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Original Article

Study of the Association of Vitamin D deficiency with Calcium in Women Patients

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Abstract

Background: Vitamin D is a fat–soluble vitamin with hormonal functions. Vitamin D helps calcium and phosphorus homeostasis and bone metabolism, Exposure to sunlight, dietary intake and supplementation with vitamin D is the main source of vitamin D in human. Furthermore, vitamin D deficiency plays an important role in many other diseases such as diabetes, hypertension, cardiovascular disease, immune disorders, osteoporosis and cancers.

Aims of the study: The study was carried out to evaluation the levels of vitamin D deficiency withcalcium in employees women .

Material and methods: The study was conducted on normal healthy volunteers and patients with Vitamin D and calcium disorder at laboratory of National university of sciences and technology at 7.2.2022 after recording their age and gender patients group were have a disorder of vitamin D and Calcium. The examination about (20) patients and (10) as a control group. Whom selected randomly in age group from((20) to (25) years old

Result: The result showed that the deficiency of the levels of vitamin D and calcium in women with age less than the normal range, also, showed that the Vitamin D in the patient group (12.28 ± 7.980) was less than the healthy group (25.33 ± 12.81) , The calcium in the patient group was(7.830 ± 1.619),while in the healthy group was (9.167 ± 0.4285). Both of vitamin D and calcium were significant in the patients group compared to the control group at P value p≤ 0.05.

Conclusions: The study sowed a high prevalence of vitamin D deficiency, with detrimental health effects- as deficiency of level of calcium- among women those who work as students or employees in places far from the sun during the winter season. Public health campaigns are needed for education and awareness about vitamin D deficiency to improve vitamin D status for women working in closed places.

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Introduction:

Vitamin D, a fat-soluble prohormone, is synthesized in response to sunlight. metabolism of vitamin D to its major circulating form (25(OH)D) and hormonal form (1,25(OH)2D) takes place in the liver and kidney, respectively .The active form, 1a,25-(OH)2D, binds to the vitamin D receptor (VDR) to modulate gene transcription and regulate mineral ion homeostasis [1].

In addition to food sources such as fatty fish, eggs, fortified milk and cod liver oil, the human body uses ultraviolet B (UVB) radiation from sunlight to synthesis a significant portion of vitamin D requirements. [2]

There are two forms of vitamin D: vitamin D2 (ergocalciferol) and D3 (cholecalciferol). The skin synthesis vitamin D3 after sun exposure and it may be obtained from animal sources, while vitamin D2 is the synthetic form that is often found in fortified food and is derived from plants. The primary role of vitamin D hasbeen considered to be the absorption of calcium from the intestine (i.e., calcium homeostasis in the body) and is necessary for skeletal health . [3]

Over the years, it has become increasingly clear that vitamin D not only has a function in bones, but it also significantly affects cell proliferation and differentiation, so vitamin D plays several roles in the body, influencing bone health as well as serum calcium and phosphate levels. Furthermore, vitamin D may modify immune function, cell proliferation, differentiation and apoptosis. [4]

Vitamin D is a global regulator of gene expression and signal transduction invirtually every tissue. In epithelial cells vitamin D, by binding with the vitamin D receptor (VDR), contributes to maintenance of the quiescent, differentiated phenotype and promotes pathways that defend cells against endogenous and exogenous stresses. [5]

1.2 Sources of Vitamin D

The major natural source of the vitamin is synthesis of cholecalciferol in the lower layers of epidermis of the skin through a chemical reaction that is dependent on sun exposure (specifically UVB radiation). [6]

Cholecalciferol and ergocalciferol can be ingested from the diet and supplements. Only a few foods, such as the flesh of fatty fish, naturally contain significant amounts of vitamin D. In the U.S. and other countries, cow's milk and plant-derived milk substitutes are fortified with vitamin D, as are many breakfast cereals. [7]

Mushrooms exposed to ultraviolet light contribute useful amounts of vitamin D2. Dietary recommendations typically assume that all of a person's vitamin D is taken by mouth, as sun exposure in the population is variable and recommendations about the amount of sun exposure that is safe are uncertain in view of the skin cancer risk. [8]

Vitamin D from the diet, or from skin synthesis, is biologically inactive. It is activated by two protein enzyme hydroxylation steps, the first in the liver and the second in the kidneys. As vitamin D can be synthesized in adequate amounts by most mammals if exposed to sufficient sunlight, it is not essential, so technically not a vitamin. [9]

Instead it can be considered a hormone, with activation of the vitamin D pro- hormone resulting in the active form, calcitriol, which then produces effects via a nuclear receptor in multiple locations. [10]

Although vitamin D is present naturally in only a few foods, it is commonly added as a fortification in manufactured foods. In some countries, staple foods are artificially fortified with vitamin D. [11]

In general, vitamin D3 is found in animal source foods, particularly fish, meat, offal, egg and dairy. Vitamin D2 is found in fungi and is produced by ultraviolet irradiation of ergo sterol. The vitamin D2 content in mushrooms and Cladina arbuscular, a lichen, increases with exposure to ultraviolet light, and is stimulated by industrial ultraviolet lamps for fortification. The United States Department of Agriculture reports D2 and D3 content combined in one value. [12]

Food Fortification

Manufactured foods fortified with vitamin D include some fruit juices and fruit juice drinks, meal replacement energy bars, soy protein-based beverages, certain cheese and cheese products, flour products, infant formulas,

many breakfast cereals, and milk. [13]

In 2016 in the United States, the Food and Drug Administration (FDA) amended food additive regulations for milk fortification, stating that vitamin D3 levels not exceed 42 IU vitamin D per 100 g (400 IU per US quart) of dairy milk, 84 IU of vitamin D2 per 100 g (800 IU per quart) of plant milks, and 89 IU per 100 g (800 IU per quart) in plant-based yogurts or in soy beverage products. Plant milks are defined as beverages made from soy, almond, rice, among other plant sources intended as alternatives to dairy milk. [14]

While some studies have found that vitamin D3 raises 25(OH)D blood levels faster and remains active in the body longer, others contend that vitamin D2 sources are equally bioavailable and effective as D3 for raising and sustaining 25(OH)D.[139]

Vitamin D content in typical foods is reduced variably by cooking. Boiled, fried and baked foods retained 69–89% of original vitamin D. [15]

1.2.1 Natural sources

Table (1-1): Natural Sources of Vitamin D

Animal sources	
Source	**IU/g**
Cooked egg yolk	0.7
Beef liver, cooked, braised	0.5
Fish liver oils, such as cod liver oil	100
Fatty fish species	
Salmon, pink, cooked, dry heat	5.2
Mackerel, Pacific and jack, mixed species,cooked, dry heat	4.6
Tuna, canned in oil	2.7
Sardines, canned in oil, drained	1.9

Fungal sources			
Source		***µg/g***	**IU/g**
Cladonia arbuscula (lichen), thalli, Dry	vitamin D_3	0.67-2.04	27–82
	vitamin D_2	0.22–0.55	8.8–22
Agaricus bisporus (common mushroom): D2 + D3			
Portobello	Raw	0.003	0.1
	Exposed to ultraviolet light	0.11	4.46
Crimini	Raw	0.001	0.03
	Exposed to ultraviolet light	0.32	12.8

1.3 Synthesis of Vitamin D

In humans, 90% of vitamin D comes from the skin by the sun-mediated synthesis.The remainder can be obtained from foods that contain vitamin D naturally in foods that have been fortified and the use of pharmaceutical products. Natural sources are cod liver oil, tuna, salmon, egg yolks, swiss cheese, liver and sardines. Fortified foods include milk, juices, margarines, yoghurts and cereals. In pharmaceutical forms there are the vitamin D2 and D3.

Synthesis of vitamin D in nature is dependent on the presence of UV radiation and subsequent activation in the liver and in the kidneys. Many animals synthesize vitamin D3 from 7-dehydrocholesterol, and many fungi synthesize vitamin D2 from ergosterol figure. [16]

Vitamin D production in the skin under the influence of sunlight (UVB) is maximized at levels of sunlight exposure that do not burn the skin. Further metabolism of vitamin D to its major circulating form (25(OH)D) and hormonal form (1,25(OH)2D) takes place in the liver and kidney, respectively, but also in other tissues where the 1,25(OH)2D produced serves a paracrine/autocrine function: examples include the skin, cells of the immune system, parathyroid gland, intestinal epithelium, prostate, and breast. [17]

Parathyroid hormone, FGF23, calcium and phosphate are the major regulators of the renal 1-hydroxylase (CYP27B1, the enzyme producing 1,25(OH)2D); regulation of the extra renal 1-hydroxylase differs from that in the kidney and involves cytokines. [17]

The major enzyme that catabolizes 25(OH)D and 1,25(OH)2D is the 24-hydroxylase; like the 1-hydroxylase it is tightly controlled in the kidney in a manner opposite to that of the 1-hydroxylase, but like the 1-hydroxylase it is widespread in other tissues where its regulation is different from that of the kidney[18]

Vitamin D and its metabolites are carried in the blood bound to vitamin D binding protein (DBP) and albumin--for most tissues it is the free (i.e., unbound) metabolite that enters the cell; however, DBP bound metabolites can enter some cells such as the kidney and parathyroid gland through a megalin/cubilin mechanism. [18]

Most but not all actions of 1,25(OH)2D are mediated by the vitamin D receptor (VDR). VDR is a transcription factor that partners with other transcription factors such as retinoid X receptor that when bound to 1,25(OH)2D regulates gene transcription either positively or negatively depending on other cofactors to which it binds or interacts. [18]

The VDR is found in most cells, not just those involved with bone and mineral homeostasis (i.e., bone, gut, kidney) resulting in wide spread actions of 1,25(OH)2D on most physiologic and pathologic processes. Animal studies indicate that vitamin D has beneficial effects on various cancers, blood pressure, heart disease, immunologic disorders, but these non-skeletal effects have been difficult to prove in humans in randomized controlled trials. [19]

Analogs of 1,25(OH)2D are being developed to achieve specificity for non-skeletal target tissues such as the parathyroid gland and cancers to avoid the hypercalcemia resulting from 1,25(OH)2D itself. [19]

The level of vitamin D intake and achieved serum levels of 25(OH)D that are optimal and safe for skeletal health and the non-skeletal actions remain controversial, but are

likely between an intake of 800-2000IU vitamin D in the diet and 20-50ng/ml 25(OH)D in the blood. [19]

1.3.1 Synthesis in the skin

Vitamin D3 is produced photo chemically from 7-dehydrocholesterol in the skin of most vertebrate animals, including humans. The precursor of vitamin D3, 7- dehydrocholesterol is produced in relatively large quantities. 7-Dehydrocholesterol reacts with UVB light at wavelengths of 290–315 nm. [20]

These wavelengths are present in sunlight, as well as in the light emitted by the UV lamps in tanning beds (which produce ultraviolet primarily in the UVA spectrum, but typically produce 4% to 10% of the total UV emissions as UVB, some tanning beds can use only separate UVB light bulbs specifically for vitamin production). Exposure to light through windows is insufficient because glass almost completely blocks UVB light. [21]

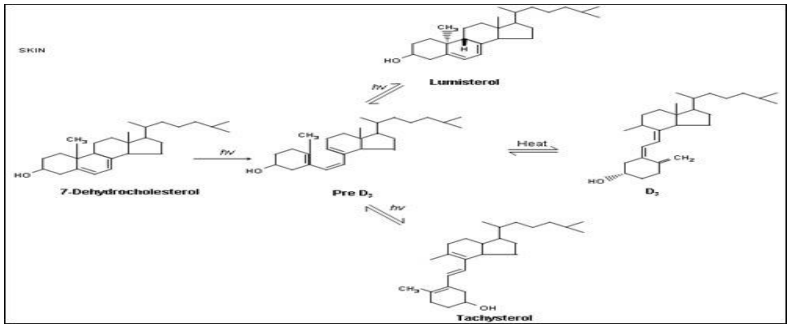


Figure (1-1): Vitamin D synthesis in the skin

Adequate amounts of vitamin D can be produced with moderate sun exposure to the face, arms and legs (for those with the least melanin), averaging 5–30 minutes twice per week, or approximately 25% of the time for minimal sunburn. The darker the skin, and the weaker the sunlight, the more minutes of exposure are needed. Vitamin-D overdose is impossible from UV exposure: the skin reaches an equilibrium where the vitamin degrades as fast as it is created. [22]

The skin consists of two primary layers: the inner layer called the dermis, and the outer, thinner epidermis. Vitamin D is produced in the keratinocytes of two innermost strata of the epidermis, the stratum Basale and stratum spinosum, which also are able to produce calcitriol and express the VDR. [23]

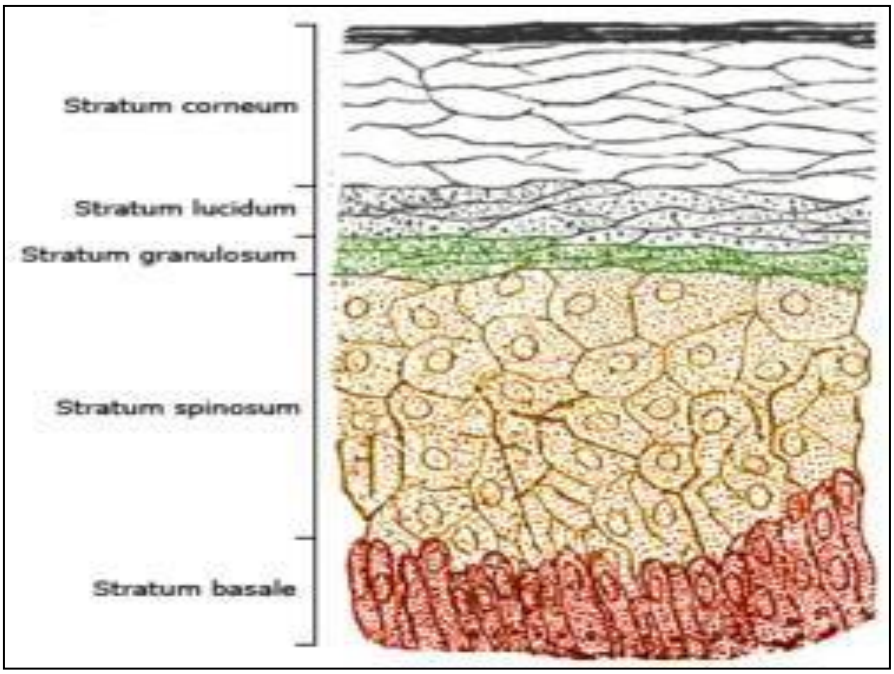
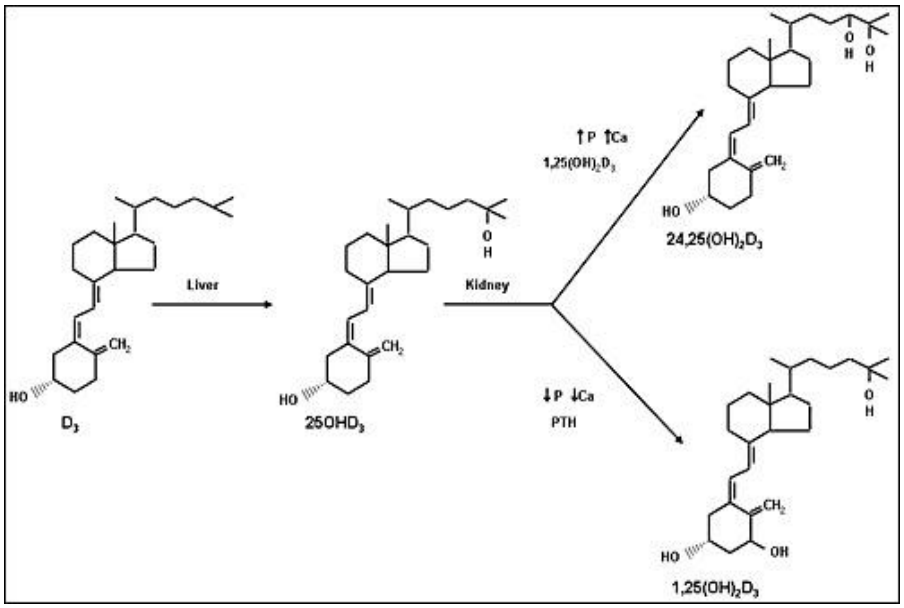


Figure (1-2):The production of vitamin D3 from 7-dehydrocholesterol in the epidermis. Sunlight (the ultraviolet B component) breaks the B ring of the cholesterol structure to form pre- D3. Pre-D3 then undergoes a thermal induced rearrangement to form D3. Continued irradiation of pre- D3 leads to the reversible formation of lumisterol3 and tachysterol3 which can revert back to pre-D3 in the dark.



Figure(1-3):The metabolism of vitamin D. The liver converts vitamin D to 25OHD. The kidney converts 25OHD

to 1,25(OH)2D and 24,25(OH)2D. Other tissues contain these enzymes, but the liver is the main source for 25-hydroxylation, and the kidney is the main source for 1α-hydroxylation. Control of metabolism of vitamin D to its active metabolite, 1,25(OH)2D, is exerted primarily at the renal level where calcium, phosphorus, parathyroid hormone, FGF23, and 1,25(OH)2D regulate the levels of 1,25(OH)2D produced.

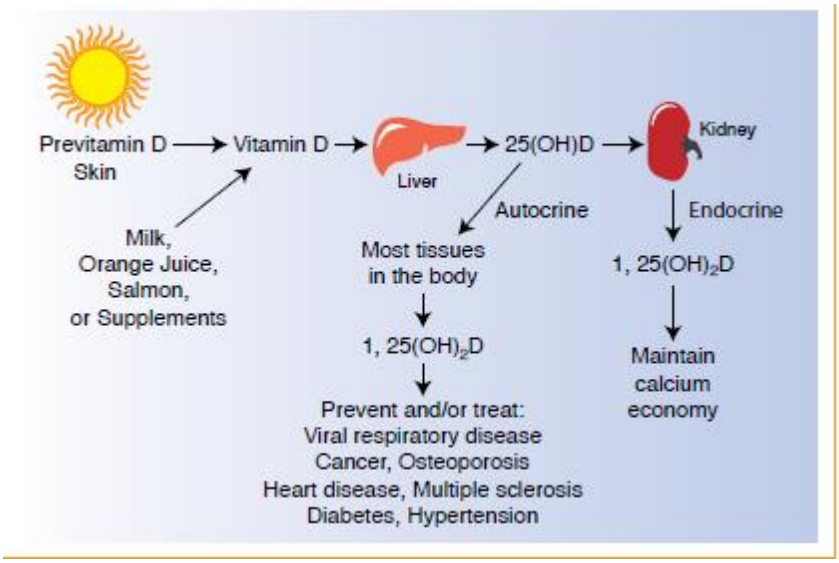


Figure (1-4): Functions of vitamin D

1.3.2 Industrial synthesis

Vitamin D3 (cholecalciferol) is produced industrially by exposing 7- dehydro cholesterol to UVB and UVC light, followed by purification. The 7- dehydro cholesterol is a natural substance in fish organs, especially the liver, or in wool grease (lanolin) from sheep. Vitamin D2 (ergocalciferol) is produced in a similar way using ergosterol from yeast or mushrooms as a starting material. [24]

1.4 Relation between Vitamin D & Parathyroid hormones

It is clear that parathyroid hormone and vitamin D have many metabolic effects in common, and for years a close relationship between them has been suspected. It seems basically unlikely that two substances so different in chemical structure, one a polypeptide and the other sterol-like, should both affect calcium metabolism completely independently of one another, and yet in so similar a manner.It was first suggested that vitamin D might act by stimulating the parathyroid glands [25]

This was soon shown to be incorrect, however, since vitamin D can maintain normal levels of serum calcium after removal of the parathyroid glands, and in other forms of hypoparathyroidism. The vitamin also produces its usual effect on intestinal absorption of calcium in parathyroid rats. Nevertheless, evidence for a functional relationship between vitamin D and parathyroid hormone has continued to accumulate[26]

More recent experiments have shown that parathyroid hormone fails to raise the serum levels of calcium in rats with vitamin D deficiency, whose serum levels of calcium are low and of phosphorous high [27]

After the vitamin deficient rats had received vitamin D, a dose of parathyroid hormone as small as 25 units was sufficient to raise serum levels of calcium, while a dose of vitamin D of only 0.3 unit restored sensitivity to parathyroid hormone.

1.5 Vitamin D Deficiency

Vitamin D deficiency is found worldwide in the elderly and remains common in children and adults.[28] Deficiency results in impaired bone mineralization and bone damage which leads to bone-softening diseases,[29] including rickets in children and osteomalacia in adults. Low blood calcifediol (25-hydroxy-vitamin D) can result from avoiding the sun. [28]

Being deficient in vitamin D can cause intestinal absorption of dietary calcium to fall to 15%. When not deficient, an individual usually absorbs between and 80%.[29]

Several high-risk groups for vitamin D deficiency have been identified including individuals who avoid sun exposure, living at high latitudes, having darkly pigmented skin, obese and those suffering from chronic kidney disease. Serum 25- (OH)D concentration <50 nmol/L (< 20 ng/mL) has recently been defined as vitamin D deficiency. [29]

vitamin D deficiency is marked by a threshold <25 nmol/L (<10 ng/mL) and vitamin D insufficiency by concentration in the range 25–49 nmol/L (10–19 ng/mL) .At a concentration below 25 nmol/L (<10 ng/mL) adverse effects are observed in children and adults, and increased bone resorption and an elevated risk for secondary hyperthyroidism are seen at concentration of 25–49 nmol/L (10–19 ng/mL) [29]

A 25-(OH)D threshold of 75 nmol/L (30 ng/mL) is needed for optimal bone mineral density in younger (19–49 years) and middle-aged adults (>50 years). Increasing evidence suggests that 25-(OH)D serum concentration of 75–110 nmol/L (30–44 ng/mL) may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease and infectious disease [30]

Although the body can create vitamin D, some people are more likely to be at risk of a deficiency than others. Factors that can influence this include: [31]

- Skin color: Pigmentation in the skin reduces the body's ability to absorb ultraviolet B (UVB) rays from the sun. Absorbing sunlight is essential for the skin to produce vitamin D.
- Lack of sun exposure: People who live in northern latitudes or areas of high pollutionTrusted Source, work night shifts, or are homebound should aim to consume vitamin D from food sources whenever possible.
- Breastfeeding: The American Academy of Pediatrics recommends that all breastfed infants receive 400 international unitsTrusted Source (IU) per day of oral vitamin D.
- Older adults: The skin's ability to synthesize vitamin D decreasesTrusted Source with age. Older adults may also spend more time indoors.
- Those with conditions that limit fat absorption: Vitamin D is fat-soluble, meaning intake is dependent on the gut absorbing dietary fats. Conditions that limit fat absorption can decrease vitamin D intake from the diet.
- People with obesity: High levels of body fat can limit the body's ability to absorb vitamin D from the skin.

1.6 Vitamin D & Diseases

Vitamin D exerts various effects on homeostasis, which are summarized below. In bone, vitamin D prevents osteopenia, osteoporosis, osteomalacia, rickets and fractures. Vitamin D is required for maintenance of plasma calcium by increasing calcium absorption from the small intestine, mobilizing calcium from bone and reducing its renal clearance. Vitamin D plays important roles in the absorption and bone deposition. [32]

Low calcium absorption generates a number of physiological problems, since calcium is important for most metabolic functions, as well as the muscular activity[32]

In relation to cells, it has been shown that vitamin D may prevent certain types of cancer, such as prostate, pancreatic, breast, ovarian and colon cancer. Also prevents infectious diseases and infections of the upper airways, asthma and other respiratory illnesses.These effects occur because the genes regulated by vitamin D influence biological processes such as inhibition of cell proliferation, apoptosis and stimulate the production of bactericidal proteins. [33]

Considering the immune system, adequate levels of Vitamin D appear to prevent multiple sclerosis, type 1 diabetes, Crohn's disease and rheumatoid arthritis. This occurs because the effect on the immune system of vitamin D translates into increased innate immune regulation associated with an acquired immunity. [33]

As a fat-soluble vitamin, vitamin D requires the presence of dietary fat in the gut for absorption. Certain pathological conditions, such as Crohn's disease, cystic fibrosis (CF), surgical removal of part of the stomach or

intestines are associated with fat malabsorption and thus may lead to vitamin D deficiency. [34]

In order to become biological active vitamin D, kidney plays an important role in this transforming process. Chronic kidney disease such as patients with stage 4 or 5 chronic kidney disease, as well as those requiring dialysis, leads to an inability to make sufficient 1,25-dihydroxyvitamin D which has a direct effect in inhibiting parathyroid hormones expression [38, 39]. Thus 1,25-dihydroxyvitamin D3 intake is needed to maintain calcium level in blood as well as to control parathyroid hormone levels[34]

Approximately 33% of women aged between 60 to 70 and 66% of those over 80 have osteoporosis . The link between vitamin D deficiency and osteoporosis has been well established especially in the elderly. Vitamin D deficiency is associated with the marked suppression in intestinal Ca absorption and the impairment of Ca balance, which results in low bone mineral content and density. Reduced bone mineral density (BMD) increases the risk of fractures, which significantly contributes to morbidity and mortality of older persons [35].

Millions of people are affected by hypertension worldwide. Growing evidence in recent years suggests that vitamin D has an important association with blood pressure. [36]

1.7 Calcium (Ca+)

Calcium is a chemical element with the symbol Ca and atomic number 20. As an alkaline earth metal, calcium is a reactive metal that forms a dark oxide-nitride layer when exposed to air. Its physical and chemical properties are most similar to its heavier homologues strontium and barium. It is the fifth most abundant element in Earth's crust, and the third most abundant metal, after iron and aluminium. [37]

The most common calcium compound on Earth is calcium carbonate, found in limestone and the fossilised remnants of early sea life; gypsum, anhydrite, fluorite, and apatite are also sources of calcium. The name derives from Latin calx "lime", which was obtained from heating limestone. [37]

Some calcium compounds were known to the ancients, though their chemistry was unknown until the seventeenth century. Pure calcium was isolated in 1808 via electrolysis of its oxide by Humphry Davy, who named the element. Calcium compounds are widely used in many industries: in foods and pharmaceuticals for calcium supplementation, in the paper industry as bleaches, as components in cement and electrical insulators, and in the manufacture of soaps. On the other hand, the metal in pure form has few applications due to its high reactivity; still, in small quantities it is often used as an alloying component in steelmaking, and sometimes, as a calcium–lead alloy, in making automotive batteries. [38]

Calcium is the most abundant metal and the fifth-most abundant element in the body. As electrolytes, calcium ion play a vital role in the physiological and biochemical processes of organisms and cells: in signal transduction pathways where they act as a second messenger; in neurotransmitter release from neurons; in contraction of all muscle cell types; as cofactors in many enzymes; and in fertilization. Calcium ions outside cells are important for maintaining the potential difference across excitable cell membranes, protein synthesis, and bone formation. [38]

Calcium is an essential element needed in large quantities. The Ca^{2+} ion acts as an electrolyte and is vital to the health of the muscular, circulatory, and digestive systems; is indispensable to the building of bone; and supports synthesis and function of blood cells. For example, it regulates the contraction of muscles, nerve conduction, and the clotting of blood. As a result, intra- and extracellular calcium levels are tightly regulated by the body. [39]

Calcium can play this role because the Ca^{2+} ion forms stable coordination complexes with many organic compounds, especially proteins; it also forms compounds with a wide range of solubility, enabling the formation of the skeleton. [39]

Foods rich in calcium include dairy products, such as yogurt and cheese, sardines, salmon, soy products, kale, and fortified breakfast cereals. [40]

Because of concerns for long-term adverse side effects, including calcification of arteries and kidney stones, both the U.S. Institute of Medicine (IOM) and the European Food Safety Authority (EFSA) set Tolerable Upper Intake Levels (ULs) for combined dietary and supplemental calcium. From the IOM, people of ages 9–18 years are not

to exceed 3 g/day combined intake; for ages 19– 50, not to exceed 2.5 g/day; for ages 51 and older, not to exceed 2 g/day.[52] EFSA set the UL for all adults at 2.5 g/day, but decided the information for children and adolescents was not sufficient to determine ULs. [41]

1.8 Calcium Homeostasis

In biology, homeostasis is the state of steady internal, physical, and chemical conditions maintained by living systems. This is the condition of optimal functioning for the organism and includes many variables, such as body temperature and fluid balance, being kept within certain pre-set limits (homeostatic range). Other variables include the pH of extracellular fluid, the concentrations of sodium, potassium and calcium ions, as well as that of the blood sugar level, and these need to be regulated despite changes in the environment, diet, or level of activity. Each of these variables is controlled by one or more regulators or homeostatic mechanisms, which together maintain life. [42]

Calcium homeostasis refers to the maintenance of a constant concentration of calcium ions in the extracellular fluid. It includes all of the processes that contribute to maintaining calcium at its "set point." Because plasma [Ca2+] rapidly equilibrates with the extracellular fluid, ECF [Ca2+] is kept constant by keeping the plasma [Ca2+] constant. [43]

Maintaining a constant plasma [Ca2+] is important for:

- nerve transmission
- nerve conduction
- muscle contraction
- cardiac contractility
- blood clotting
- bone formation
- excitation–secretion coupling
- cell-to-cell adhesion
- cell-to-cell communication.

Some of these (bone formation, blood clotting, and cell adhesion) depend directly on the extracellular [Ca2+]; others depend directly on intracellular [Ca2+]. But since ICF [Ca2+] depends indirectly on plasma [Ca2+], all are linked to plasma [Ca2+]. Calcium homeostasis can be viewed as having two components: a microcomponent dealing with the intracellular environment and a macrocomponent dealing with the extracellular environment. This chapter concerns regulation of [Ca2+] and phosphate concentrations in the extracellular fluid. [44]

1.9 Relation between Vitamin D & Calcium

Vitamin D is synthesized in the skin by exposure to sunlight, but can also be obtained exogenously from the diet. Dehydrocholesterol in the skin is converted to previtamin D by exposure to sunlight. Previtamin D is transported to the liver where it is converted into 25-hydroxyvitamin D [25(OH)D], which is the major circulating form. 25(OH)D is further converted in the kidney into the active form 1,25-dihydroxyvitamin D [1,25(OH)2D] [45]

To assess vitamin D levels, measurement of serum 25(OH) D, which has a half-life of about three weeks is performed. Vitamin D, which is fat soluble, plays an important role not only in the musculoskeletal system, but also in all tissues, which have vitamin D receptors [46]

The main function of vitamin D is to maintain calcium (Ca) balance in the body by promoting Ca absorption from the intestines and kidneys.

In vitamin D deficiency, only 10%-15% of calcium and 50%-60% of phosphorus can be absorbed from ingested foods [47]

Serum 25(OH)D levels are interpreted as follows; <10 ng/mL-severe deficiency,<20 ng/mL-deficiency, 20-30

ng/mL-insufficiency, >30 ng/mL-sufficient, and>150 ng/mL-intoxication [48]

It is reported that the main underlying cause of vitamin D deficiency, which is now considered to be a global health issue, is insufficient exposure to sunlight. Vitamin D levels can also be affected by other factors such as age, sex, ethnicity, and seasonal variations [49]

Low levels of vitamin D were found to be associated with hypertension, cardiovascular diseases, chronic musculoskeletal pain, and various malignancies. Our study aimed to determine the relationship between vitamin D deficiency and calcium and phosphorus levels. [50]

Methodology

2.1 The study population

The study was conducted on normal healthy volunteers and patients with Vitamin D and calcium disorder at laboratory of National university of sciences and technology at 2024 (winter season) after recording their age and gender in patients group and control group, were included in this study and compared with age and sex matched healthy individuals group in our study.

The study was carried out to evaluation vitamin D deficiency with calcium in women.

The examination about (20) patients and (10) as a control group. Whom selected randomly in age group from((20) to (25) years old .

2.2 Collect Blood Samples

The Blood samples of the patients and control groups were collected by take 5ml of the blood sample from their at gel tube. After collecting the blood sample, it is separated through the Centrifuge device to obtain the serum.

2.3 Methods

2.3.1 Vitamin D level

During the test

Most often, a small blood sample is taken from a vein in thier arm. We taking the sample may tie a band around upper arm to make thier veins easier to locate. Then we disinfect a small patch of skin with an antiseptic wipe. Next, we were insert a needle attached to a collection tube into them skin and withdraw a small amount of blood.

The method for measurement the Vitamin D level is automatic by using the (Cobas 411) a device.

25-OH Vitamin D Level	Reference Range (ng/ml)	Reference Range (nmol/l)
Deficient	0 – 10	0 – 25
Insufficient	10 – 30	25 – 75
Sufficient	30 – 100	75 – 250
Excess, but not toxic	100 - 150	250 - 375
Toxicity	>150	>375

Figure (2-1): The levels of Vitamin D in the body

2.3.2 Calcium level

At this study we measured the calcium level by using (Geno TEK advice) . we talked with patients to stop taking certain medications or supplements before the test. These medications can include:

- lithium
- thiazide diuretics
- antacids containing calcium

- vitamin D supplements
- calcium

□ Test Procedure

- The test is performed by withdrawing a sample of blood from the vein in the arms.
- The site of puncture is cleaned with antiseptic and a band is tied on the upper arm. This makes the vein swell with blood.
- Blood is withdrawn with a syringe, collected and sent to the lab.
- The band is removed and the site of the puncture is covered with a bandage.

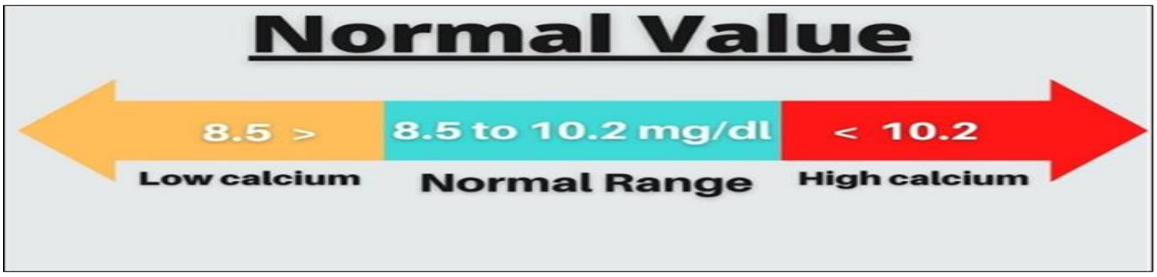


Figure (2-2) : Calcium "Ca+ " levels

2.4 Statistical analysis

Statistical calculations were made using the Statistical Package for the Social Sciences (SPSS) (version 20.0) program (IBM SPSS Statistics, SPSS Inc., Chicago, Illinois, USA).

The Anderson-Darling test was performed to test the adherence of continuous, parametric, variables to the normal distribution. Normally distributed continuous parametric variables, with no significant outlier, presented using their mean and standard deviation (mean ± SD) and parametric tests were used; independent 2 samples student t-test was used to analyze the differences between the mean of two groups.

The correlation between the groups of study was analyzed by Pearson correlation.

The statistical tests were approved by assuming a null hypothesis of no difference between mean of variables, a P value ≤ 0.05 was considered statistically significant.

Result

3.1 Result

Table 3-1: Comparison of study variables among patient and healthy control groups.

Variables	patients group (n=100) (mean ±SD)	Healthy control group (n=100) (mean ±SD)	t – test (p – value)
Age (years)	22.85 ± 1.226	22.20 ± 2.300	0.3175†
Ca (mg/dL)	7.830 ± 1.619	9.167 ± 0.4285	0.0015**
25OHD3 (ng/ml)	12.28 ± 7.980	25.33 ± 12.81	0.0018**

*= difference of statistical significance, p≤ 0.05.

**= difference of high statistical significance, p≤ 0.005.

†= difference of no statistical significance, p≥ 0.05.

Table(3-1) Show that the Vitamin D in the patient group (12.28 ± 7.980) was less than the healthy group (25.33 ± 12.81) While the calcium in the patient group was (7.830 ± 1.619) , In the healthy group was (9.167 ± 0.4285). Both of vitamin D and calcium were significant in the patients group compared with the control group at P value p≤ 0.05 .

correlation of study variables among patient and healthy control groups:

Our results showed that there is a significant positive correlation between the level of vitamin D and the level of calcium in the group of patients, as well as a stronger correlation than that in the control group at P value p≤ 0.05 .

Also, there was an inverse correlation between the level of vitamin D3 and the level of calcium with age in the group of patients, but their correlation was positive in the control group as shown in the table (3-2)

Table 3-2: correlation of study variables among patient and healthy control groups.

	Ca patients	Ca control	D3 patients	D3 control	Age patients	Age control
Ca patients	1	-0.30233	0.18083*	0.117724	-0.2185	-0.27869
Ca control	-0.30233	1	-0.21723	0.645841	-0.12934	0.392037
D3 patients	0.18083*	-0.21723	1	-0.42857	-0.1715	0.017234
D3 control	0.117724	0.645841*	-0.42857	1	-0.16382	0.173967
Age patients	-0.2185	-0.12934	-0.1715	-0.16382	1	0.570259
Age control	-0.27869	0.392037	0.017234	0.173967	0.570259	1

*= difference of statistical significance, p≤ 0.05.

Discussion

4.1 Discussion

Our results showed that there is a deficiency in vitamin D 100% among the women employees in the group of patients. Although the country of Iraq is one of the sunny countries, we believe that the reasons for this deficiency are related to not being exposed to the sun in sufficient quantity because our patients work in closed places away from the sun's rays in addition to clothes covering the entire body due to the prevailing religious beliefs. Our results also showed that there is a positive and significant correlation between the level of vitamin D with the level of calcium, and therefore we found a deficiency in the level of calcium also in the group of patients.

Vitamin D plays an important role in cellular growth and proliferation, homeostasis, oxidative stress and cellular transport . Vitamin D enhances calcium absorption in the intestine to maintain adequate serum calcium concentrations and is essential for bone growth and remodeling by osteoblasts and osteoclasts. A meta-analysis study found that synergistic administration of calcium and vitamin D could reduce general bone fractures by 15% and hip fractures by 30% . [51]

Anyway, one should avoid radical guidelines, such as avoiding the sun at any time and continuously use sunscreen during the day in all age groups, because there is no general rule. The physician should be alert, before prescribing the best treatment, to some issues such as the disease the patient presents.

Vitamin D plays an important role in diverse physiological functions. Vitamin D promotes calcium and phosphorus absorption, which is necessary to build and maintain bones and teeth, and is also a transcription factor in most cells in the body. 1a,25-(OH)2D/VD complex triggers global changes in gene expression via classical transcriptional mechanisms that contribute to induction of quiescence and maintenance of the differentiated phenotype in epithelial cells. In addition, novel mechanisms of vitamin D signaling have been identified, including regulation of miRNAs, rapid signaling through kinase pathways and protein-protein interactions. The demonstration that vitamin D metabolites and analogs that do not activate VDR-mediated transcription can mimic some of the anti-tumor actions of 1a,25-(OH)2D indicates that additional mechanisms of action remain to be discovered. [52]

Receptors for vitamin D were found in a variety of cells and tissues. Therefore, the likely disturbances due to vitamin D deficiency and the therapeutic potential of vitamin D are expanding. In spite of the substantial advancement of our understanding of the metabolism of vitamin D, the distribution of 1a,25-(OH)2D and 25-(OH)D in body pools, including their storage and mobilization, is notably lacking. Vitamin D deficiency is a worldwide health problem. Vitamin D insufficiency has become a common problem for many individuals and is now linked to various diseases.

Serum 25(OH)D levels are inversely associated with overweight, abdominal obesity, metabolic syndrome, systolic blood pressure and stroke, and plasma glucose concentrations. Vitamin D deficiency is associated with secondary hyperparathyroidism, higher systolic blood pressure, lower serum calcium, lower high-density lipoprotein levels, and increased incidence of insulin resistance. Moreover, lower serum 25(OH)D levels are associated with increased morbidity and mortality, all-cause mortality, myocardial infarction and diabetes. Normalisation of vitamin D reverses some of these negative phenomena. Several studies on vitamin D level in different countries have demonstrated the magnitude of the problem. Vitamin D deficiency is common in the Middle East. A low vitamin D level in the Saudi Arabian population has been reported despite the fact that sunny days are almost all year round. [53]

Although the optimal concentration for overall health is currently under debate, lower levels of vitamin D have been associated with a greater risk of rickets in children or osteomalacia in adults, increased risk of fractures, falls, breast cancer, colorectal cancer and adenoma, poo immunity and cardiovascular and other diseases such as multiple sclerosis. This therefore has led to substantial interest in identifying determinants of vitamin D. As many of environmental determinants of vitamin D are known, identifying genetic determinants of vitamin D is likely to help in our overall understanding of the biological processes that may increase or decrease vitamin D levels. Sunlight exposure often is limited by lifestyle and other choices, making it difficult to obtain enough vitamin D from diet alone; thus, patients with deficiency are likely to require long-term supplementation. Considering the available facts, the introduction of a national policy to provide routine supplementation of vitamin D to vulnerable populations not only would reduce various morbidities, falls and fractures, but also would eliminate other morbidities with minimal cost. Extra vitamin D should be provided to premature infants and those who are exclusively breast-fed. [54]

Conclusion

5.1 Conclusion

In conclusion, vitamin D deficiency/insufficiency is a global public health problem not only limited to high risk groups of elderly or the housebound, but also young physicians and nurses have an alarmingly high prevalence of vitamin D deficiency. This review highlights the findings that confirm the widespread prevalence of vitamin D deficiency and the need for a population-wide policy to solve this problem. Moreover, further genomic investigations in larger groups as well as functional studies need to performed to confirm previous findings.

Vitamin D is very important for the health of the human being, and maintaining adequate levels of vitamin D not only brings benefits as it prevents a number of diseases. However, the data are contradictory and there is no consensus within the medical society both with respect to the existence of a sufficient and safe level of sun exposure in order to maintain an optimal level of vitamin D, as well as what would be the amount of vitamin D that should be administered in patients with deficiency/ insufficiency. There are uncertainties also concerning its usage for specific pathological conditions, time of treatment and the maintenance dose.

Anyway, one should avoid radical guidelines, such as avoiding the sun at any time and continuously use sunscreen during the day in all age groups, because there is no general rule. The physician should be alert, before prescribing the best treatment, to some issues such as the disease the patient presents.

There are some groups of people to which sun exposure is contraindicated as transplant patients, individuals with lupus, those with a predisposition to develop cancer skin, or in use of immunosuppressive drugs, among others. There are other groups of patients who have risk factors for vitamin D deficiency, but that can sunbathe, such as patients with lactose intolerance, intestinal malabsorption, renal failure, cystic fibrosis, liver disease. Also, there is another group of people who use some medication that decrease the level of vitamin D as antifungal drugs, anticonvulsants, antiretroviral, and glucocorticoids. Thus, the best treatment should be the one in which the doctor examines the patient and all his medical history and, based on the risk-benefit, prescribes what is most appropriate for the patient in that

circumstance.

References

1. "Vitamin D". Micronutrient Information Center, Linus Pauling Institute, Oregon State University, Corvallis. February 11, 2021. Retrieved March 14, 2022.
2. "Office of Dietary Supplements - Vitamin D". ods.od.nih.gov. October 9, 2020. Retrieved October 31, 2020.
3. Norman AW (August 2008). "From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health". The American Journal of Clinical Nutrition. 88 (2): 491S–499S. doi:10.1093/ajcn/88.2.491S. PMID 18689389.
4. Bikle DD (March 2014). "Vitamin D metabolism, mechanism of action, and clinical applications". Chemistry & Biology.
5. Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts JT, Anderson RR, et al. (October 1980). "Photosynthesis of previtamin D3 in human skin and the physiologic consequences". Science.
6. Lehmann U, Gjessing HR, Hirche F, Mueller-Belecke A, Gudbrandsen OA, Ueland PM, et al. (October 2015). "Efficacy of fish intake on vitamin D status: a meta- analysis of randomized controlled trials". The American Journal of Clinical Nutrition. .
7. "Vitamin D Tests". Lab Tests Online (USA). American Association for Clinical Chemistry. Retrieved June 23, 2013.
8. Hollis BW (January 1996). "Assessment of vitamin D nutritional and hormonal status: what to measure and how to do it". Calcified Tissue International. .
9. Holick MF, Schnoes HK, DeLuca HF (April 1971). "Identification of 1,25- dihydroxycholecalciferol, a form of vitamin D3 metabolically active in the intestine". Proceedings of the National Academy of Sciences of the United States of America.
10. Norman AW, Myrtle JF, Midgett RJ, Nowicki HG, Williams V, Popják G (July 1971). "1,25-dihydroxycholecalciferol: identification of the proposed active form of vitamin D3 in the intestine". Science. .
11. Wolf G (June 2004). "The discovery of vitamin D: the contribution of Adolf Windaus". The Journal of Nutrition. .
12. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. (January 2014). "Vitamin D supplementation for prevention of mortality in adults". .
13. Reid IR, Bolland MJ, Grey A (January 2014). "Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis".
14. Bolland MJ, Grey A, Gamble GD, Reid IR (April 2014). "The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta- analysis". The Lancet. Diabetes & Endocrinology (Meta-analysis).
15. "The Lancet Diabetes & Endocrinology: Vitamin D supplementation in adults does not prevent fractures, falls or improve bone mineral density". EurekAlert!. Retrieved February 23, 2022. The authors conclude that there is therefore little justification to use vitamin D supplements to maintain or improve musculoskeletal health, except for the prevention of rare conditions such as rickets and osteomalacia in high risk groups, which can occur due to vitamin D deficiency after a prolonged lack of exposure to sunshine.
16. "IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN): Nomenclature of vitamin D. Recommendations 1981".

17. Fleet JC, Shapses SA (2020). "Vitamin D". In BP Marriott, DF Birt, VA Stallings, AA Yates (eds.). Present Knowledge in Nutrition, Eleventh Edition. London, United Kingdom: Academic Press (Elsevier). pp. 93–114. ISBN 978-0-323-66162-1.

18. Boron WF, Boulpaep EL (March 29, 2016). Medical Physiology E-Book. Elsevier Health Sciences. ISBN 978-1-4557-3328-6.

19. Bouillon R, Van Cromphaut S, Carmeliet G (February 2003). "Intestinal calcium absorption: Molecular vitamin D mediated mechanisms".

20. Del Pinto R, Pietropaoli D, Chandar AK, Ferri C, Cominelli F (November 2015). "Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis". Inflammatory Bowel Diseases. .

21. Guzman-Prado Y, Samson O, Segal JP, Limdi JK, Hayee B (May 2020). "Vitamin D Therapy in Adults With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis". Inflammatory Bowel Diseases.

22. Zhang Y, Tan H, Tang J, Li J, Chong W, Hai Y, et al. (July 2020). "Effects of Vitamin D Supplementation on Prevention of Type 2 Diabetes in Patients With Prediabetes: A Systematic Review and Meta-analysis". Diabetes Care.

23. Sahebi R, Rezayi M, Emadzadeh M, Salehi M, Tayefi M, Parizadeh SM, et al. (February 2019). "The effects of vitamin D supplementation on indices of glycemic control in Iranian diabetics: A systematic review and meta-analysis". Complementary Therapies in Clinical Practice

24. Mohammadi S, Hajhashemy Z, Saneei P (June 2021). "Serum vitamin D levels in relation to type-2 diabetes and prediabetes in adults: a systematic review and dose- response meta-analysis of epidemiologic studies". .

25. Brophy, Sinead; Davies, Helen; Mannan, Sopna; Brunt, Huw; Williams, Rhys (September 7, 2011). "Interventions for latent autoimmune diabetes (LADA) in adults". Cochrane Database of Systematic.

26. Khoshbakht Y, Bidaki R, Salehi-Abargouei A (January 2018). "Vitamin D Status and Attention Deficit Hyperactivity Disorder: A Systematic Review and Meta- Analysis of Observational Studies". Advances in Nutrition.

27. Gan J, Galer P, Ma D, Chen C, Xiong T (November 2019). "The Effect of Vitamin D Supplementation on Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trials". Journal of Child and Adolescent Psychopharmacology.

28. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, et al. (April 2014). "Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials". Psychosomatic Medicine. .

29. Balion C, Griffith LE, Strifler L, Henderson M, Patterson C, Heckman G, et al. (September 2012). "Vitamin D, cognition, and dementia: a systematic review and meta-analysis". Neurology..

30. Nazik Yüksel, Rabia; et al. (2014). "Correlation between total vitamin D levels and psychotic psychopathology in patients with schizophrenia: therapeutic implications for add-on vitamin D augmentation". Ther Adv Psychopharmacol.

31. Greenwood, Norman N.; Earnshaw, Alan (1997). Chemistry of the Elements (2nd ed.). Butterworth-Heinemann. p. 112.

32. Krieck, Sven; Görls, Helmar; Westerhausen, Matthias (2010). "Mechanistic Elucidation of the Formation of the Inverse Ca(I) Sandwich Complex [(thf)3Ca(μ- C6H3-1,3,5-Ph3)Ca(thf)3] and Stability of Aryl-Substituted Phenylcalcium Complexes". Journal of the American Chemical Society. .

33. Weast, Robert (1984). CRC, Handbook of Chemistry and Physics. Boca Raton, Florida: Chemical Rubber Company Publishing. pp. E110. ISBN 0-8493-0464-4.

34. "Calcium". Linus Pauling Institute, Oregon State University, Corvallis, Oregon. 1 September 2017. Retrieved 31 August 2019.

35. "Calcium: Fact Sheet for Health Professionals". Office of Dietary Supplements, US National Institutes of Health. 9 July 2019. Retrieved 31 August 2019.

36. Greenwood and Earnshaw, pp. 112–13.

37. Parish, R. V. (1977). The Metallic Elements. London: Longman. p. 34. ISBN 978-0- 582-44278-8.

38. Fukuma, Chihito (2013). . p. 126.

39. Ropp, Richard C. (2012). Encyclopedia of the Alkaline Earth Compounds. pp. 12– 15. ISBN 978-0-444-59553-9.

40. Hluchan and Pomerantz, p. 484

41. C. R. Hammond The elements (pp. 4–35) in Lide, D. R., ed. (2005). CRC Handbook of Chemistry and Physics (86th ed.). Boca Raton (FL): CRC Press. ISBN 0-8493- 0486-5.

42. Harder, S.; Feil, F.; Knoll, K. (2001). "Novel Calcium Half-Sandwich Complexes for the Living and Stereoselective Polymerization of Styrene". Angew. Chem. Int. Ed. .

43. Crimmin, Mark R.; Casely, Ian J.; Hill, Michael S. (2005). "Calcium-Mediated Intramolecular Hydroamination Catalysis". Journal of the American Chemical Society..

44. Jenter, Jelena; Köppe, Ralf; Roesky, Peter W. (2011). "2,5-Bis{N-(2,6-diisopropylphenyl)iminomethyl}pyrrolyl Complexes of the Heavy Alkaline Earth Metals: Synthesis, Structures, and Hydroamination Catalysis". .

45. Arrowsmith, Merle; Crimmin, Mark R.; Barrett, Anthony G. M.; Hill, Michael S.; Kociok-Köhn, Gabriele; Procopiou, Panayiotis A. (2011). "Cation Charge Density and Precatalyst Selection in Group 2-Catalyzed Aminoalkene Hydroamination". Organometallics. 30 (6): 1493–1506. doi:10.1021/om101063m.

46. Penafiel, J.; Maron, L.; Harder, S. (2014). "Early Main Group Metal Catalysis: How Important is the Metal?". Angew. Chem. Int. Ed. 54.

47. Greenwood and Earnshaw, pp. 136–37

48. Cameron, A. G. W. (1973). "Abundance of the Elements in the Solar System" (PDF).

49. Clayton, Donald (2003). Handbook of Isotopes in the Cosmos: Hydrogen to Gallium. Cambridge University Press. pp. 184–98. ISBN 9780521530835.

50. Audi, G.; Kondev, F. G.; Wang, M.; Huang, W. J.; Naimi, S. (2017). "The NUBASE2016 evaluation of nuclear properties" (PDF). Chinese Physics C. 41

51. Holick MF (2020). "Sunlight, UV Radiation, Vitamin D, and Skin Cancer: How Much Sunlight Do We Need?". Advances in Experimental Medicine and Biology.

52. Holick MF (February 2002). "Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health". Current Opinion in Endocrinology, Diabetes and Obesity.

53. ^ Bikle DD (March 2010). "Vitamin D and the skin". Journal of Bone and Mineral Metabolism.

54. ^ Bouillon R, Suda T (January 2014). "Vitamin D: calcium and bone homeostasis during evolution". BoneKEy Reports. 3: 480