

Primary ovarian insufficiency (AKA premature menopause)

► Marcy Lash, MD, and Lawrence M. Nelson, MD

JD, a 35-year-old woman, presents seeking a second opinion regarding her premature menopause. The patient received this diagnosis at age 30 during a workup for oligomenorrhea. One year following her diagnosis, JD unexpectedly conceived and gave birth to a male infant who is now experiencing developmental delay. She complains of hot flashes and vaginal dryness that are

not adequately relieved by her current hormone therapy regimen of continuous combined oral conjugated equine estrogen 0.625 mg and 2.5 mg of medroxyprogesterone acetate. JD and her husband have decided that they are content with the size of their family (3 children). Her main reason for this visit is to obtain more information about her condition and to plan a healthy lifestyle in view of her premature menopause.

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This article reviews the evaluation and management of what we and others prefer to call primary ovarian insufficiency (POI), also known as premature menopause, premature ovarian failure, ovarian dysgenesis, and hypergonadotropic hypogonadism.^{1,2} We will categorize this disorder

by mechanism and provide examples of the major etiologies, describe associated symptoms and clinical findings, and end with a review of the evaluation and treatment of the disorder.

Background

Fuller Albright first described a condition he termed primary ovarian insufficiency in 1942 when he reported a syndrome of amenorrhea, estrogen deficiency, and menopausal follicle-stimulating hormone (FSH) levels in young women.³ He used this term to make it clear that ovarian function was the primary defect, as evidenced by high FSH levels, rather than failure of gonadotropin secretion. Amenorrhea related to inadequate release of gonadotropins and low FSH levels would be categorized as secondary ovarian insufficiency, ie, inadequate ovarian function would be secondary to a pituitary or hypothalamic disorder. Albright reported on women with Turner syndrome as well as women with isolated POI who had none of the associated physical stigmata. In the latter case, subsequent investigators used the terms premature menopause or premature ovarian failure to herald complete depletion of potentially functional primordial follicles,

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FROM THE EDITOR



Now is the winter of our discontent made glorious summer...

William Shakespeare

During the bleak and snowy March day I wrote this editorial, it seemed appropriate to evoke Shakespeare in describing the current issue of *Menopausal Medicine* since you will be reading it in May when the dream of summer will be close to reality. Just as the change of seasons gives us reason to renew our outlook, the two articles in this issue each provide a new twist on conventional wisdom and a glimmer of optimism.

Drs Marcy Lash and Lawrence M. Nelson present us with another twist on generally held views about one of the more vexing conditions faced by the clinician: premature ovarian failure/primary ovarian insufficiency (POF/POI). There are no known remedies for the condition; patients are usually shocked and saddened by the diagnosis, and there have been few clinical trials that have provided medical evidence for optimal therapy.

Using the resources established at the intramural National Institutes of Health Reproductive Sciences Branch, Dr Nelson has devoted several decades of effort addressing the needs of women with this diagnosis, trying to learn more about POF/POI through research into its causes, symptoms, and patterns. Hormones, genes, the immune system, and other factors may all play a role. Drs Lash and Nelson provide clinical evidence that gives optimal support for women with this disorder.

By engaging with our patients, applying appropriate screening techniques, and treating long-term health problems early and proactively, we may not be able to cure POF/POI, but we can certainly ameliorate its consequences and help patients live with the uncertainties that this diagnosis brings.

Dr Ruth Freeman brings us up to date on vitamin D, the “non-hormone.” The so-called “sunshine vitamin” has come under increasing scrutiny for its role in health and disease ever since its receptor was first identified as a member of the nuclear receptor superfamily along with estrogen and progesterone. The positive outcome of these investigations has been astonishing. New data is beginning to redefine a role for vitamin D3 supplementation as well as the level of intake needed for optimal health. From cognition to cardiovascular disease, adequate vitamin D intake has been associated with a large array of health benefits far and above merely preventing rickets, which it will do at low doses.

Most inhabitants of northern climates do not get enough sun exposure to bioconvert vitamin D2 to D3. This bioconversion occurs only in the skin after at least 15 minutes of daily, non-sunscreen-protected exposure. Rather than having to balance the risks of premature aging skin and skin cancer against the benefits of adequate bioconversion of vitamin D, now women can simply take a daily vitamin D3 supplement to get their daily dose of “sunshine.”

March came in like a lion and went out like a lamb, so enjoy the current issue and retain your sunny optimism—summer is on its way!

Nanette F. Santoro, MD

permanent cessation of menses, and irreversible termination of fertility, similar to menopause.⁴⁻⁶ Albright's original terminology is more accurate.^{1,2} About half of all women with POI have intermittent ovarian function, and approximately 5% to 10% of these women subsequently conceive without medical intervention, often many years after diagnosis.⁷ Moreover, most patients with POI find this term less stigmatizing than premature ovarian failure or premature menopause.

POI affects approximately 1 in 10,000 US women by age 20, 1 in 1000 by age 30, and 1 in 100 by age 40.⁸ Most cases of POI are sporadic. However, approximately 10% to 15% of women with POI have a family history of the disorder.⁹

Etiology of POI

Women are born with a fixed number of primordial follicles, which are expended over time. Primordial germ cells proliferate in female fetuses until about 4 months' gestation, when a peak store of about 7 million primordial follicles is established. The number declines from that point forward, reaching approximately 1 million to 2 million primordial follicles at birth and about 0.5 million at puberty. Menopause occurs on the basis of a depletion of potentially functional primordial follicles.

The etiologies of POI can be divided into two major mechanisms: (1) follicle depletion, and (2) follicle dysfunction. Turner syndrome, chemotherapy, and radiation therapy are examples of POI due to follicle depletion. Mutation in the FSH receptor and autoimmune oophoritis are examples of POI due to follicle dysfunction.^{10,11} Inadequate follicle numbers can be caused by a low number of primordial follicles generated in utero or by accelerated follicle loss.

Follicle depletion: Turner syndrome

Turner syndrome results from a monosomy X karyotype (45,X). Features of

this syndrome include webbed neck, shield chest, high arched palate, cardiac anomalies (including aortic coarctation), hearing impairment, autoimmune diseases, and POI, among others. Women with Turner syndrome often have a mosaic karyotype, meaning that some of their cells contain both copies of the X chromosome, whereas others contain only one (typically the maternal) copy. Other women with Turner syndrome lack only portions of one of their X chromosomes. Deletions of the short arm of chromosome X are associated with somatic abnormalities, whereas deletions of the long arm tend to be associated with ovarian insufficiency alone.

POI in Turner syndrome is caused by accelerated follicle loss due to atresia. Evidence shows that a normal ovary with a normal number of germ cells forms in utero in these patients, but the store is most commonly depleted even before menarche takes place.¹² The terms ovarian and gonadal dysgenesis, ie, defective embryonic development, are not accurate in this case because normal ovaries form in utero in Turner syndrome.

Follicle dysfunction: Fragile X syndrome

The *FMRI* gene occurs at locus Xq27.3. A normal genotype has fewer than 40 cytosine-guanine-guanine (CGG) repeats in the *FMRI* gene. A genotype of 50 to 200 CGG repeats is considered an *FMRI* premutation and is associated with low to normal levels of the FMR1 protein.¹³ More than 200 CGG repeats at this locus—the full mutation—causes DNA methylation, gene inactivation, absent FMR1 protein, and fragile X syndrome.

Inheritance patterns of fragile X syndrome differ according to maternal or paternal origin of the *FMRI* gene. Maternal *FMRI* premutations can expand into full mutations in offspring. Paternal premutations are relatively

stable. Fragile X is the most common cause of heritable mental retardation in males. Other features of this syndrome include long face, macrocephaly, large ears, strabismus, high palate, and hyperextensible fingers. Interestingly, unlike women carrying the *FMRI* premutation, women with the full mutation do not develop POI.

Approximately 21% of women who carry the *FMRI* premutation develop POI. Approximately 2% of women with sporadic POI have a premutation in the *FMRI* gene. And approximately 14% of women with familial POI harbor an *FMRI* premutation.¹⁴ The risk of POI in these women is associated with the number of CGG repeats. Interestingly, women with mid-sized premutations (approximately 80 repeats) are at greatest risk of POI.¹⁵

The fragile X premutation has also been associated with a neurologic syndrome—fragile X-associated tremor-ataxia syndrome (FXTAS). FXTAS is characterized by an action tremor, gait ataxia, and Parkinsonism. In contrast to POI, an increasing number of repeats is associated with worse neurologic disease.¹⁶ It is unclear exactly how the *FMRI* premutation causes POI or FXTAS, but evidence supports an RNA gain of function toxicity as a possible mechanism.¹⁷

Autoimmune oophoritis

Another cause of POI is autoimmune oophoritis, in which inflammatory cells invade the theca cells of preantral and antral follicles, impairing their function. Primordial follicles, however, are spared.¹¹ Thus, in this situation, POI is predominantly a case of follicle dysfunction. Autoimmune oophoritis may occur alone or in addition to other autoimmune endocrine disorders.

Approximately 4% of cases of spontaneous 46,XX POI are associated with adrenal insufficiency or adrenal autoimmunity.¹⁸ Approximately 60% of women with type 1 autoimmune

TABLE 1 Diagnostic criteria for primary ovarian insufficiency

• Age <40 years
• Cycle irregularity \geq 4 months
Amenorrhea
Oligomenorrhea
Polymenorrhea
Menometrorrhagia
Dysfunctional uterine bleeding
• FSH in the menopausal range*
On 2 occasions
\geq 1 month apart
FSH, follicle-stimulating hormone. * The menopausal range as defined by the reporting laboratory.

TABLE 2 Evaluation of primary ovarian insufficiency

Tests for the following should be performed after diagnosis of POI
• Karyotype
• <i>FMR1</i> premutation
• Adrenal autoantibodies
• Thyroid peroxidase antibodies
• TSH
• Pelvic ultrasound
• Bone mineral density
POI, primary ovarian insufficiency; TSH, thyroid-stimulating hormone.

polyglandular syndrome (APS) and 10% of women with type 2 APS have POI.¹

Symptoms of POI

Patients with Turner syndrome most commonly develop POI that presents as primary amenorrhea. Patients who develop POI related to radiation and chemotherapy generally have an acute onset of the disorder. For women with the *FMR1* premutation, autoimmune oophoritis, or an idiopathic mechanism of POI, no characteristic menstrual history precedes onset. However, many patients develop a prodrome of oligomenorrhea or dysfunctional uterine bleeding. Usually, but not always,

idiopathic cases of POI develop after establishing regular menses following menarche. Some patients have menarche but experience polymenorrhea or oligomenorrhea from the start until POI is eventually diagnosed, sometimes many years later. Frequently, girls in this circumstance are prescribed oral contraceptives to “regulate the cycles,” with no evaluation to determine the mechanism of the menstrual irregularity. In some women, menses don’t resume after pregnancy or after stopping oral contraceptives. Overall, approximately 10% of women with POI present with primary amenorrhea.^{19,20}

Many, but not all, women with POI develop symptoms of estrogen deficiency, including hot flashes, vaginal dryness, and sleep disturbances. Lack of symptoms of estrogen deficiency is perhaps due to continuing intermittent ovarian function, which is known to occur in many women with POI. Some women experience hot flashes despite continued regular menses.

As a group, women with POI are less satisfied with their sexual lives than are control women, but most have sexual function scores in the normal range.^{21,22} A controlled, cross-sectional study by Kalantaridou et al comparing sexual function in women with POI who were receiving hormone therapy (HT) vs control women found that women with POI have lower self-reported sexual function than controls do. However, it is important to note that only 7% of the women with POI reported sexual function clearly below the normal range. In women with POI, sexual function scores correlated weakly with serum testosterone values, whereas there was no correlation between sexual function and serum testosterone in control women.²¹

Evaluation

The diagnostic criteria for POI are listed in TABLE 1. A woman diagnosed with POI will need further testing to rule out

associated medical problems, as noted in TABLE 2. A karyotype should be performed. Notably, approximately half of cases of primary amenorrhea associated with POI are caused by an abnormal karyotype.¹⁹ Genetic testing for the fragile X premutation should also be offered.²³⁻²⁵

Women with POI are at increased risk of developing hypothyroidism and adrenal insufficiency. Measurement of thyroid-stimulating hormone, thyroid peroxidase antibodies, and adrenal antibodies is indicated. Ovarian antibodies lack specificity and are not indicated. Women who test positive for adrenal antibodies should be tested annually for the presence of adrenal insufficiency. Those with positive thyroid antibodies should have annual thyroid function studies.

Hypogonadism is a well-recognized risk factor for osteoporosis. At the time of diagnosis, women with POI should have a baseline measurement of bone mineral density to help guide management. Also, an ultrasound examination at the time of diagnosis is indicated to detect those unusual cases that are associated with ovarian enlargement and the associated risk of ovarian torsion, such as in 17,20-desmolase deficiency or autoimmune oophoritis.²

Treatment

Treatment of women with POI should address their endocrine, genetic, emotional, and reproductive health, as outlined in TABLE 3. POI is associated with a number of endocrine disturbances that can be treated with HT. HT with transdermal estradiol will restore normal estradiol levels, alleviate vasomotor symptoms, maintain the vaginal epithelium, and maintain bone density. There are no evidence-based guidelines for selecting an HT regimen for women with POI. Our preference is to prescribe a 100 mcg estradiol patch (taken continuously) and 10 mg of

TABLE 3 Treatment for women with primary ovarian insufficiency

ENDOCRINE HEALTH	GENETIC HEALTH (AS NEEDED)	EMOTIONAL HEALTH	REPRODUCTIVE HEALTH OPTIONS
<ul style="list-style-type: none"> • Full replacement HT • Calcium supplementation • Vitamin D supplementation • Weight-bearing exercise 	<ul style="list-style-type: none"> • Genetic counseling • Medical geneticist consultation 	<ul style="list-style-type: none"> • Be considerate when relating diagnosis • Assess support network • Suggest alternative outlets for emotional turmoil, if helpful (pastoral or mental health professional counseling, journaling, meditation) 	<ul style="list-style-type: none"> • Opt out of parenthood • Foster care • Adoption • Donor egg • Donor embryo
HT, hormone therapy.			

medroxyprogesterone acetate, taken for 12 days of each month. Transdermal estradiol administration avoids the first-pass effect on the liver. The 100 mcg dose achieves a serum estradiol level near the mean level for cycling women of 100 pg/mL.^{26,27} Medroxyprogesterone acetate is used as first-line therapy. This progestin has proven efficacy for protecting against endometrial hyperplasia in women receiving the full replacement dose of estrogen that is appropriate for these young women. Other progestins have not been evaluated in this regard but, rather, in conjunction with the lower estrogen doses that are now recommended for treatment of menopausal women. Women experience regular menses on this regimen. Use of oral contraceptives (OCs) as HT is not advised. In this population, OCs provide more steroid hormone than is required for replacement, and oral estrogen is associated with a higher risk of thromboembolism.²⁸⁻³⁰ The use of a continuous combined HT regimen to induce amenorrhea in these women is not advised, as it may result in prolonged fetal exposure should an unexpected pregnancy occur.

It is important to note that HT is not a contraceptive. In fact, there is some suggestion that even the higher doses of hormones in normal steroid contraceptives may be inadequate to prevent pregnancy in women with POI. Because women with POI have a 5% to 10% risk of spontaneous pregnancy, they should keep a menstrual calendar

and take a pregnancy test if they miss a menses. If the test is positive, they should stop HT. Women with POI who do not wish to conceive should be counseled on nonhormonal forms of contraception, such as barrier methods or possibly an intrauterine device.

Because of the increased risk of osteoporosis in women with POI, it is important to optimize factors that maintain bone health, such as adequate calcium intake and vitamin D levels (see “Vitamin D: The sunshine hormone,” on page S8), and weight-bearing exercise. Approximately half of our patients have inadequate calcium intake (<1200 mg of elemental calcium per day) and serum vitamin D levels in the insufficiency range (<30 ng/mL). Therefore, calcium and vitamin D supplements are indicated for women with POI. Typically, it is reasonable to administer 1500 mg of calcium carbonate daily (this contains 600 mg of elemental calcium, one-half the daily requirement) and cholecalciferol 1000 IU daily.³¹ A few women have difficulty obtaining even 600 mg of elemental calcium in their diet and require a full replacement dose of 1200 mg of elemental calcium daily. Bisphosphonates are not advised if pregnancy is possible because these agents have long skeletal half-lives and the effects on the fetus are uncertain.

In addition to endocrine therapies, women with POI who are found to have an abnormal karyotype and those harboring the *FMRI* premutation

will also require genetic counseling. Not only might these diagnoses affect the patient’s health, they may also have important health implications for the patient’s relatives and potential offspring. For instance, women harboring the *FMRI* premutation are at risk of having children with fragile X syndrome, the most common form of heritable intellectual disability, as well as having children who themselves carry the premutation. Relatives of these women are also at risk of harboring a premutation in the *FMRI* gene, placing them at risk for POI and FXTAS and for bearing children with developmental delay. A trained genetic counselor can effectively convey this information to patients and family members.

The emotional impact

The diagnosis of POI carries significant emotional impact. Infertility in general can affect women’s self-esteem, identity, sexuality, body image, and relationships with others.^{32,33} In most cases of infertility due to other causes, the problem becomes apparent after many failed attempts at conception; usually, such couples uncover the infertility problem themselves. In contrast, the inability to conceive as a result of POI is most commonly diagnosed suddenly and unexpectedly during a workup for other symptoms, such as irregular menses. In one study, 84% of women reported moderate to severe suffering as a result of their diagnosis of POI.³⁴ Further, 81% of women stated that their

diagnosis made them feel angry, 76% felt depressed, 74% felt generally less healthy, 68% felt older, and 63% reported an altered self-image.³⁴ Approximately 70% of women were dissatisfied with the way in which they learned of their diagnosis.³⁴ The patient's level of discontent correlated with their degree of emotional distress. Most women would have preferred that their physicians had spent more time relating the diagnosis and provided them with more information on POI.³⁴ In the same study, many women reported that their mothers and husbands were their main sources of social support. One-third of women sought help from a mental health professional. Two-thirds found spirituality important in coping with their diagnosis. Still others found support groups helpful.

Given the emotional impact of POI, we recommend that physicians relating this diagnosis meet with patients in an office setting and take the time necessary to explain the disorder and to answer patients' questions. Communicating the diagnosis in a caring fashion and assessing patients' emotional support system can help women to better cope with this disease. Physicians may possibly recommend other avenues of emotional support such as pastoral counseling or other mental health professionals. Evidenced-based methods for providing peer support to women with POI are sorely needed.^{35,36}

After endocrine, genetic, and emotional issues have been addressed, patients can approach aspects of family

planning in a more comprehensive manner. Although many women with POI desire a pregnancy, it is important to recognize that this is not the case for everyone. For those women who desire pregnancy, we generally recommend waiting 3 years to allow the small but real chance that a spontaneous conception will occur. This gives the patient and her partner time to adjust emotionally to the diagnosis and to carefully consider all of their options for family planning. In certain circumstances it may be perfectly appropriate to move ahead sooner. Since ovarian function is intermittent and unpredictable in these patients, we recommend those who wish to conceive have intercourse 2 to 3 times per week so that sperm will be present should ovulation take place. Some patients are content to "wait and see," acknowledging their 5% to 10% chance of pregnancy occurring without medical intervention. Others may choose to call their family complete as a couple, while still others may want to become foster parents or adopt children. Egg or embryo donation is an option for some women. Currently, no established therapy to improve ovarian function and restore fertility has been determined by controlled trials to be safe and effective.

JD undergoes a number of tests. Her adrenal and thyroid peroxidase antibody testing are negative. Her TSH is normal. Her karyotype is 46,XX. However, she is found to have 82 CGG repeats in her FMR1 gene, therefore making

her an FMR1 premutation carrier. She sees a genetic counselor, who describes the inheritance and clinical implications of the premutation in detail. JD elects to tell the rest of her family about her diagnosis. Her youngest son also undergoes FMR1 testing and is found to have the full FMR1 mutation with 500 CGG repeats. Her father, who has a degenerative neurologic disorder of unknown etiology, is also tested and found to be an FMR1 premutation carrier. With this knowledge, his neurologic condition is diagnosed as FXTAS. JD has two sisters who decline testing. Her husband makes plans to have a vasectomy, both because the couple considers their family complete and because of the newly identified genetic risk.

JD is very appreciative of all of the information she has received about her condition from both the clinician who made the diagnosis and the genetic counselor. Now, many health issues in her family have come together in a way that makes sense. The family now feels more confident about accessing, in an integrated manner, the specifically targeted health care that it needs. Now that JD is on a full replacement dose of estradiol (100 mcg patch) and progesterin (10 mg of medroxyprogesterone acetate per day for the first 12 days of each month), her symptoms of estrogen deficiency have resolved, she is sleeping better, and she feels more rested. She plans to continue a healthy lifestyle that, based on the clinician's recommendations, includes both a calcium and a vitamin D supplement and regular weight-bearing exercise.

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Vitamin D: The sunshine hormone

How and when to treat deficiencies

► Ruth Freeman, MD

Vitamin D was discovered as the factor in cod-liver oil that prevented rickets in children in the early 20th century.¹ Soon thereafter it was discovered that exposure to sunlight gave equivalent protection.² Based on findings in the 1920s and 1930s, the dose of 400 units of vitamin D was established as essential for prevention of rickets. In the last 10 years, as treatments for osteoporosis have become available, many patients given such treatments did not respond as expected. One of the likely causes is that 52% of patients treated for osteoporosis had insufficient levels (<30 ng/mL 25-hydroxyvitamin D) of vitamin D.³ Based on data from the National Health and Nutrition Examination Survey (NHANES), the extent of vitamin D insufficiency in the population at large has been estimated to vary between 50% to 75%, depending on the ethnic group.⁴ Levels of vitamin D decline with age despite equal intake of vitamin supplements or equal exposure to sunlight.²

As measurement of the blood levels of vitamin D has become available, many other disorders, besides metabolic bone diseases, have been shown to be worse in people with insufficient vitamin D levels. The simple administration of adequate vitamin D may in fact

prevent a number of chronic diseases as well as disability in the elderly.⁵

Sources of vitamin D

The skin is the major natural source of vitamin D. Exposure to UVB rays from sunshine and heat converts 7-dehydrocholesterol to cholecalciferol (vitamin D₃). It is secreted into the blood and rapidly hydroxylated in liver microsomes at the 25 position, resulting in 25-hydroxycholecalciferol (hereafter referred to as 25 OH vit D). This is the major form of vitamin D, which is stored in the liver and secreted into the circulation. In blood, 25 OH vit D, which is a steroid, is carried on a vitamin D-binding protein.⁶ The liver stores vitamin D for many months, providing the vitamin when no sunshine is present. Several factors reduce the ability of the skin to produce vitamin D: sunscreen containing USP 8 will decrease active vitamin D formation by 97.5%; USP 15 sunscreen or higher will decrease formation of vitamin D₃ by 99.9%. Aging itself reduces the skin's ability to form vitamin D₃ even when exposed to adequate sunshine.^{2,7} Skin pigmentation also plays a role, with much lower levels of vitamin D found in people with darker pigmented skin. People who only go outdoors fully covered and get no exposure of their skin to sunshine have been found to have very low levels of vitamin D.⁸

The other main source of vitamin D is diet: Vitamin D is present in fish livers (therefore, the former intake of fish liver oil was common). Vitamin D has been added to many products. Milk

contains 100 units of vitamin D₃ in each cup. Orange juice that has added calcium may also contain 100 units of vitamin D₃. There are two forms of the vitamin provided by foods or supplements. One is vitamin D₃, which is the form in fish liver or in animals; the other is vitamin D₂, ergocalciferol, which is present in vegetables and is estimated to be less potent, one-third to one-fourth as effective as vitamin D₃. Vitamin D₂ has to be converted into vitamin D₃. The daily requirement of 400 units of either vitamin D has been shown to be inadequate for normal maintenance of adequate blood levels (see below).

Vitamin D actions

Bone effects

The major function of vitamin D has always been the adequate growth and mineralization of bone. This requires the further conversion of 25 OH vit D by the addition of a hydroxyl group at the 1 position, which occurs in the kidney mitochondria under stimulation by parathyroid hormone, resulting in 1,25-dihydroxycholecalciferol, or 1,25 OH vit D (FIGURE 1).^{6,7} It is this compound that acts in the gastrointestinal (GI) system to activate calcium absorption. To prevent excessive calcium absorption, the 1 hydroxylation enzyme is modulated by blood calcium levels. High levels of blood calcium shut off 1 hydroxylation but cause the 25 OH vit D to be hydroxylated at the 24 position, resulting in the formation of 24,25-dihydroxyvitamin D, which does not increase GI absorption of calcium. In animal studies,

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bone can be adequately mineralized if the animal is given sufficient calcium systemically, suggesting that the key role of vitamin D is adequate calcium absorption. In fact, the amount of calcium absorbed is largely dependent on adequate vitamin D levels and not on which preparation of calcium has been ingested.⁹ Other lesser effects of vitamin D occur at the kidney, with slight increased reabsorption of calcium, and at the bone for both mineralization and resorption. The adequate calcium allows new bone matrix to become calcified normal bone tissue. Patients who are vitamin D deficient may have low bone density, but they are not lacking bone matrix. Their bone disorder is osteomalacia and not osteoporosis (in which there is loss of bone matrix as well as low mineral content). When given adequate vitamin D and calcium, their bone density (which measures only mineral content of bone) may go up 10% to 15% in one year. Some have both osteomalacia and osteoporosis. In older patients, supplementation of vitamin D to adequate levels (≥ 800 units vitamin D3/day) has been shown to decrease hip and other nonvertebral fractures.¹⁰ Adequate nutrition and physical therapy for balance training and fall prevention have been shown to decrease hip fractures in older people.

Non-bone effects

Over the last decade it has been demonstrated that many cells can add the 1 hydroxyl group to 25 OH vit D. Therefore, local effects in those tissues seem reasonable. The following are areas in which such effects have been suggested:

Muscle. Vitamin D increases muscle strength. In older people who had vitamin D deficiency, measurements of speed of walking a specific distance were markedly improved after vitamin D administration. Children with rickets have been shown to have muscle weakness.¹¹

TABLE 1 Diagnosis and management of low, normal, and high serum levels of vitamin D

VITAMIN D	25 OH VIT D, NG/ML	TREATMENT
Normal	30-100	No change
Insufficient	10-29	Vitamin D3, 1000-2000 units/day
Deficient	<10	Vitamin D2, 50,000 units/week for 8 weeks then biweekly, or vitamin D3, 1000-2000 units/day

TABLE 2 Monitoring therapy

Monitor for toxicity: 24-hour urine calcium and creatinine as well as blood calcium*	
URINE CALCIUM LEVEL, MG/24 HR	TREATMENT
50-280	Normal level, no change
>280	Decrease calcium intake
<50	Increase calcium intake and evaluate for GI problem
Blood calcium elevated	Reduce vitamin D intake and calcium intake; check PTH

GI, gastrointestinal; PTH, parathyroid hormone.

*Only for patients who are given nonstandard but very high doses of calcium.

Immune system. Vitamin D may improve immunity to infectious diseases. It has been specifically implicated in reducing tuberculosis (TB) infections.⁷ In the past, TB patients were known to improve when exposed to sunshine. This effect is likely due to vitamin D, which can be given directly, improving resistance to the disease. Increased resistance to other immune disorders has also been shown.¹²

Chronic diseases. Recent data suggest that people who have adequate vitamin D develop diabetes later than those deficient in this vitamin.¹³ Newer information has also implicated vitamin D deficiency as a risk factor for hypertension and heart disease.^{7,14} Most of these studies are based on population observational studies. Whether vitamin D can effectively improve or reduce the risk of developing certain diseases is being tested actively.

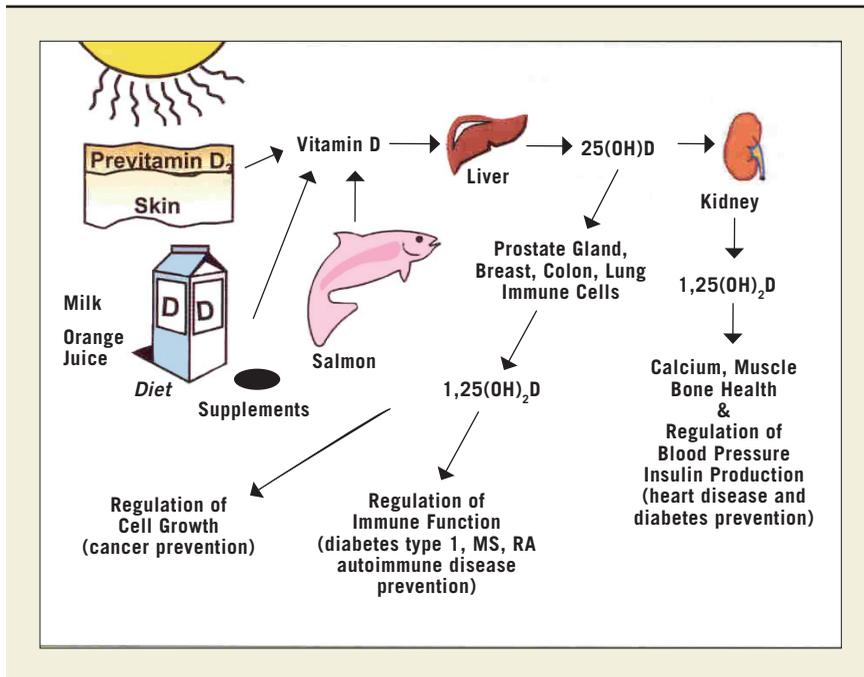
Reproduction. Women who had rickets were known to have difficulty during delivery due to deformities of the pelvis. Merewood et al have recently documented a higher incidence of primary cesarean sections in women who have vitamin D deficiency.¹⁵

Cancer prevention. A new area of research suggests that adequate vitamin D reduces the risk of developing a variety of cancers. It has been implicated in reducing the incidence of colon cancer, breast cancer, prostate cancer, and other malignancies, as well as cancer mortality.¹⁶

Measurement issues

The blood level of 25-hydroxyvitamin D reflects the intake of the vitamin, since this is the major form that is consistently carried in blood. Although this is a stable level, it is not necessarily an accurate measure of vitamin intake for two reasons.

FIGURE 1 Actions of vitamin D



Schematic representation of the multitude of other potential physiologic actions of vitamin D for cardiovascular health, cancer prevention, regulation of immune function, and decreased risk of autoimmune diseases (Copyright Michael F. Holick, 2003, used with permission).⁶

First of all, this vitamin is a steroid and is carried on a protein (vitamin D-binding globulin). The active vitamin is the free material, not necessarily the total protein-bound vitamin D.⁷ Conditions that affect the protein will alter the total vitamin D but not necessarily the active free vitamin D. There are no adequate measurements available of the free form. Obesity, a rather common problem at present, reduces binding proteins and, therefore, may lower total 25 OH vit D levels.

The second problem concerns measurement of the total blood level of this vitamin. There are many different methods of measuring vitamin D. Some are immunoassays, others are some form of direct assay, and the only sure one is the most expensive, the chromatographic double MS method (Quest presently uses this method for its 25-hydroxyvitamin D assay as do many medical centers). The cost of the assay, runs from \$244 (Quest 2009) to \$288. Most insurance plans cover the cost. None of these methods have been

sufficiently standardized, resulting in confusing and often incorrect results. For a comprehensive review of the assay methods, see Binkley et al.¹⁷

Measuring 1,25-dihydroxycholecalciferol, although this is the active form of the vitamin, reflects kidney function and not vitamin D sufficiency. It is abnormal in people with significant renal disease who are commonly given calcitriol (1,25 [OH]₂ vitamin D) replacement.

To be adequate, blood levels of 25 OH vit D must be greater than 30 ng/mL. Deficiency is defined as levels below 10 ng/mL (previously known to be the level at which children develop rickets and adults have osteomalacia). Between 10 ng/mL and 29 ng/mL has been described as vitamin D insufficiency (TABLE 1). These are the insufficiency levels that are seen in many patients who have low bone density.

The resultant low calcium absorption causes secondary increases in parathyroid hormone, which then resorbs calcium from bone in order to

maintain the blood level of calcium that is essential for many physiologic and enzymatic activities. Blood levels below 30 ng/mL have been associated with increasing parathyroid hormone levels.¹⁸

Although bone mineral is low at the vitamin D insufficiency level, specific symptoms are only seen when levels go below 10 ng/mL. Such individuals may have aches and pains all over their bodies, particularly over muscles and bones. They have general tenderness all over, not related to any specific organ system. Some also have joint pains. On providing adequate vitamin D, all symptoms disappear promptly. Patients with osteoporosis who have extremely low vitamin D levels and are started on a bisphosphonate may develop hypocalcemia.

When and how should vitamin D deficiency be treated?

If the individual is deficient in vitamin D, with blood levels below 15 ng/mL, the administration of large amounts of vitamin D is warranted. The only prescription preparation of vitamin D in the United States is vitamin D2 in 50,000 unit capsules. This can be given weekly for at least 8 weeks, which will bring levels to normal in most patients who have normal absorption capacity (ie, no gastrointestinal illness).

Thereafter, patients will most likely continue to need the high-dose capsules 2 or 3 times per month (personal observation suggests that about one-third of patients will need the 50,000 unit vitamin D2 every 10 days). Maintenance with 1000 to 2000 units of vitamin D3 daily may be adequate but has not been tested. For those with higher levels, every 400 units of vitamin D3 will raise the level of 25 OH vit D by about 5 ng/mL.

The average person (ie, one who does not have low levels of vitamin D) needs to take at least 1000 units of vitamin D3 daily.¹⁹ These over-the-counter preparations are available at

very reasonable cost (some are sold for \$6 or less for 100 pills).

In people with adequate vitamin D levels, calcium intake need only be 1000 mg/day in food or supplements. Overdosage is unlikely, as the administered vitamin D is not the final effective material.

The kidney can modulate how much 1,25-dihydroxyvitamin D is produced depending on the patient's blood calcium levels. Levels over 5000 units of vitamin D3 per day have been associated with elevated blood calcium and/or elevated urinary calcium levels (TABLE 2). Excessive absorption of calcium may, however, ultimately lead to

kidney stones. Measurement of the calcium content of 24-hour urine should contain less than 280 mg of calcium per 24 hours. Reduction of the supplemental calcium may be all that is needed to prevent the high calcium excretion. Vitamin D requirements for children have also been increased, as reported by Gordon et al in 2008.²⁰

Summary

Vitamin D is an essential ingredient in everyone's daily diet unless they get a significant amount of sun exposure without sunscreen. It is important for normal bone strength, fracture prevention, and muscle activity. Recent

information has implicated low vitamin D levels as being associated with increased rates of developing diabetes, coronary heart disease, hypertension, immune disorders, and increases in primary cesarean section rates. At this time, vitamin D is good for many systems, including preventing the common cold.²¹ Further investigation will show us which areas of disease are truly related to, or caused by, vitamin D deficiency. At present, the main effects clearly show improvement of calcium absorption from the bowel, improvement in bone and muscle strength, and the prevention of osteoporotic fractures.

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