. The most studied, 24,25-dihydroxy-Vitamin D is proposed to either have alternative hormonal functions or to represent the first step in an inactivation pathway. Some data suggest that 24-hydroxylated Vitamin D metabolites are required for maintaining normal bone structure, although they do not bind the Vitamin D receptor.

Regulation of 1α,25-dihydroxy-Vitamin D Biosynthesis

Unlike the cascade pathways for the other steroid hormones, the last step in 1 ,25-dihydroxy-Vitamin D synthesis, the step catalyzed by 1 -hydroxylase, is the regulated step. Note that the variation of 1 ,25-dihydroxy-Vitamin D concentration in serum with calcium concentration (Figure 4) is very similar to that for PTH (see Chapter 8); **1α-hydroxylase activity is stimulated by PTH**. Although the effect of PTH is probably mediated by cAMP, it requires several hours, and therefore probably involves synthesis of new enzyme. The production of 1 ,25-dihydroxy-Vitamin D is under feedback control; 1 ,25-dihydroxy-Vitamin D decreases PTH secretion from the parathyroid, probably decreases 1 -hydroxylase gene transcription, and also stimulates liver degradation of 25-hydroxy-Vitamin D; elevated serum calcium also inhibits 1 -hydroxylase by direct effects on the kidney.
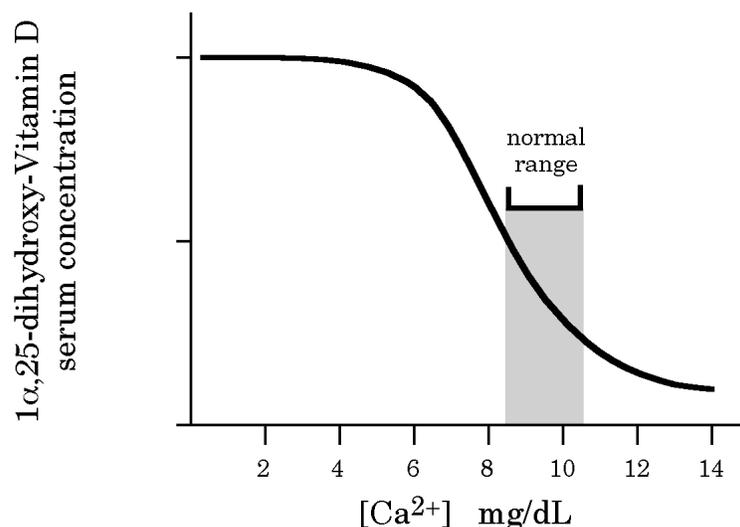

Figure 4. Variation of serum 1 ,25-dihydroxy-Vitamin D levels with serum calcium.

Physiological Actions of 1α,25-dihydroxy-Vitamin D

The major function of 1α,25-dihydroxy-Vitamin D is to stimulate calcium uptake in the small intestine. 1 ,25-Dihydroxy-Vitamin D also stimulates calcium and phosphate reabsorption in the kidney, and increases calcium mobilization from bone.

The 1 ,25-dihydroxy-Vitamin D receptor (VitDR) is the smallest member of the steroid hormone receptor superfamily. The N-terminal variable domain is very small (about 25 amino acids). The VitDR is probably constitutively associated with its HRE, and is thought to act in a manner similar to that of the other members of the steroid hormone receptor superfamily, by regulating gene transcription.

The mechanisms by which the calcium regulatory functions of 1 ,25-dihydroxy-Vitamin D are mediated are not clear; although several VitDR-responsive genes are known (*e.g.,* calbindin, osteocalcin, osteopontin), the functions of the protein products of these genes are poorly understood. The level of VitDR is thought to be important in these effects; 1 ,25-dihydroxy-Vitamin D up-regulates the VitDR in the intestine, kidney, bone, and parathyroid.

The VitDR has been found in a variety of cell types other than intestine, kidney, bone, and parathyroid. These non-classical tissues include: skin, the hematopoietic and immune system, cardiac, skeletal, and smooth muscle, brain, liver, pituitary, pancreas, adrenal, thyroid, ovary, and testis. In cardiac and Sertoli cells in culture (and probably a variety of other cell types as well), 1 ,25-dihydroxy-Vitamin D stimulates calcium uptake. The effect was inhibited by the protein synthesis inhibitor cycloheximide; combined with the observed time course of the calcium uptake response, this suggests a VitDR-mediated transcriptional mechanism.

1 ,25-Dihydroxy-Vitamin D induces differentiation in osteoclasts and in some other cell types, and has some tumor growth inhibitory effects (in VitDR containing melanoma, myeloid leukemia, and breast cancer). This, however, is not a general phenomenon: 1 ,25-dihydroxy-Vitamin D appears to be a proliferative agent in bone marrow cells. The clinical usefulness of the growth inhibition has thus far been limited by the hypercalcemic effects of 1 ,25-dihydroxy-Vitamin D, leading to attempts to produce non-calcemic analogs that retain the anti-proliferative effects.

Calcium Homeostasis-Related Abnormalities

Rickets': Mentioned in the introduction of this Chapter, Rickets' is a disorder of improper mineralization of bone in children. Classical Rickets' is a nutritional problem, abolished by Vitamin D supplements or exposure to sunlight.

Vitamin D-resistant Rickets': A rare form of Rickets' is caused by either a deficiency in 1 -hydroxylase (presenting with high PTH, but low 1 ,25-dihydroxy-Vitamin D) or by a receptor defect (presenting with both high PTH and 1 ,25-dihydroxy-Vitamin D). Both are characterized by bone abnormalities and hypocalcemia, and neither is reversible by dietary supplementation with Vitamin D. Patients with 1 -hydroxylase deficiency respond to exogenous 1 ,25-dihydroxy-

Vitamin D, while those with the receptor defect do not.

Some forms of Vitamin D-resistant Rickets' present with abnormalities that appear unrelated to calcium homeostasis (*e.g.,* alopecia), possibly as a result of improper formation of heterodimers of VitDR with other members of the steroid receptor superfamily. One characterized mutation is in the second zinc-finger of the VitDR; this apparently interferes with DNA-binding. The symptoms in these receptor-defect patients thus support the hypothesis that 1 ,25-dihydroxy-Vitamin D and/or its receptor alone have other roles beyond maintenance of serum calcium levels.

Other causes of Rickets': Rickets' may also be caused by disorders of phosphate metabolism. These disorders may directly result in improper bone formation (*e.g.*, serum alkaline phosphatase deficiency), or may have indirect effects via stimulating excessively high PTH secretion (*e.g.*, hypophosphatemia). While these disorders are relatively rare, they do point out that simple treatment with Vitamin D will not cure all forms of childhood Rickets'.

Osteomalacia: The "adult form of Rickets'" is characterized by softening and demineralization of the bones. Osteomalacia usually arises from a severe deficiency in Vitamin D or dietary calcium.

Osteopetrosis: Abnormalities in osteoclast differentiation and function result in a disorder called osteopetrosis, a disorder in which minimal remodeling occurs, resulting in fragile bones. One form of osteopetrosis appears to be a result of defective carbonic anhydrase II, an enzyme required for osteoclast function. Osteopetrosis is also the major disorder in mice homozygous for c-*src* tyrosine kinase and for c-*fos* proto-oncogene knockout mutations, which suggests that these proteins are required for osteoclast recruitment or maturation.

Paget's disease: Paget's disease is probably viral in origin (although there is also evidence for a genetic component in susceptibility) and is characterized by elevated rates of bone resorption and formation. The high rate of turnover results in disorganized bone structure, bone pain, malformities, fractures, and deafness. The first clinically approved use of salmon calcitonin (a long-acting analog of the human hormone) was the treatment of Paget's disease. Calcitonin apparently acts as an analgesic against bone pain as well as affecting osteoclast function. An alternative treatment is the administration of bisphosphonate drugs (see box). Paget's disease probably affects about 1-3% of the population in the Unites States, although only 10-20% of those individuals experience symptoms severe enough to warrant treatment. (The incidence of Paget's disease is higher in individuals of European decent, and is much higher in some parts of Europe.)

Bisphosphonates are non-hydrolyzable pyrophosphate analogs (note the P-C-P bond instead of the P-O-P bond in pyrophosphate). These compounds inhibit osteoclast function, probably both via direct actions in osteoclasts, and via actions in osteoblasts resulting in decreased osteoclast recruitment and differentiation, and possibly increased osteoclast apoptosis. At high doses bisphosphonates inhibit kidney stone formation; unfortunately, at these doses, they also inhibit bone formation. Etidronate and the more potent alendronate are clinically approved in the United States; several pharmaceutical companies are searching for improved compounds with reduced side effects.

Bisphosphonate drugs are used to treat Paget's disease and to reduce bone resorption in hypercalcemia of malignancy; alendronate is also currently in use as an anti-osteoporotic drug.

Pyrophosphate   Etidronate   Alendronate
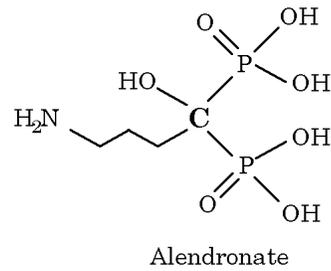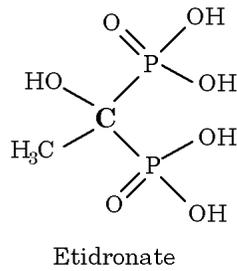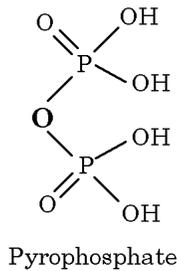
Hypercalcemia of malignancy: About 10% of patients with solid tumors become hypercalcemic (the fraction varies depending on the type of tumor, with ~35% of lung tumors, but only 3% of prostate tumors leading to hypercalcemia). In rare cases, the tumor may induce hypercalcemia by secreting 1 ,25-dihydroxy-Vitamin D; in some cases, the hypercalcemia is the result of bone metastases causing local destruction and releasing calcium in large amounts; and in some cases, the elevated calcium is solely the result of tumor-secreted PTHrP. In most cases, however, the hypercalcemia is due to a combination of bone metastases and tumor PTHrP production. Hypercalcemia of malignancy is associated with poor prognosis; PTHrP stimulates growth factor production, especially in bone, and may stimulate tumor cell growth directly. Although single injections of PTH and PTHrP result in similar effects, hypercalcemia of malignancy exhibits clinical findings not observed in hyperparathyroidism (*e.g.*, low serum 1 ,25-dihydroxy-Vitamin D and bone resorption without formation), probably due to differences in release profiles or biological actions of PTHrP and PTH.

Hyperparathyroidism: A number of disorders result from excessive PTH secretion. Unlike hypercalcemia of malignancy, in which PTH secretion is suppressed, in hyperparathyroidism the hypercalcemia is a result of excessive PTH secretion. The most common cause of hyperparathyroidism is a benign parathyroid adenoma; more rarely hyperparathyroidism is due to a parathyroid tumor. It is possible that parathyroid adenomas revert to the calcium sensing set-point of the fetus (*i.e.* 30% higher than the adult). This could explain the release of PTH; the cells sense a (for them) hypocalcemic state and attempt to respond by secreting hormone and by hyperplasia. In some cancer patients, hyperparathyroidism unrelated to the tumor may occur; this is the most common reason for elevated PTH (as opposed to PTHrP) in cancer patients, although a very small fraction of tumors aberrantly secrete PTH.

Hyperparathyroidism may also be a secondary consequence of another disorder that results in decreased serum calcium, such as phosphate metabolism disorders or renal failure.

Osteoporosis

Osteoporosis is an excessive demineralization of bone. Osteoporosis is a major

health issue: 30-50% of all post-menopausal women, and nearly 50% of all people over 75 are affected. Osteoporotic bone weakening is associated with 65% of the 2 million bone fractures occurring in the United States annually, with annual costs of ~$15 billion. About 25% of the 1.7 million people world-wide who suffer hip fractures each year will die within 6 months.

Figure 5 is a graph showing the variation of total bone calcium with age. It is clear from the graph that men tend to have higher bone calcium levels at all ages (the graph only shows average values and a range around these values; individual variation from these average values can be quite marked). Note the sharp decrease in calcium in women at about 50 years of age. The threshold lines indicate bone density associated with fractures in the absence of significant causative trauma, the types of fractures characteristic of osteoporosis.
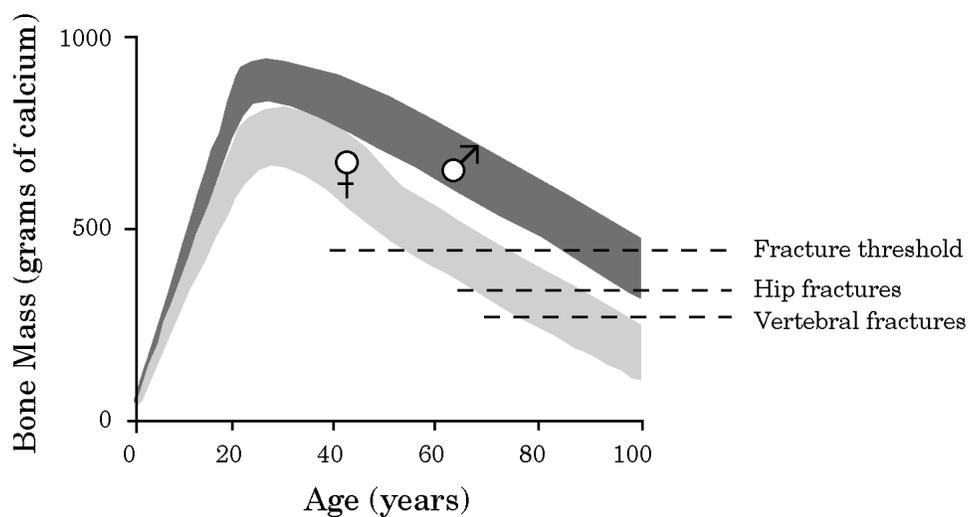

Figure 5. Decline in bone mass with age (from Mundy, 1994).

Osteoporosis can be divided into Type I and Type II forms. Type I affects 10-20% of women, and usually begins 10-15 years after menopause (due to the rapid loss of bone that occurs in women during this period; see below), manifesting itself primarily by fractures in trabecular bone (especially crush fractures of vertebrae, although wrist and ankle fractures also occur). In contrast, Type II is age related (incidence increases exponentially with age), being predominant in people older than 70, and is less gender dependent, although still twice as many women as men suffer from the disorder. The typical fractures are of both trabecular and cortical bone; for example, wedge fractures of the vertebrae and fractures of the hip. In essence the difference between Type I and Type II is that in Type I, the rapid loss of bone following menopause is the proximate cause of the disorder, while in Type II the rapid loss associated with menopause is insufficient in itself to result in osteoporosis, and further loss secondary to aging is required; the menopause effect partially explains the higher incidence of Type II among women compared to age-matched men.

Men appear less susceptible to osteoporosis as a result of greater peak bone mass, higher average calcium intake, the lack of an equivalent to menopause, and, possibly, a somewhat greater frequency of exercise. In addition, males are somewhat less susceptible to fractures than females, because the strength of a given bone is highly dependent on its size, and men tend to have larger bones than women. Although incidence in men is rising, it is currently significantly less than is observed in women. The most common risk factors in men are high glucocorticoid levels (as a result of either hypersecretion or pharmacological administration), alcohol abuse, and hypogonadism.

Causes of Osteoporosis

Effects of aging: All individuals undergo loss of bone mass after age 35. Aging is associated with decreased osteoblast function, decreased calcium absorption, and, in some cases, decreased ability to synthesize Vitamin D (probably at least one cause of decreased calcium absorption). The decrease in osteoblast function is probably responsible for the observed decrease in bone density, and for the decrease in remodeling and repair (and therefore mechanical strength) that occurs with aging. PTH levels increase with age in normal individuals, probably to compensate for decreased calcium absorption.

Decline in estrogen: An accelerated phase of bone loss (a 3 to 4-fold increase in rate), probably related to estrogen deficiency, occurs in women for 4–8 years after cessation of ovarian function; a similar loss may occur in hypogonadal men. This bone loss appears to be associated with decreased PTH secretion, probably because of suppression by increased bone calcium release. Decline in estrogen levels results in a variety of effects; the main cause of bone abnormalities appears to be increased osteoclast function to the point that the bone is irreversibly damaged. Estrogen receptors are thought to be present primarily in osteoblasts, suggesting that the effects of estrogens are mediated by cell-cell interactions and altered levels of paracrine effectors.

Genetics: Some rare genetic disorders in collagen synthesis, such as osteogenesis imperfecta, result in osteoporosis. In addition, there is clearly a genetic component related to susceptibility to osteoporosis in individuals without overt genetic disorders. What genes are involved, and how important they are relative to other risk factors is not clear. One proposed candidate gene is the Vitamin D receptor; one allele of the gene appears to be associated with higher risk for osteoporosis. The only difference between the alleles is in the 3´ untranslated region of the Vitamin D receptor gene, suggesting that the difference probably results in altered regulation of VitDR gene expression.

Lifestyle: A sedentary lifestyle is a known risk factor for osteoporosis; on the other hand, excessive exercise may also be a risk factor. Amenorrheic female athletes generally exhibit lower bone density than their eumenorrheic counterparts. This effect on bone may, like the amenorrhea, be a result of poor diet, since many of these individuals ingest large quantities of minerals and Vitamins A and D, but low amounts of calcium; alternatively, it may be a result of the high cortisol and low estrogen levels generally observed in these individuals. Elevated glucocorticoids,

low levels of sex steroids, and low dietary calcium are also observed in anorexia nervosa. Current data suggest that increasing caloric intake to levels that restore normal menstrual cyclicity prevents further negative effects on bone, although it may not reverse the damage that had already occurred. Males are somewhat less vulnerable to the effects of excessive exercise, but also can experience bone loss due to anorexia or other causes of inadequate dietary calcium.

Child-bearing: The fetus must absorb calcium during development (usually >20 g). Lactation also requires calcium; the breast secretes significant amounts of PTHrP to support milk production (this is probably at least part of the reason that breast cancer is frequently associated with hypercalcemia). In women with insufficient dietary calcium, the calcium requirements of pregnancy and lactation are met by resorption of bone, and therefore increased later risk of osteoporosis.

Obesity: Somewhat surprisingly obesity is not associated with osteoporosis, and may even have some protective effects, possibly as a result of elevated estrogen levels due to production in adipose tissue, or of greater gravitational stresses on the bones.

Glucocorticoids: Elevated cortisol levels are directly related to rate of bone loss. This appears to be a result of both inhibition of bone formation and stimulation of bone resorption, and of both decreased calcium absorption in gut and increased excretion in urine. At least some of these effects are mediated by glucocorticoid stimulation of PTH secretion, both directly and via the mild hypocalcemia that results from the altered uptake and excretion. In addition, there is some evidence that glucocorticoids enhance the sensitivity of osteoblasts to PTH. Glucocorticoids also inhibit collagen and proteoglycan synthesis as well as stimulating collagen breakdown. Long term treatment with glucocorticoids is strongly correlated with later development of osteoporosis; 30-50% of patients given prolonged pharmacological glucocorticoid therapy are later diagnosed with osteoporosis.

Thyrotoxicosis: Excessive amounts of thyroid hormones as a cause of osteoporosis is fairly rare, because thyroid disorders are normally treated prior to extensive modification in bone structure. Untreated hyperthyroidism, however, can result in osteoporotic bone loss, especially during the perimenopausal period of increased bone loss in women. In addition, many individuals on thyroid hormone replacement therapy receive levels which result in mild hyperthyroid status; this has been correlated with increased rate of bone loss.

Drugs: Ethanol is an osteoblast toxin. While small quantities of ethanol may actually promote bone formation, alcoholism is strongly associated with development of osteoporosis. This effect is probably due to a combination of the systemic toxicity of chronic ethanol consumption (which often includes hypogonadism), the poor nutrition generally associated with alcoholism, and direct effects of ethanol on bone formation.

Hypervitaminosis A and D can result in bone remodeling abnormalities. Chemotherapeutic agents are toxic to both osteoblasts and osteoclasts, leading to decreased bone remodeling and increased fragility. High doses of aluminum (*e.g.*, from antacids) may result in poorly mineralized bone.

Cigarette smoking interferes with estrogen synthesis (aromatase inhibitors are present in smoke), and its effects on bone may be mediated by this inhibition; in addition, a number of toxins are present in smoke. Smoking is also often associated with caffeine consumption; caffeine reduces absorption and increases excretion of calcium.

Renal failure: Renal failure results in decreased kidney calcium reabsorption, decreased 1 ,25-dihydroxy-Vitamin D synthesis, and elevated PTH levels, all of which lead to osteoporotic bone loss. In addition, patients with renal failure are often hyperparathyroid, even under conditions of elevated serum calcium, suggesting reduced parathyroid sensitivity to serum calcium levels.

Treatments for Osteoporosis

Hormone replacement therapy: Estrogen replacement decreases risk of both osteoporosis and heart disease in many women, although it is associated with additional risk of endometrial cancer (and possibly breast cancer, although this is controversial) and of thrombosis. The risk of endometrial cancer is markedly reduced by the use of a progestin in combination with the estrogen. There is some evidence that estrogen therapy is of less value following age 70. In general, estrogen therapy appears to be of significant overall benefit (up to 40% lower mortality) unless contraindicated as a result of the presence of hormone-responsive cancer or liver disease. Estrogen therapy decreases the rate of bone loss, but normally does not increase bone density (except for a period of 12-18 months in previously untreated postmenopausal women).
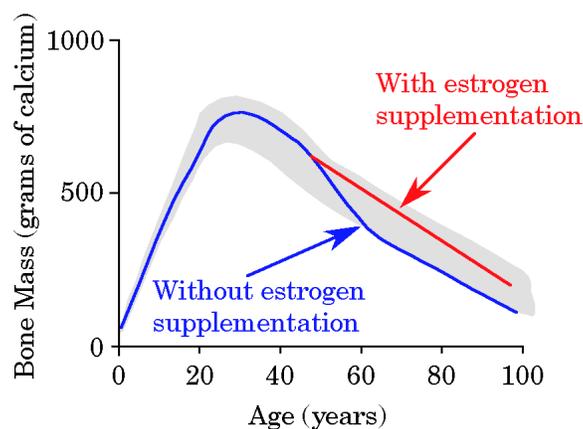
Figure 6. The effect of estrogen replacement on a woman at high risk for osteoporosis. The blue curve shows a fairly typical curve of bone density with age for an untreated woman. Not that the bone density of this individual dropped from somewhat above average to the lower limit of normal during the post-menopausal period. Estrogen replacement typically does not halt the loss of bone mass, but does prevent the dramatically increased rate associated with menopause.

Hypogonadal males at risk for osteoporosis may be treated with androgens; however, this increases the risk for a variety of problems, including prostate cancer and heart disease.

Antiestrogen therapy: In an ongoing clinical trial, 16,000 women are being treated with either the antiestrogen tamoxifen or a placebo to assess the effects of tamoxifen on women at high risk for breast cancer. Perhaps due to its partial-agonist character, tamoxifen treatment may actually be able to substitute for estrogen treatment in decreasing bone loss. In previous trials, while tamoxifen had little effect on cortical bone (in the radius for example), tamoxifen treatment was associated with a decreased rate of loss of bone density in trabecular bone (*e.g.*, the lumbar spine). However, tamoxifen is not as potent as estrogen in this process, and does not have the protective effect of estrogen on cortical bone.

Since tamoxifen acts as a partial agonist, at least in some bone types, other anti-estrogenic compounds have also been tested for anti-osteoporotic activity. One of these, raloxifene, appears to have effects in most bone types similar to that of estrogen, while lacking estrogenic effects in uterus and breast; raloxifene was recently approved for use as an anti-osteoporotic drug in female patients for whom estrogen therapy is inappropriate. In this context, raloxifene and tamoxifen are classified as SERMs (selective estrogen receptor modulators). Identifying new SERM-type compounds is an active area of research.

Calcium supplements: Sufficient dietary calcium is of primary importance in preventing excessive bone loss. While adding calcium to diet beyond that necessary to maintain the homeostatic balance appears to have little or no value, and in fact, may result in further deleterious effects on bone density, excessive intake is rarely a problem. The average calcium intake in females in the Unites States is 400 to 500 mg, which is far below the required level (1000 mg/day) for pre-menopausal and estrogen-treated post-menopausal women, and is about 30% of requirements (1500 mg/day) for non-estrogen-treated post-menopausal women.

Exercise: Regular exercise significantly decreases the rate of bone loss. Exercise normally stimulates increased deposition and increased turnover; the latter is necessary to maintain normal structure and repair damage. Exercise also maintains muscle tone and coordination, decreasing the likelihood of falls that can result in fractures, and increasing the resiliency of the body and thereby aiding in cushioning impacts that do occur.

Other approaches: Calcitonin has been used to attempt to reverse bone loss. In some trials, modest gains in density (~5%) have been observed; however, calcitonin is expensive and may have significant side effects. Fluoride has been shown to increase bone density. Unfortunately, this increase in density is not usually associated with a decrease in fracture rate, although some recent trials have suggested that slow-release formulations of fluoride may be beneficial. PTH, somewhat paradoxically, may be capable of stimulating bone formation. In preliminary trials using pulsed administration of PTH, significant increases in bone density and strength were observed. Finally, research into the mechanism by which bone strength is enhanced by exercise is ongoing. The hypothesis is that the exercise effect may be mediated by a paracrine factor, and that it may be possible to design drugs which yield similar results.

Alendronate (Fosamax) is a second generation bisphosphonate drug recently approved for use as an anti-osteoporotic agent. Alendronate probably functions

primarily by inhibiting osteoclast resorption of bone, although it may also inhibit osteoclast maturation, and appears to have effects on osteoblasts as well. Alendronate is the first drug shown to yield clinically significant increases in both bone density and bone strength in patients with osteoporotic levels of bone loss. The mechanism of the bisphosphonate drugs appears to be separate from that of estrogen (or androgen in males), and concurrent hormone replacement therapy may have greater effects than either treatment alone. It should be noted, however, that little information is available about long term effects of alendronate.

Prevention: Once the bone loss has reached a threshold level, fractures will occur. Current evidence suggests that this is an inescapable consequence of aging. However, the peak bone mass and the rate of bone mass loss are significantly affected by regular exercise involving the weight bearing bones. In combination with a balanced diet (including enough calcium and Vitamin D), and hormone replacement therapy when indicated, most normal individuals who exercise regularly will extend the time required to reach the fracture threshold level of bone density well beyond any likely life-span.

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