Awareness of Calcium & Vitamin D among college going students in Bangladesh.

A Research Report submitted to the Department of Pharmacy, East West University in partial fulfillment of the requirement for the Degree of Bachelor of Pharmacy.

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Dedication

This Research paper is dedicated to
My beloved parents,
Who are my biggest Inspirations and to
My Research Supervisor

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Abstract

Calcium is essential to maintaining total body health, normal growth and development, metabolizing iron, helping blood clotting & regulating blood pressure, keeping bones & teeth strong over lifetime, the action of the number of hormones, cell structure etc. Vitamin D is required for regulation of cell growth, bone formation, immune function, muscle strength, hair growth, reducing autoimmune disease, fighting infection etc.

Previous works intended to determine the status of these micronutrients in local population have reported that the people in Bangladesh are at high risk of calcium insufficiency and hypovitaminosis D related health complications. Lack of awareness and insufficient knowledge of the essentiality of these two nutrients are assumed to cause this problem in Bangladesh. The present study was designed and conducted to establish a basic understanding on the level of gap of knowledge and awareness among college going students in Bangladesh.

Bangladesh is a one of the most overpopulated country of the world. That's why the most important part in living is to be as healthy as possible avoiding all the diseases. From the survey it was found that about the 75% & 80% college going students know Calcium & Vitamin D as a food supplement while 25% & 20% do not know about the Calcium & Vitamin D. The college going students have come to largely know about milk (41%), Sea fish (8.5%), Meat (12.%), Cheeses(10.5%) and others(27%) as Calcium containing food. They also know about Meat(13%),Liver(12%),Milk(43%),Eggs(10.5%),Banana(10.5%),Others (12%) as a Vitamin D containing food. On the basis of drinking milk is response mainly daily (31%).They remain in the high sun exposure per day like >1hr (35%).The term of "Osteoporosis" are known (22%) of college going students while (78%) & do not know about it. (65%) and (70%) ever been prescribed any Calcium & Vitamin D supplement by a physician while (35%) and (30 %) ever not been prescribed. The college going student have come to highly know about Calcium and Vitamin D from those source as books (45%).

Key words: Calcium, Vitamin D, Calcitriol, Cholecalciferol, awareness.

Chapter 1

Introduction

INTRODUCTION

1.1 Calcium

Calcium (Ca^{2+}) is the major extracellular divalent cation. The normal adult man and women posses about 1300 and 1000 gm of Ca^{2+} of which more than 99% in bone. Ca^{2+} is present in small amount in extracellular fluids and to a minor extent within the cell (Goodman and Gillman, 2002). Calcium accounts for 1 to 2 percent of adult human body weight. Over 99 percent of total body calcium is found in teeth and bones. The remainder is present in blood, extracellular fluid, muscle, and other tissues, where it plays a role in mediating vascular contraction and vasodilation, muscle contraction, nerve transmission, and glandular secretion. In bone, calcium exists primarily in the form of hydroxyapatite (Ca_{10} $(PO_4)_6$ $(OH)_2$), and bone mineral is almost 40 percent of the weight of bone. Bone is a dynamic tissue that is constantly undergoing osteoclastic bone resorption and osteoblastic bone formation. Bone formation exceeds resorption in growing children, is balanced with resorption in healthy adults, and lags behind resorption after menopause and with aging in men and women. Each year, a portion of the skeleton is remodeled (reabsorbed and replaced by new bone). The rate of cortical (or compact) bone remodeling can be as high as 50 percent per year in young children and is about 5 percent per year in adults (Parfitt, 1988). Trabecular (or cancellous) bone emodeling is about five-fold higher than cortical remodeling in adults. The skeleton has an obvious structural role and it also serves as a reservoir for calcium.

The skeleton contains 99% of total body calcium in a crystalline form. The steady state content of calcium in bone reflects the net effect of bone resorption and bone formation. In addition, a liable pool of bone calcium is readily exchangeable with intestinal fluid. The rate of exchanges are modulated by drug, hormone, vitamin and other factor that directly alter bone turnover or that influence the level of Ca^{2+} in intestinal fluid (Goodman and Gillman, 2002).

Figure 1.1: Calcium Containing Foods.

1.1.2 Source of Calcium

There are many foods to choose from that provide calcium. Milk and milk products—such as low-fat or fat-free cheese and yogurt—are excellent sources because they are high in calcium. Most types of milk have approximately 300 milligrams of calcium per 8 fluid ounces (1 cup), or about 25 percent of the calcium that twins and teens need every day. The best choices are low fat or fat-free milk and milk products. Because these items contain little or no fat, it's easy to get enough calcium without adding extra fat to the diet. Flavored milk has just as much calcium as

plain milk, but is higher in sugar and calories than plain milk. Young people may choose to drink chocolate or other flavored milk if they prefer the taste, but they should remember to factor in the additional calories into their overall daily needs. Whether plain or flavored, remember to choose low-fat or fat-free milk and milk products. For those individuals who do not consume adequate amount of milk or dairy products, a supplement may be necessary (Autajay, 2003).

Table: 1.1 Sources of Calcium (Nutrient values from Agricultural Research Service (ARS).

Food	Milligrams of Calcium
Yogurt, fat-free plain (1 cup)	45
Soy beverage with added calcium (1 cup)	368
Orange juice with added calcium (1 cup)	35
Fruit yogurt, low-fat (1 cup)	345
Cheese (e.g., low-fat or fat-free American, 2 oz., about 3 slices)	33
Milk, fat-free (1 cup)	306
Milk, 1% low-fat (1 cup)	90
Tofu, firm, with added calcium sulfate (1/2 cup)	53
Cheese pizza (1 slice)	8
Bok Choy, boiled (1 cup)	58
Spinach, cooked from frozen (1 cup)	46
Soybeans, cooked (1 cup)	30
Frozen yogurt, soft-serve vanilla (1/2 cup)	03
Macaroni and cheese (1 cup)	9

Almonds (1 oz.)	70
Broccoli, cooked (1 cup, chopped)	6
Tortillas, flour	58
Broccoli, raw (1 cup, chopped)	43
Tortillas, corn	4

1.1.3 Physioloycal Roles of calcium

- Control excibility of nerves and muscles and regulate permeability of cell membrane.
- Maintain integrity of cell membrane and regulate cell adhesion.
- Ca^{2+} ions are essential for excitation-contraction of all type of muscle.
- Ca^{2+} ions are essential for excitation-secretion coupling in exocrine and endocrine glands.
- Ca^{2+} ions releases of transmitter from nerve ending.
- Act as intracellular messenger for hormones and autacoids.
- Generate impulse in heart and determine level automatically.
- Help in coagulation of blood.
- Structural function of bone and teeth (Tripathi, 2008).

1.1.4 Chemistry of Calcium

Calcium plays a pivotal role in the physiology and biochemistry of organisms and the cell. It plays an important role in signal transduction pathways, where it acts as a second messenger, in neurotransmitter release from neurons, contraction of all muscle cell types, and fertilization. Many enzymes require calcium ions as a cofactor, those of the blood-clotting cascade being notable examples. Extracellular calcium is also important for maintaining the potential difference across excitable cell membranes, as well as proper bone formation. (Brown *et al.*, 1993)

Calcium levels in mammals are tightly regulated, with bone acting as the major mineral storage site. Calcium ions, Ca^{2+}, are released from bone into the bloodstream under controlled

conditions. Calcium is transported through the bloodstream as dissolved ions or bound to proteins such as serum albumin. Parathyroid hormone secreted by the parathyroid gland regulates the restoration of Ca^{2+} from bone, reabsorption in the kidney back into circulation, and increases in the activation of vitamin D_3 to Calcitriol. Calcitriol, the active form of vitamin D_3, promotes absorption of calcium from the intestines and the mobilization of calcium ions from bone matrix. Calcitonin secreted from the par follicular cells of the thyroid gland also affects calcium levels by opposing parathyroid hormone; however, its physiological significance in humans is dubious.

1.1.5 Calcium regulation in the human body

Different tissues contain calcium in different concentrations. For instance, Ca^{2+} (mostly calcium phosphate and some calcium sulfate) is the most important (and specific) element of bone and calcified cartilage. In humans, the total body content of calcium is present mostly in the form of bone mineral (roughly 99%). In this state, it is largely unavailable for exchange/bioavailability. The way to overcome this is through the process of bone resorption, in which calcium is liberated into the bloodstream through the action of bone osteoclasts. The remainder of calcium is present within the extracellular and intracellular fluids (Forsen and Kordel, 1990).

Figure 1.2: Calcium regulation in Human body (Boron *et al.*, 2003)

1.1.6 Metabolism of calcium

The extracellular fluid (ECF) ionized calcium (1 mmol/L) concentration is 10^{4} times the concentration of the intracellular fluid (ICF) ionized calcium with the latter varying during normal function by up to 10-fold (e.g. from 10^{-4} to 10^{-3} mmol/L). Non ionized calcium is predominantly found in bone providing an important structural function to the human body, whereas the ionized calcium is responsible for a variety of physiological effects that are characteristic of the cell type (e.g. secretion, neuromuscular impulse formation, contractile functions, clotting).

While the plasma ionized calcium can be directly measured, the total plasma calcium is commonly measured, which varies with the variation in plasma protein levels However, in critically ill patients, there are large variations in ionized calcium due to:

a) P^{H} alterations in calcium binding by albumin (e.g. for every 0.1 unit reduction in plasma pH, the albumin bound calcium decreases by 0.07 mmol/L and ionized calcium increases by 0.07 mmol/L) and

b) Alterations in calcium complexes with:

1) lactate (e.g. for each 1 mmol/L increase in lactate the ionized calcium decreases by 0.006 mmol/L, due largely to an increase in unionized calcium lactate, although lactic acidosis in patients with a normal ventilator response and previously normal albumin and bicarbonate levels usually has little effect on ionized calcium levels) and bicarbonate (e.g. for each 1 mmol/L decrease in bicarbonate, the ionized calcium increases by 0.004 mmol/L, due largely to a liberation of Ca^{2+} from unionized calcium bicarbonate).

Therefore in the critically ill patient, for an accurate assessment of plasma ionized calcium status, direct measurement of the ionised calcium should be performed, and is often readily available (using an ion specific electrode) in association with standard blood gas estimations.

Numerous hormones can influence calcium metabolism (e.g. 1, 25 dihydroxycholecalciferol, parathyroid hormone, Calcitonin, parathyroid hormone related protein, estrogen, corticosteroids, thyroxin, growth hormone) although only 1, 25 dihydroxycholecalciferol, parathyroid hormone,

Calcitonin are primarily concerned with the regulation of calcium metabolism (Baker and Worthley, 2002).

1.7 Absorption and Excretion of calcium

Calcium absorption refers to the amount of calcium that is absorbed from the digestive tract into body's circulation. Another term for this is calcium bio-availability. Calcium absorption can be affected by the amount of calcium in body, vitamin D and vitamin K_2 status, magnesium and trace mineral status, age, pregnancy and certain plant substances in diet. The amount of calcium consumed at one time such as in a meal can also affect absorption. Though ca^{2+} are poorly absorbed from intestine in presence of vitamin D 35% ca^{2+} ions are absorbed from intestine.

Approximately 10% of ingested calcium is excreted through the urine. About 41% of plasma calcium is bound to plasma protein and not filtered by the glomerular capillary. The rest arecombine with anion and filtered through the glomeruli in to the renal tubules. Normally the renal tubules reabsorb 90% of filtered calcium and rests are excreted through the urine (Guyton, 2003).

1.1.8 Factors that decrease calcium absorption

1.1.8.1 Oxalic Acid — Oxalic acid is a substance that binds to calcium directly in some plant-foods making the calcium unavailable for absorption. The amount of calcium absorbed from foods high in oxalic acid, such as spinach, soybeans, and cocoa, is small. However, the calcium absorption from other food sources, consumed at the same meal, will not be affected (Linda and Vanessa, 2004).

1.1.8.2 Phytates — Phytates are substances found in some plant foods that can bind calcium in the intestine and decrease its absorption. Phytates, unlike oxalic acid, will bind the calcium from other food sources consumed at the same meal (Linda and Vanessa, 2004).

1.1.8.3 Dietary fiber — Although the effects are relatively small, high dietary intake of insoluble fiber, found in foods such as wheat bran, can bind calcium in the intestine and decrease absorption (Linda and Vanessa,2004).

1.8.4 Laxatives or anything that induces diarrhea — Diarrhea can move substances through the intestine very rapidly, not leaving enough time for calcium to be absorbed (Linda and Vanessa, 2004).

1.8.5 Great excesses of the minerals phosphorous and magnesium in proportion to calcium — The absorption of both magnesium and phosphorous requires vitamin D. If phosphorous and magnesium minerals are consumed in excess, there will be less vitamin D available for aiding calcium absorption (Linda and Vanessa, 2004).

1.8.6 Tannins in tea — Tannins are substances found in tea which can bind with calcium in the intestine, therefore decreasing its absorption (Linda and Vanessa, 2004).

1.8.7 Medications — Long term use of medications, such as corticosteroids, and anti-convulsants can be damaging to bone. These medications are used for chronic conditions such as asthma, rheumatoid arthritis, and psoriasis. If you need to take these medications for extended periods of time, consult your doctor about ways to help prevent bone loss (Linda and Vanessa, 2004).

1.9 Effects of calcium on cell

The effects of calcium on human cells are specific, meaning that different types of cells respond in different ways. However, in certain circumstances, its action may be more general. Ca^{2+} ions are one of the most widespread second messengers used in signal transduction. They make their entrance into the cytoplasm either from outside the cell through the cell membrane via calcium channels (such as Calcium-binding proteins or voltage-gated calcium channels), or from some internal calcium storages such as the endoplasmic reticulum and mitochondria. Levels of intracellular calcium are regulated by transport proteins that remove it from the cell. For example, the sodium-calcium exchanger uses energy from the electrochemical gradient of sodium by coupling the influx of sodium into cell (and down its concentration gradient) with the transport of calcium out of the cell. Calcium's function in muscle contraction was found as early as 1882 by Ringer. Subsequent investigations were to reveal its role as a messenger about a century later. Because its action is interconnected with cAMP, they are called synarchic messengers. Calcium can bind to several different calcium-modulated proteins such as trooping -

C (the first one to be identified) and calmodulin, proteins that are necessary for promoting contraction in muscle (Boron *et al.*, 2003).

Table 1.2: Effect of calcium on cell

Cell type	Effect
Secretoty cells	Increase secretion
Juxtaglomerular cell	decrease secretion
Parathyroid chief cell	decrease secretion
neurons	transmission
t-cells	Response to antigen presentation
myocytes	contraction
various	Activation and function of protein kinase C

1.10 Deficiency of Calcium

Many people do not get enough calcium. Unfortunately, there are not usually any obvious symptoms of a calcium deficiency, and people can go for years in a calcium-deficient state before any noticeable problems occur. Calcium deficiencies are usually easily treatable.

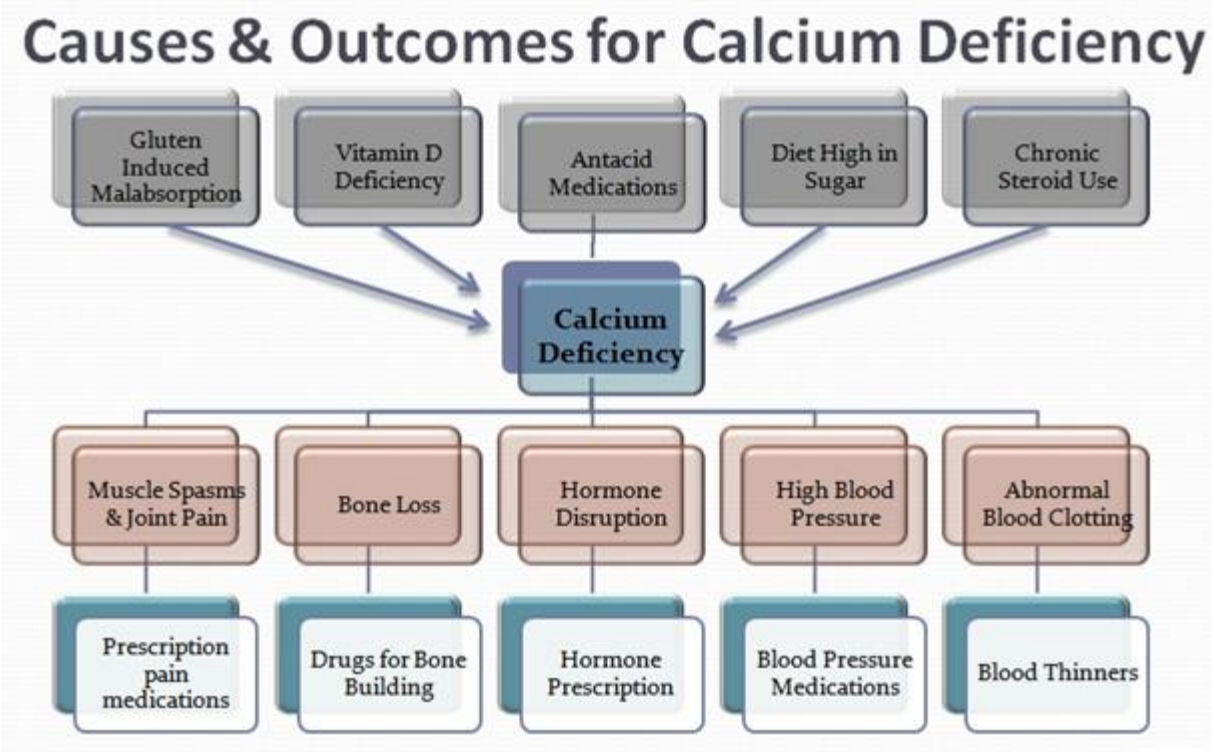


Figure 1.3: Calcium deficiency and its outcome (Dr. peter Osborne, 2005)

1.10.1 Possible Signs of Calcium Deficiency:

Typically, there are no obvious signs of a calcium deficiency for most people until osteoporosis is discovered, either through bone scans or though a broken bone. Most of the calcium in the human body is stored in the bones and the teeth. While many people think of bones and teeth as being permanent, unchanging structures, they are actually being constantly broken down and rebuilt. It is absolutely essential to keep a certain steady level of calcium in the blood. If blood calcium levels are too low, the body will break down bone and teeth to increase the blood calcium levels. If the blood levels are high, then the body uses the extra calcium to rebuild bone and teeth. Most of the symptoms that might occur due to a calcium deficiency would be seen only if calcium levels are low in the blood. Because the body is very good at keeping the blood

calcium levels steady (often at the expense of bone strength), most people will never experience any symptoms of a deficiency until their bone.

Calcium is arguably the most important nutrient in our body. As the most abundant mineral it has several important functions. More than 99% of your calcium is stored in your bones and teeth where it supports their structure and is ready to be called into action for many other critical functions. A few of these calcium functions are muscle contraction, blood vessel contraction and expansion, the secretion of hormones and enzymes, and sending messages through the nervous system. The amount of calcium in our body fluid and tissues is closely regulated so that these vital body processes function efficiently. Bones are continuously breaking down and being formed at the same time. This process of remodeling involves a constant breakdown of bone (reabsorption) and deposition of calcium into newly deposited bone (bone formation). The balance between bone reabsorption and deposition changes as you age. When you are a child there is a higher amount of bone formation and less breakdown. In early and middle adulthood, these processes are relatively equal. As an aging adult, particularly among postmenopausal women, our bone breakdown exceeds its formation, resulting in bone loss, which increases your risk for osteoporosis (porous, weak bones which can easily fracture).

1.11 Pharmacological action of Calcium regulating drugs

1.11.1 Calcium channel blockers:

Three types of calcium channels have been identified voltage-sensitive, receptor operated (cardiac muscle and vascular smooth muscle) and stretch operated (in some blood vessels) channels. Using electrophysiological and pharmacological techniques, three different types of voltage-gated calcium channels have been identified, namely, L-type (for long lasting, large channels), T–type (for transient, tiny channels) and N–type (for neuronal, neither L nor T). Many compounds are known to have a calcium channel inhibitory effect. Calcium antagonists, based on the specificity of inhibition of the slow calcium current, can be classified into three groups: Group A: for 90 to 100 percent inhibition of calcium influx without change in the sodium current (verapamil, diltiazem and the Dihydropyridines); Group B: for 50 to 70 percent inhibition of calcium influx current without change in the sodium current (bepridil, cinnarizine and prenylamine) and Group C: for agents exhibiting some inhibition of calcium influx (Phenytoin, indomethacin and propranolol). There is now increasing evidence that, certain calcium channel blockers especially the Dihydropyridines are more strongly associated with vasodilation of afferent arterioles than of efferent arterioles and also with increase intra glomerular pressure and

albuminuria. Thus they have a beneficial effect in terms of reducing proteinuria and slowing the progression of diabetic renal failure (Yousef *et al.*, 2005).

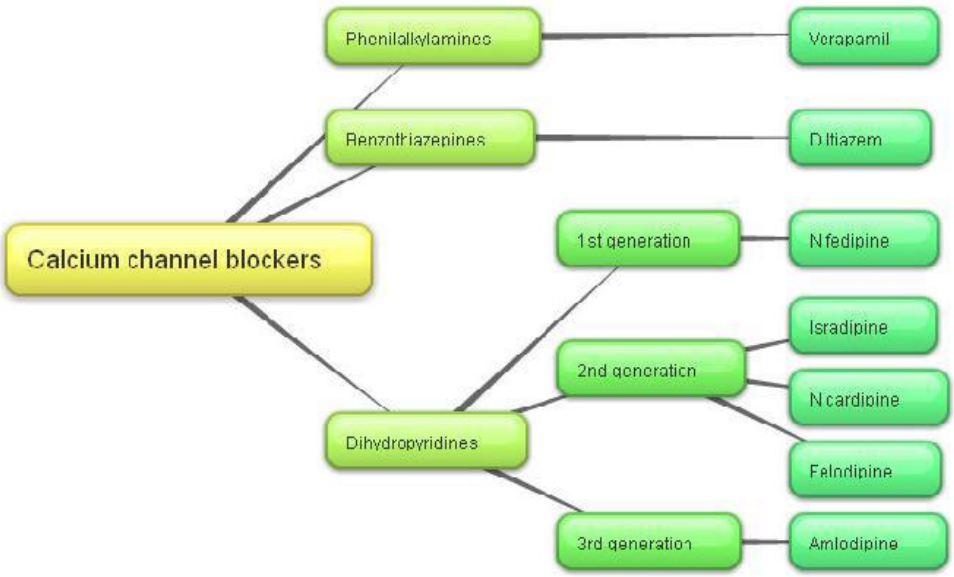


Figure 1.4: Classification of calcium channel blockers

1.11.2 Classification of calcium channel blockers

Calcium channel blockers comprise three chemical groups, all of them bind the L-type Ca^{++} channel, but each class binds to different binding sites of the same channel:

- Phenylalkylamines: verapamil is the only drug in this group; it binds to the V binding site.
- Benzodiazepines: diltiazem binds to the D binding site in the L-type Ca^{++} channel. It shows cardiovascular effects similar to those of verapamil.
- Dihydropyridines: the prototype agent in this group is nifedipine, a first generation Dihydropyridine that binds to the N binding site. Second generation agents include

Isradipine, nicardipine, and felodipine. Amlodipine is considered a third generation Dihydropyridine (Lippincott, 2009).

1.11.3 Mechanism of action and pharmacological effects of drugs

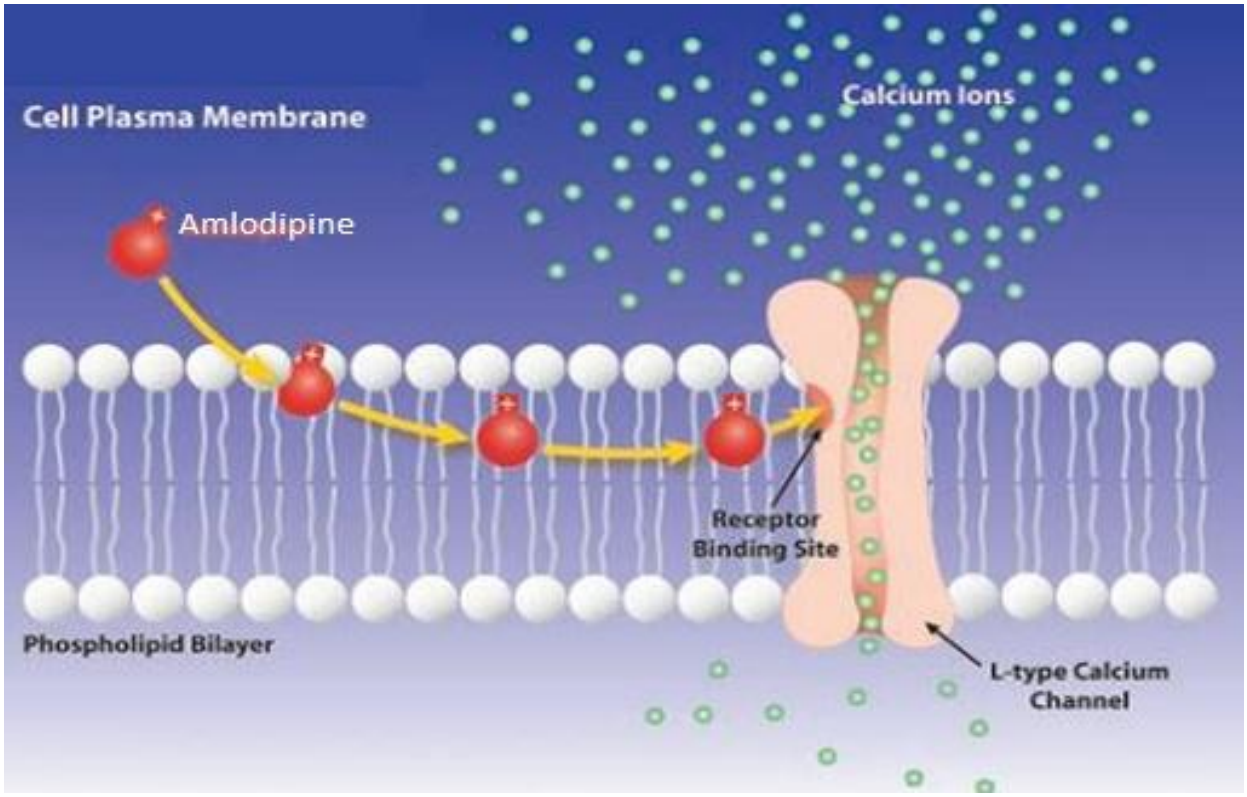


Figure 1.5: Mechanism of action of Amlodipine on calcium channel

Calcium channel antagonists block the inward movement of calcium by binding to the L-type calcium channels in the heart and in smooth muscle of the peripheral vasculature. CCB's dilate coronary arteries and peripheral arterioles, but not veins. They also decrease cardiac contractility (negative isotropic effect) ,automaticity at the SA node and conduction at the AV node. Dilation of the coronary arteries increases myocardial oxygen supply (Berridge, 1993)

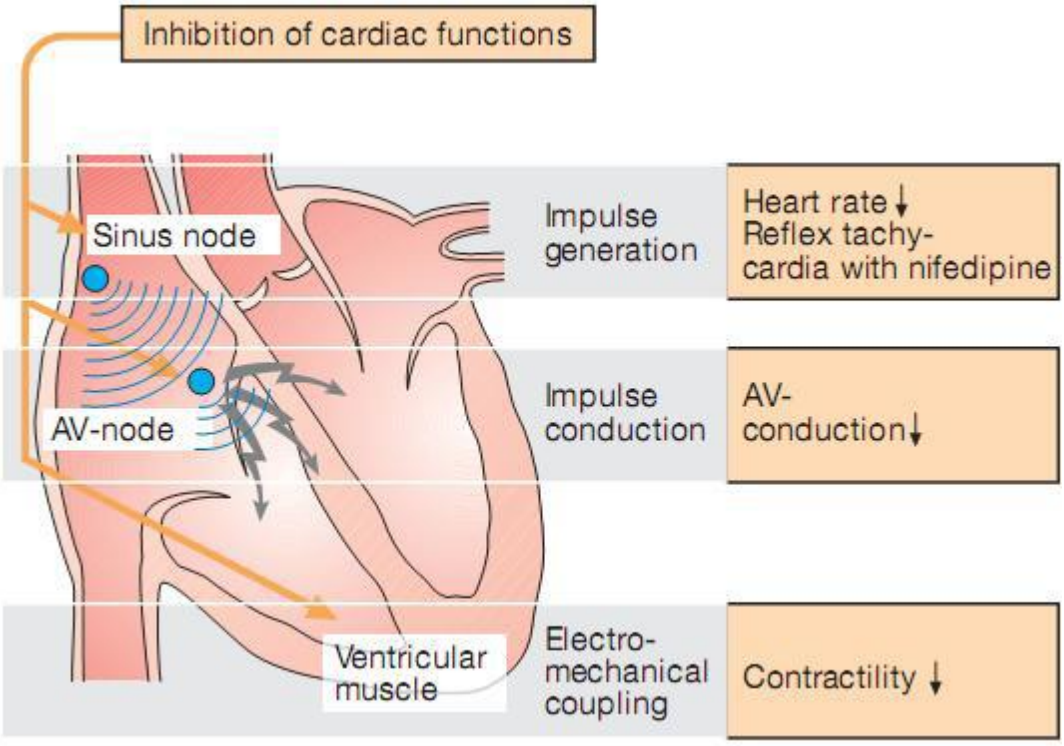


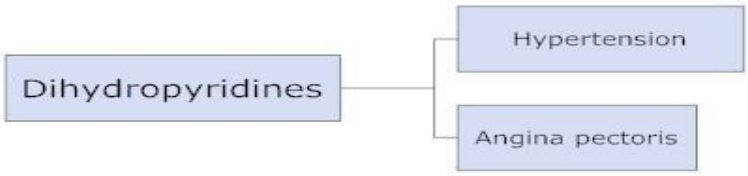
Figure 1.6: influence of nifedipine on control of cardiac impulse conduction and contractility

1.11.4 Effects of CCBs on heart contraction and conduction

Dihydropyridines have minimal effect on cardiac conduction or heart rate, while they have potent actions as arteriolar vasodilators. This class of drugs can cause reflex tachycardia when peripheral vasodilatation is marked. On the other hand, verapamil and diltiazem slow AV conduction and decrease SA node automaticity, they also decrease heart rate. Diltiazem is used in the treatment of variant angina because of its coronary antispasmodic properties (Joseph and Pasco, 2000)

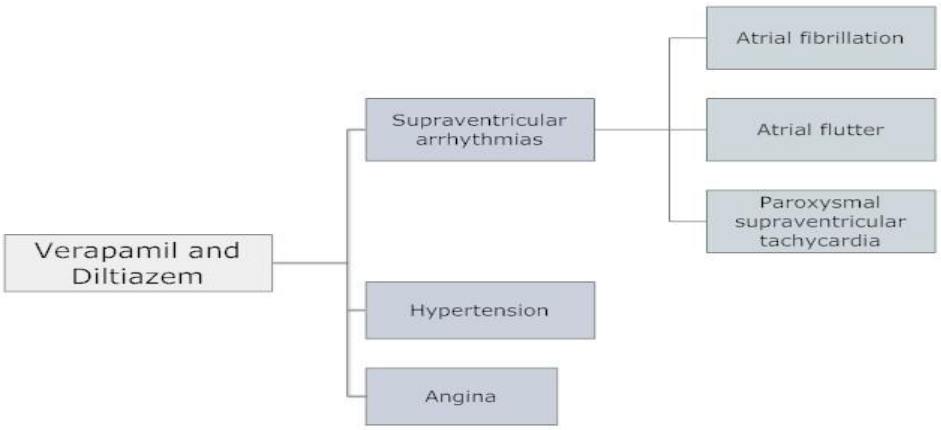
1.11.5 Indications of drugs

Dihydropyridines indications (Hypertension)



Calcium channel blockers act as coronary vasodilators, producing variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective.

In the presence of heart failure, the use of calcium channel blockers can cause further worsening of heart failure as a result of their negative isotropic effect.



1.12 Disorder related with Calcium

1.12.1 Osteoporosis

Osteoporosis is a major public health issue affecting more than 10 million Americans. It is usually diagnosed in later life, but the most important time to focus on building healthy bones is during the first 3 decades of life. Providing sufficient bone-building nutrients, along with weight bearing exercise, may be the best protection against this disease. Pharmaceutical agents can be effective in treating osteoporosis, but there is an increased interest in non-pharmacological

prevention and treatment for the condition. Healthcare providers can help prevent and treat osteoporosis by supporting the improvement of nutritional status through diet and nutritional supplementation, along with suggestion for an increase in exercise training. Osteoporosis is a disease of the skeletal system that is characterized by deterioration of bone tissue, along with a decrease in bone mass. It can strike anyone at any age, although it is most prevalent in Caucasian and Asian, small-boned women over 50. The term osteoporosis describes a condition inside the bones in which large porous areas develop, weakening the bone structure. Bone is a living tissue that maintains a balance through the bone-building activity of osteoblasts, with the reabsorptive activity of osteoclasts. When factors such as advancing age cause a change in this balance toward reabsorption, bone mass decreases. After reaching a fracture threshold, bone that was normally able to withstand a minor stress, such as a fall or blow, becomes subject to break or fracture more easily (Kamhi and Zampieron, 2010).

Calcium supplements reduce bone turnover and slow the rate of bone loss. However, few studies have demonstrated reduced fracture incidence with calcium supplements, and meta-analyses show only a 10% decrease in fractures, which is of borderline statistical and clinical significance. Trials in normal older women and in patients with renal impairment suggest that calcium supplements increase the risk of cardiovascular disease. To further assess their safety, we recently conducted a meta-analysis of trials of calcium supplements, and found a 27%–31% increase in risk of myocardial infarction, and a 12%–20% increase in risk of stroke. These findings are robust because they are based on pre-specified analyses of randomized, placebo-controlled trials and are consistent across the trials. Co-administration of vitamin D with calcium does not lessen these adverse effects. The increased cardiovascular risk with calcium supplements is consistent with epidemiological data relating higher circulating calcium concentrations to cardiovascular disease in normal populations. There are several possible pathophysiological mechanisms for these effects, including effects on vascular calcification, vascular cells, blood coagulation and calcium-sensing receptors. Thus, the non-skeletal risks of calcium supplements appear to outweigh any skeletal benefits, and are they appear to be unnecessary for the efficacy of other osteoporosis treatments (Reid, 2013).

1.12.2 Hypercalcemia

Moderate elevations of the concentration of Ca^{2+} in the extracellular fluid may have no clinically detectable effects. The degree of hypercalcemia and the rate of onset of the elevation in the serum calcium concentration largely dictate the extent of symptoms. Chronic elevation of serum Ca^{2+} to 12 to 14 mg/dl (3 to 3.5 mmol/L) generally causes few manifestations, whereas an acute rise to the same levels may cause marked neuromuscular manifestations owing to an increased threshold for excitation of nerve and muscle. Symptoms include fatigue, muscle weakness, anorexia, depression, diffuse abdominal pain, and constipation.

Hypercalcemia can result from a number of conditions. Ingestion of large quantities of calcium by itself generally does not cause hypercalcemia; exceptions are hyperthyroid subjects, who absorb Ca^{2+} with increased efficiency (Benker *et al.,* 1988), and subjects with the uncommon milk-alkali syndrome, a condition caused by concurrent ingestion of large quantities of milk and absorbable alkali, resulting in impaired renal Ca^{2+} excretion and attendant hypercalcemia.

In an outpatient setting, the most common cause of hypercalcemia is primary hyperparathyroidism, which results from hypersecretion of PTH by one or more parathyroid glands. Secondary hyperparathyroidism, in contrast, arises as a compensation for reductions of circulating Ca^{2+} and is not associated with hypercalcemia. Many of the difficulties with previous assays and, in conjunction with elevated serum calcium, possess a diagnostic accuracy of greater than 90% (Silverberg *et al.,* 2003).

Familial benign hypercalcemia (or familial hypocalciuric hypercalcemia) is a genetic disorder generally accompanied by extremely low urinary calcium excretion. Familial benign hypercalcemia results from heterozygous mutations in the Ca^{2+}-sensing receptor **(**Pollak *et al.*, 1996). Hypercalcemia usually is mild, and circulating PTH often is normal to slightly elevated. The importance of making this diagnosis lies in the fact that patients mistakenly diagnosed as having primary hyperparathyroidism may undergo surgical exploration without discovery of an adenoma and without therapeutic benefit. Patients do not experience long-term clinical consequences, except for homozygous infants, who may have severe, even lethal, hypercalcemia. Diagnosis is established by demonstrating hypercalcemia in first-degree family members and a decreased fractional excretion of calcium.

Newly diagnosed hypercalcemia in hospitalized patients is caused most often by a systemic malignancy, either with or without bony metastasis. PTH-related protein (PTHrP) is a primitive, highly conserved protein that may be abnormally expressed in malignant tissue, particularly by squamous cell and other epithelial cancers. The substantial sequence homology of the amino-terminal portion of PTHrP with that of native PTH permits it to interact with the PTH-1 receptor in target tissues, thereby causing the hypercalcemia and hypophosphatemia seen in humoral hypercalcemia of malignancy (Grill *et al.,* 1998). Other tumors release cytokines or prostaglandins that stimulate bone resorption. In some patients with lymphomas, hypercalcemia results from overproduction of 1,25-dihydroxyvitamin D by the tumor cells owing to expression of 1a-hydroxylase. A similar mechanism underlies the hypercalcemia that is seen occasionally in sarcoidosis and other granulomatous disorders.

Hypercalcemia associated with malignancy generally is more severe than in primary hyperparathyroidism (frequently with calcium levels that exceed 13 mg/dl) and may be associated with lethargy, weakness, nausea, vomiting, polydipsia, and polyuria. Assays for PTHrP may aid diagnosis.

1.12.3 Hypocalcemia

Mild hypocalcemia [i.e., reduction in ionized serum Ca^{2+} concentrations from normal to concentrations above 3.2 mg/dl (0.8 ml), approximately equal to a total serum Ca^{2+} concentration of 8 to 8.5 mg/dl (2 to 2.1 ml)] is usually asymptomatic. Again, the rapidity of change affects the clinical picture because patients exhibit greater signs and symptoms if the hypocalcemia develops acutely. The signs and symptoms of hypocalcemia include tetany and related phenomena such as paresthesias, increased neuromuscular excitability, laryngospasm, muscle cramps, and tonic-clonic convulsions. In chronic hypoparathyroidism, ectodermal changes ¾ consisting of loss of hair, grooved and brittle fingernails, defects of dental enamel, and cataracts ¾ are encountered; calcification in the basal ganglia may be seen on routine skull radiographs. Psychiatric symptoms such as emotional lability, anxiety, depression, and delusions often are present.

Combined deprivation of Ca^{2+} and vitamin D, as observed with malabsorption states or dietary deficiency, readily promotes hypocalcemia. When caused by malabsorption, hypocalcemia is accompanied by low concentrations of phosphate, total plasma proteins, and magnesium. Mg^{2+} deficiency may accentuate the hypocalcemia by diminishing the secretion and action of PTH. In infants with malabsorption or inadequate calcium intake, Ca^{2+} concentrations usually are depressed, with attendant hypophosphatemia resulting in rickets.

Pseudohypoparathyroidism is a diverse family of hypocalcemia and/or hyperphosphatemic disorders. Pseudohypoparathyroidism results from resistance to PTH rather than PTH deficiency; this resistance is not due to mutations of the PTH receptor but rather to mutations in G_sa (GNAS1), which normally mediates hormone-induced adenylyl cyclase activation (Yu *et al.*, 1999). The variable phenotypes arising from GNAS1 defects apparently are due to differential genomic imprinting of the maternal and paternal alleles. Multiple hormonal abnormalities have been associated with the GNAS1 mutation, but none is as severe as the deficient response to PTH.

Hypocalcemia is not unusual in the first several days following removal of a parathyroid adenoma. If hyperphosphatemia is also present, the condition is one of functional hypothyroidism owing to temporary failure of the remaining parathyroid glands to compensate for the missing adenomatous tissue. In patients with parathyroid bone disease, postoperative hypocalcemia associated with hypophosphatemia may reflect rapid uptake of calcium into bone, the "hungry bone" syndrome. In this setting, persistent, severe hypocalcemia may require administration of vitamin D and supplemental calcium for several months (Levine *et al.*, 2003).

Hypocalcemia is associated with advanced renal insufficiency accompanied by hyperphosphatemia. Many patients with this condition do not develop tetany unless the accompanying acidosis is treated, which decreases the ionized calcium. High concentrations of phosphate in plasma inhibit the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. Hypocalcemia also can occur following massive transfusions with citrated blood, which chelates calcium.

1.13 Minimum Dose of Calcium

For general supplementation purposes, the recommended Adequate Intakes (AIs) for calcium are as follows:

Table 1.3: Minimum Dose of Calcium. (Calcium Dosing Guidelines For General Supplementation.)

Age	Adequate Intakes (AIs)
0 to 6 months	210 mg daily
7 to 12 months	270 mg daily
1 to 3 years	500 mg daily
4 to 8 years	800 mg daily
9 to 18 years	1300 mg daily
19 to 50 years	1000 mg daily
51 years and older	1200 mg daily

The recommended Adequate Intake for pregnant or breastfeeding women is the same as for non-pregnant individuals. For nutrients that can cause toxicity, a "Tolerable Upper Intake Level" (UL) is given. This is the maximum that can be taken (from all sources, including the diet) without causing significant toxicity. The UL of calcium for infants up to 12 months old has not been established. For everyone else, the UL is 2500 mg (2.5 grams) daily.

1.14 Use of calcium

Calcium supplements are needed for patients who are unable to get enough calcium in their regular diet or who have a need for more calcium. They are used to prevent or treat several conditions that may cause hypocalcaemia. The body needs calcium for proper bone formation.

Calcium is also needed for the heart, muscles, and nervous system to work effectively. The bones serve as a storage site for the body's calcium. They are constantly exchanging calcium with the bloodstream and then replacing it as the body's need for calcium changes from day to day. If there is not enough calcium in the blood to be used by the heart and other organs, the body will absorb the calcium from the bones weakening the bones and causing osteoporosis. Pregnant women, nursing mothers, children, and adolescents may need more calcium than they normally get from eating calcium-rich foods. Post menopausal women may need to take calcium supplements to help prevent osteoporosis, which may occur in women after menopause.

1.15 Contraindications

Calcium may be contraindicated in Cardiac disease: Calcium by injection may increase the chance of cardiac arrhythmias. Hypocalcaemia, Hypercalciuria: Calcium supplements may worsen these conditions. Hyperparathyroidism, Sarcoidosis.

1.16 Precautions

Hypersensitivity reactions to the drug may occur. Precautions must be taken when taking the drug during pregnancy and lactation. It may also cause adverse effects in patients with renal disease.

1.17 Interactions

Cellulose sodium phosphate: Use with calcium supplements may decrease the effects of cellulose sodium phosphate. Digitalis glycosides: Use with calcium supplements by injection may increase the chance of Cardiac arrhythmias. Etidronate: Use with calcium supplements may reduce the potency of Etidronate. Magnesium sulfate: Use with calcium supplements may reduce its effectiveness. Phonation: Use with calcium supplements may reduce the effects of both drugs - calcium supplements should not be taken within 1 to 3 hours of Phenytoin. Oral Tetracycline: may decrease the potency of tetracycline, hence calcium supplements should not be taken within 1 to 3 hours of tetracycline’s (Lanham, 2008).

1.18 Calcium and body weight

Data from six observational studies and three controlled trials in which calcium intake was the independent variable (and either bone mass or blood pressure the original outcome variable) have been reanalyzed to evaluate the effect of calcium intake on body weight and body fat. Analysis reveals a consistent effect of higher calcium intakes, expressed as lower body fat and/or body weight, and reduced weight gain at midlife. Similarly, studies relating nutrient intake to body composition report negative associations between calcium intake and body weight at midlife and between calcium and body fat accumulation during childhood. There is a fairly consistent effect size, with each 300 mg increment in regular calcium intake associated with _1 kg less body fat in children and 2.5–3.0 kg lower body weight in adults. Taken together these data suggest that increasing calcium intake by the equivalent of two dairy servings per day could reduce the risk of overweight substantially, perhaps by as much as 70 percent (Heaney *et al.,* 2002)

1.2 Vitamin D

Vitamin D is the general name given to a group of fat-soluble compounds that are essential for maintaining the mineral balance in the body. Vitamin D (calciferol) comprises a group of fat soluble seco-sterols found naturally only in a few foods, such as fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. The two major physiologically relevant forms of vitamin D are D_2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D_3 is photosynthesized in the skin of vertebrates by the action of solar ultraviolet (UV) B radiation on 7-dehydrocholesterol (Fieser, 1959).

Vitamin D_2 is produced by UV irradiation of ergosterol, which occurs in molds, yeast, and higher-order plants. Under conditions of regular sun exposure, dietary vitamin D intake is of minor importance. However, latitude, season, aging, sunscreen use, and skin pigmentation influence the production of vitamin D_3 by the skin (Institute of Medicine 1997). Most of the dietary intake of vitamin D comes from fortified milk products and other fortified foods such as breakfast cereals and orange juice .Both vitamin D_2 and D_3 are used in nonprescription vitamin D supplements, but vitamin D_2 is the form available by prescription in the United States. As

cholecalciferol is synthesized in the skin by the action of ultraviolet light on 7-dehydrocholesterol, a cholesterol derivative, and vitamin D does not fit the classical definition of a vitamin. Nevertheless, because of the numerous factors that influence its synthesis, such as latitude, season, air pollution, area of skin exposed, pigmentation, age, etc., vitamin D is recognized as an essential dietary nutrient (Holick, 2007).

1.2.1. Physioloycal Roles of Vitamin D

- Favor calcium absorption from the intestine
- Promotes the absorption of phosphate
- Assist to govern the equilibrium between bone calcium and blood calcium.
- Promotes calcium mobilization from bone via reabsorption
- Helps in development of normal teeth.
- Maintain normal structure of bone and necessary for proper bone growth.
- Controls the retention of calcium and parathyroid level.
- Lowers the pH of colon, caecum, ileum and increase the urinary p^H simultaneously.
- Increase the citrate concentration in bone, blood and other tissue (Chatterjee, 1985).

1.2.2 Food Sources of Vitamin D

Table: 1.4 Vitamin D containing food

a) Salmon, Mackerel and Other Fatty Fish
b) Vitamin D_3 Fortified Milk or Raw milk**min**
c) Butter, Cheese, Egg
d) Cod Liver Oil and Other Fish Oils
e) Beef Liver, Chicken Liver and Pork Liver
f) Mushrooms

Very few foods in nature are good sources of vitamin D. This is one of the main reasons that vitamin D deficiency is so common, since it’s very easy to leave these foods out of our diet.

1.2.2.1 Salmon, Mackerel and Other Fatty Fish

Just 3 ounces of salmon, mackerel or other fatty fish contain over 400 IU of vitamin D. This amount alone is enough to prevent many deficiency-related issues such as rickets or depression.

1.2.2.2 Vitamin D3 Fortified Milk or Raw Milk

While the pasteurization process destroys much of milk's natural vitamin D content, most pasteurized milk is fortified with vitamin D3 to compensate. Drinking a glass or two of milk each day will help, and if we have access to raw milk and can afford it, it's a great investment in our health.

Figure 1.7: Vitamin D containing food

1.2.2.3 Butter, Cheese and Eggs

Like milk, all of these products contain vitamin D but it's difficult to eat them in high enough quantities to really compensate for a lack of sun exposure. One egg, for example, only has about 40 IU of vitamin D. keep in mind though that most people get the majority of their vitamin D intake from sun exposure.

1.2.2.4 Cod Liver Oil and Other Fish Oils

Perhaps it is the best natural source of vitamin D. One tablespoon of cod liver oil contains 1,360 IU of vitamin D. If we're worried about deficiency, cod liver oil (and other fish oils to a lesser extent) is great sources.

1.2.2.5 Beef Liver, Chicken Liver and Pork Liver

These and some other organ meats contain vitamin D, but to a lesser degree than cod liver oil. Liver and other organ meats offer a host of other health benefits, so it's worth incorporating them into our diet even if you're vitamin D levels are sufficient.

1.2.2.6 Other Fortified Foods

Many foods are now fortified with vitamin D, Which can range from margarine to breakfast cereals. The trouble with many of these foods is that they tend to be otherwise unhealthy. If we're unable to get sufficient vitamin D intake without eating fortified processed foods, it's generally best to eat more whole foods and take a vitamin D supplement.

1.2.3 Sun Exposure as a Source of Vitamin D in skin

Exposing our self to sunlight is the most important source of vitamin D because sunlight is far more likely to provide without vitamin D requirement than food. UV rays from the sun trigger vitamin D production in our skin. Lights from our home are not strong enough to produce vitamin D. Season, geographic latitude, time of day, cloud cover, smog, and sunscreen affect UV ray exposure and vitamin D synthesis (Guyton, 2003)

Vitamin D is essential for the control of normal calcium and phosphate blood levels. It is known to be required for the absorption of calcium and phosphate in the small intestine, their

mobilization from the bones, and their reabsorption in the kidneys. Through these three functions it plays an important role for the proper functioning of muscles, nerves and blood clotting and for normal bone formation and mineralization. It has been suggested that vitamin D also plays an important role in controlling cell proliferation and differentiation, immune responses and insulin secretion.

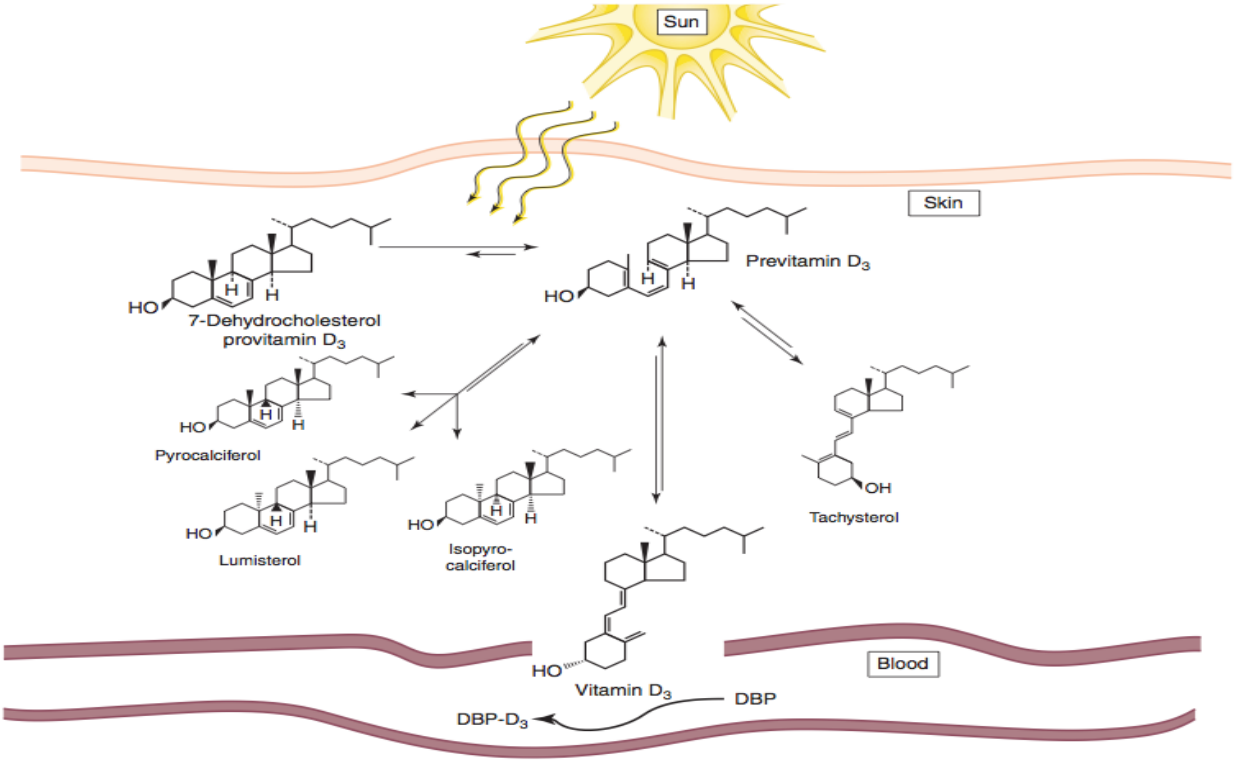


Figure 1.8: Synthesis of vitamin D in presence of UV light and absorption through skin

1.2.4 Conversion of cholecalciferol to Calcitriol in liver

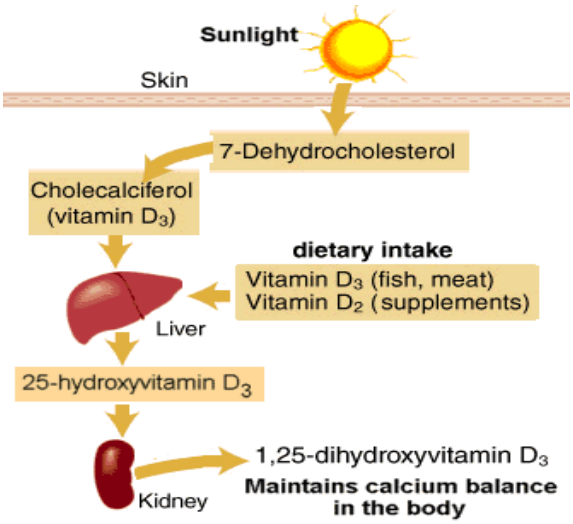


Figure 1.9: Conversion of cholecalciferol to Calcitriol in liver

1.2.5 Metabolism of Vitamin D

Vitamin D itself does not act upon intestine, kidney and bone but must be bioactivated in the liver and kidney. To be biologically activated at physiologic concentrations, Calcifediol [25(OH)D_3] must be converted in the kidneys to 1,25-dihydroxyvitamin D or Calcitriol [1,25$(OH)_2$D] which is thought to be responsible for most, if not all, of the biologic functions of vitamin D. The production of Calcifediol in the liver and of Calcitriol in the kidney is tightly regulated. In the liver, vitamin D-25-hydroxylase is down-regulated by vitamin D and its metabolites, thereby limiting any increase in the circulating concentration of Calcifediol following intakes or following production of vitamin D after exposure to sunlight. In the kidney, in response to serum calcium and phosphorus concentrations, the production of Calcitriol is regulated through the action of parathyroid hormone (PTH) (DeLuca 1988).

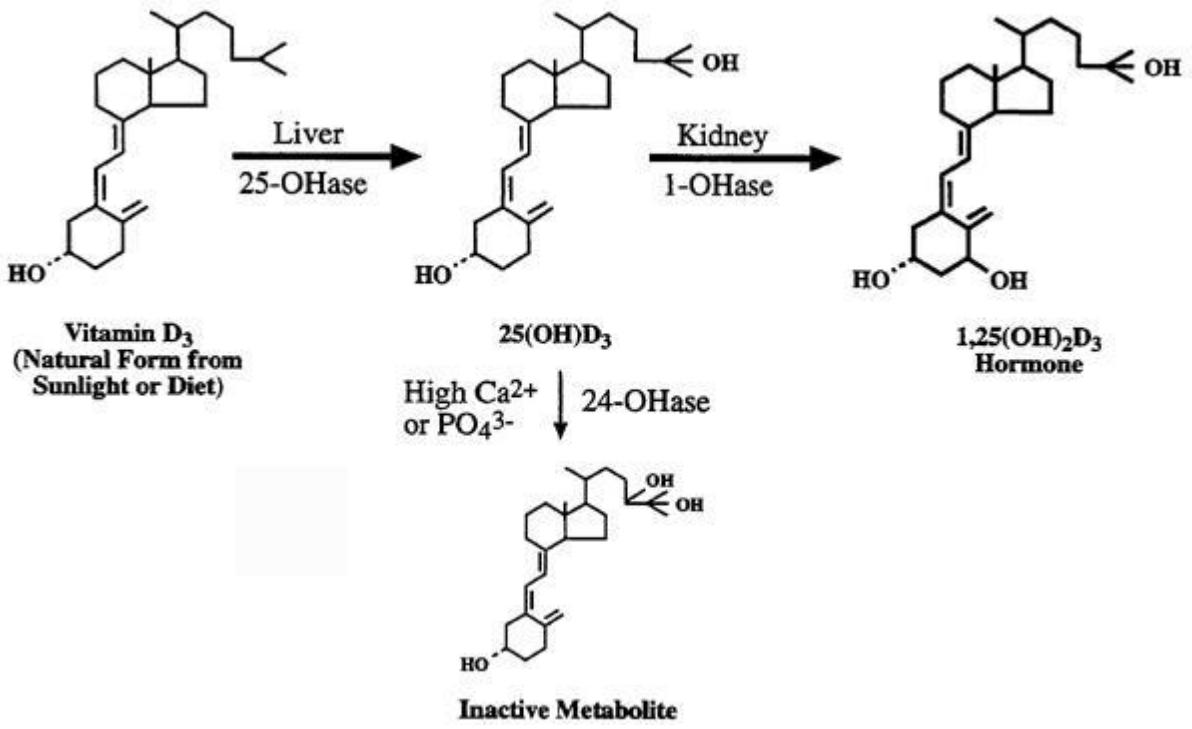


Figure 1.10: Metabolism of vitamin D

1.2.5.1 Metabolic Activation

Whether derived from diet or endogenously synthesized, vitamin D requires modification to become biologically active. The primary active metabolite of the vitamin is calcitriol [1a,25-dihydroxyvitamin D, $1,25(OH)_2D$], the product of two successive hydroxylation of vitamin D

1.2.5.2 25-Hydroxylation of Vitamin D

The initial step in vitamin D activation occurs in the liver, where cholecalciferol and ergocalciferol are hydroxylated in the 25-position to generate 25-OH-cholecalciferol (25-OHD, or calcifediol) and 25-OH-ergocalciferol, respectively. 25-OHD is the major circulating form of vitamin $D_{3;}$ it has a biological half-life of 19 days, and normal steady-state concentrations are 15 to 50 mg/ml. Reduced extracellular Ca^{2+} levels stimulate 1a-hydroxylation of 25-OHD, increasing the formation of biologically active $1,25(OH)_2D_3$. In contrast, when Ca^{2+}

concentrations are elevated, 25-OHD is inactivated by 24-hydroxylation. Similar reactions occur with 25-OH-ergocalciferol. Normal steady-state concentrations of 25-OHD in human beings are 15 to 50 mg/ml, although concentrations below 25 mg/ml may be associated with increased circulating PTH and greater bone turnover.

1.2.5.3. 24-Hydroxylase Calcitriol and 25-OHD are hydroxylated to 1, 24, $25(OH)_2D$ and $24,25(OH)_2D$, respectively, by another renal enzyme, 24-hydroxylase, whose expression is induced by calcitriol and suppressed by factors that stimulate the 25-OHD-1a-hydroxylase. Both 24-hydroxylated compounds are less active than calcitriol and presumably represent metabolites destined for excretion

Active vitamin D functions as a hormone, and its main biologic function in people is to maintain serum calcium and phosphorus concentrations within the normal range by enhancing the efficiency of the small intestine to absorb these minerals from the diet (DeLuca, 1988)**.** When dietary calcium intake is inadequate to satisfy the body's calcium requirement, $1,25(OH)_2D$, along with PTH, mobilizes calcium stores from the bone. In the kidney, $1,25(OH)_2D$ increases calcium reabsorption by the distal renal tubules. Apart from these traditional calcium-related actions, $1,25(OH)_2D$ and its synthetic analogs are increasingly recognized for their potent antiproliferative, prodifferentiative, and immunomodulatory activities (Nagpal *et at.,* 2005).

Calcitriol is known as the active "hormonal" form of vitamin D because:

- It stimulates calcium absorption more rapidly than other forms of vitamin D.
- It is more active on a molar basis than any other form.
- It is produced in kidney in a regulated fashion, based on the need for calcium and/or phosphate.
- It has specific receptors in intestine, bone and kidney.
- It chemically resembles the steroid hormones (Nagpal *et at.,* 2005).

1.2.6. Absorption and Excretion of vitamin D

Both vitamins D_2 and D_3 are absorbed from the small intestine, although vitamin D_3 may be absorbed more efficiently. Most of the vitamin appears first within chylomicrons in lymph. Bile is essential for adequate absorption of vitamin D; deoxycholic acid is the major constituent of

bile in this regard. The primary route of vitamin D excretion is the bile; only a small percentage is found in the urine. Patients who have intestinal bypass surgery or otherwise have severe shortening or inflammation of the small intestine may fail to absorb vitamin D sufficiently to maintain normal levels; hepatic or biliary dysfunction also may seriously impair vitamin D absorption.

Absorbed vitamin D circulates in the blood in association with vitamin D-binding protein, a specific α-globulin. The vitamin disappears from plasma with a half-life of 19 to 25 hours but is stored in fat depots for prolonged periods (Goodman and Gillman, 2002).

1.2.7 Regulation of Calcitriol (1, 25$(OH)_2D_3$) Production:

Calcitriol, the active form of vitamin D, is an important player in calcium and bone metabolism, but it also has a physiological role beyond its well-known role in skeletal homeostasis. Receptors for Calcitriol are present in various immune cells, including monocytes, macrophages and dendritic cells, as well as T and B lymphocytes, thus suggesting a role for Calcitriol in both innate and adaptive immune responses. Besides being targets, immune cells express vitamin D-activating enzymes, allowing local conversion of inactive vitamin D into Calcitriol within the immune system. Data from epidemiological studies are clear: vitamin D deficiency, especially in early life, increases the risk of autoimmune diseases later on and is associated overall with an increased risk of infections. Moreover, higher levels of Calcitriol are associated with relative protection against infections and autoimmune diseases. These association data are corroborated by experiments in preclinical animal models, where data exist that even supplementing with high doses of vitamin D or analogues of Calcitriol can interfere with the course of immune diseases, especially autoimmune diseases like colitis, multiple sclerosis and type 1 diabetes.

Vitamin D without a subscript represents either D_2 or D_3 or both and is biologically inert. Vitamin D from the skin or diet is only short-lived in circulation (with a half-life of 1–2 days), as it is either stored in fat cells or metabolized in the liver (Mawer *et al.,* 1972). In circulation, vitamin D is bound to vitamin D-binding protein and transported to the liver, where it is converted to 25-hydroxyvitamin D [25(OH)D] (DeLuca 1984). This major circulating form of vitamin D is a good reflection of cumulative effects of exposure to sunlight and dietary intake of vitamin D (Haddad 1973) and is therefore used by clinicians to determine vitamin D status.

1.2.8. Vitamin D Reinvented:

An important clue to roles of vitamin D beyond calcium homeostasis came with the finding that the 1,25-dihydroxyvitamin D nuclear receptor is present in most tissues. A reevaluation of the physiological and pharmacological actions of vitamin D produced evidence that vitamin D can regulate the immune system and thereby is implicated in several immune-mediated diseases. In addition the literature contains reports that vitamin D insufficiency may play a role in the development of multiple sclerosis, rheumatoid arthritis, and asthma, and increases the risk of tuberculosis, pneumonia, poor cognitive function, periodontal disease, and reduced muscle tone and lower-extremity function**.** (Holick 1995)

Several vitamin D supplementation studies have been reported, especially related to individual cancer types, and most show a modest positive effect. However, the most striking recent study based on vitamin D supplementation is the meta analysis of randomized control trials looking at total mortality .The authors identified 18 such trials of vitamin D intake that reported results for total mortality and found a 7% reduction in total mortality from any cause for patients, most taking relatively modest supplements of vitamin D (400–800 IU/day), compared to controls (Department of Clinical Biochemistry, Glasgow G4 OSF, United Kingdom).

1.2.9 Disorders of Vitamin D

1.2.9.1 Hypervitaminosis D

The acute or long-term administration of excessive amounts of vitamin D or enhanced responsiveness to normal amounts of the vitamin leads to derangements in calcium metabolism. The responses to vitamin D reflect endogenous vitamin D production, tissue reactivity, and vitamin D intake. Some infants may be hyper reactive to small doses of vitamin D. In adults, hypervitaminosis D results from overtreatment of hypoparathyroidism or secondary hyperparathyroidism of renal osteodystrophy and from faddist use of excessive doses. Toxicity in children also may occur following accidental ingestion of adult doses.

The amount of vitamin D necessary to cause hypervitaminosis varies widely. As a rough approximation, continued daily ingestion of 50,000 units or more by a person with normal

parathyroid function and sensitivity to vitamin D may result in poisoning. Hypervitaminosis D is particularly dangerous in patients who are receiving digoxin because the toxic effects of the cardiac glycosides are enhanced by hypercalcemia.

The initial signs and symptoms of vitamin D toxicity are those associated with hypercalcemia. Since hypercalcemia in vitamin D intoxication generally is due to very high circulating levels of 25-OHD, the plasma concentrations of PTH and Calcitriol typically (but not uniformly) are suppressed. In children, a single episode of moderately severe hypercalcemia may arrest growth completely for 6 months or more, and the deficit in height may never be fully corrected. Vitamin D toxicity in the fetus is associated with excess maternal vitamin D intake or extreme sensitivity and may result in congenital supravalvular aortic stenosis. In infants, this anomaly frequently is associated with other stigmata of hypercalcemia.

1.2.9.2 Hypevitaminosis D

Vitamin D deficiency results in inadequate absorption of Ca^{2+} and phosphate. The consequent decrease of plasma Ca^{2+} concentration stimulates PTH secretion, which acts to restore plasma Ca^{2+} at the expense of bone. Plasma concentrations of phosphate remain subnormal because of the phosphaturic effect of increased circulating PTH. In children, the result is a failure to mineralize newly formed bone and cartilage matrix, causing the defect in growth known as rickets. As a consequence of inadequate calcification, bones of individuals with rickets are soft, and the stress of weight bearing gives rise to bowing of the long bones.

In adults, vitamin D deficiency results in osteomalacia, a disease characterized by generalized accumulation of undermineralized bone matrix. Severe osteomalacia may be associated with extreme bone pain and tenderness. Muscle weakness, particularly of large proximal muscles, is typical and may reflect both hypophosphatemia and inadequate vitamin D action on muscle. Gross deformity of bone occurs only in advanced stages of the disease. Circulating 25-OHD concentrations below 8 ng/ml are highly predictive of osteomalacia.

1.2.9.3 Metabolic Rickets and Osteomalacia These disorders are characterized by abnormalities in calcitriol synthesis or response.

1.2.9.3.1 Hypophosphatemic vitamin D-resistant rickets

In its most common form, is an X-linked disorder (XLH) of calcium and phosphate metabolism. Calcitriol levels are inappropriately normal for the observed degree of hypophosphatemia. Patients experience clinical improvement when treated with large doses of vitamin D, usually in combination with inorganic phosphate. Even with vitamin D treatment, calcitriol concentrations may remain lower than expected. The genetic basis for XLH has been defined (HYP Consortium, 1995). The affected protein, a phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), is a neutral endoprotease. The substrate for this enzyme likely is involved in renal phosphate transport. Syndromes closely related to XLH, in which phosphate levels are altered without significant net changes in serum concentrations of calcium, PTH, or $1,25(OH)_2D_3$, include hereditary hypophosphatemic rickets with hypercalciuria (HHRH) and autosomal dominant hypophosphatemic rickets. The latter disorder maps to chromosome 12p13.3 and is associated with mutations in the gene encoding fibroblast growth factor 23 (Econs et al., 1997)

1.2.9.3.2 Vitamin D-dependent rickets (also called vitamin D-dependent rickets type I)

Is an autosomal recessive disease caused by an inborn error of vitamin D metabolism involving defective conversion of 25-OHD to calcitriol owing to mutations in CYP1α (1α-hydroxylase). The condition responds to physiological doses of calcitriol (White et al., 2001).

1.2.9.3.3 Hereditary 1,25-dihydroxyvitamin D resistance (also called vitamin D-dependent rickets type II)

Is an autosomal recessive disorder that is characterized by hypocalcemia, osteomalacia, rickets, and total alopecia. Mutations of the vitamin D receptor cause vitamin D-dependent rickets type II (Malloy *et al.,* 1999). Absolute hormone resistance results from premature stop mutations or missense mutations in the zinc finger DNA-binding domain. Several missense mutations in the ligand-binding domain also have been described that result in partial or complete hormone

resistance. These mutations alter ligand binding or heterodimerization with the retinoid X receptor (RXR).

The 25(OH)-vitamin D values are normal, whereas $1,25(OH)_2$-vitamin D levels are elevated in type II vitamin D-dependent rickets. This clinical feature distinguishes hereditary vitamin D-dependent rickets type II from CYP1α deficiency (vitamin D-dependent rickets type I), where serum 1,25(OH)2-vitamin D values are depressed. Children affected by vitamin D-dependent rickets type II are refractory even to massive doses of vitamin D and calcitriol, and they may require prolonged treatment with parenteral Ca^{2+}. Some remission of symptoms has been observed during adolescence, but the basis of remission is unknown.

1.2.9.3.4 Renal osteodystrophy (renal rickets) is associated with chronic renal failure and is characterized by decreased conversion of 25-OHD to calcitriol. Phosphate retention decreases plasma Ca^{2+} concentrations, leading to secondary hyperparathyroidism. In addition, calcitriol deficiency impairs intestinal Ca^{2+} absorption and mobilization from bone. Hypocalcemia commonly results (although in some patients, prolonged and severe hyperparathyroidism eventually may lead to hypercalcemia). Aluminum deposition in bone also may play a role in the genesis of the skeletal disease (Goodman and Gillman, 2002).

1.2.10 Minimum Dose of Vitamin D

Naturalness ‘In the wide world of supplements, vitamin D is the superstar. For the last few years, this humble nutrient has been featured prominently in allopathic and alternative circles alike. It has basked in the rays of media publicity, and has survived an onslaught of scientific scrutiny. And while such widespread publicity is often good cause for skepticism in the realm of health and medicine, vitamin D appears to be the real deal. Whether we`re talking about heart disease, cancer, diabetes, multiple sclerosis, or Alzheimer`s disease, the "sunshine vitamin" delivers benefits unseen before our time.

1.2.11 Factors affect vitamin D status:

1.2.11.1 Sun Exposure:

Catching some rays each day is definitely desirable, and healthy young people can usually get the vitamin D they need from around 10 to 30 minutes of sun exposure per day - depending on their location and the time of year. Most adults in today`s modern world, however, do not even attempt to get this much sun exposure - much less achieve it. Location: Vitamin D is produced in the skin from a cholesterol derivative when we are exposed to UVB radiation from the sun. However, because of the axial tilt of the earth, the further north one lives, the less the sun`s UV B rays will be able to activate vitamin D in the skin. So sun exposure does not necessarily equal optimal vitamin D status if you`re living in the wrong location. Living down south is better, of course but there is still more to consider.

1.2.11.2 Age:

Say we do live close to the equator, or are significantly below the 35 N latitude line. That`s a good thing, and it probably helps. If around 35-40 years old or above, however, we`re likely losing the ability to activate sufficient levels of vitamin D in your skin, even in the unlikely event that we`re getting adequate UVB sun exposure .

1.2.11.3 Dark Skin:

If we have a lot of pigment in your skin, this is going to shield from the UVB radiation we need, and our probably deficient in vitamin D.

1.2.11.4 Weight:

Vitamin D requirements are also relative to body weight. If overweight, our body requires more vitamin D than if we are not overweight.

1.2.11.5 Chronic Illness:

The body demands more vitamin D when we`re sick, and is probably using it up faster than we can get it from the sun.

1.2.11.6 Kind of Supplements should use

In order to achieve consistent and predictable results, it is important to use the proper carrier form of vitamin D supplements. The absolute best form is an oil-based vitamin D preparation. Dry preparations, like tablets and capsules, should be avoided. Vitamin D is fat soluble, and needs to be taken with fat in order to be properly absorbed - hence the oil-based recommendation. There are two common types of vitamin D: Vitamin D_3 (cholecalciferol) and Vitamin D_2 (ergocalciferol). Will need to avoid supplementing with vitamin D_2 which is a synthetic product made by exposing certain plants to ultraviolet radiation. D_2 is not what the human body naturally uses, and compared to D3 it falls far short in terms of efficacy.

1.2.12 Our Body Uses Vitamin D

Vitamin D is a fat-soluble vitamin that promotes absorption of calcium and phosphorus. Most people associate the nutrient calcium with healthy bones and teeth, but no matter how much calcium we have in your diet, without vitamin D, our body can't absorb and use the mineral. So vitamin D is vital for building — and holding — strong bones and teeth.

Researchers at the Bone Metabolism Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston say vitamin D may also reduce the risk of tooth loss by preventing the inflammatory response that leads to periodontal disease, a condition that destroys the thin tissue (ligaments) that connects the teeth to the surrounding jawbone.

Vitamin D comes in three forms: calciferol, cholecalciferol, and ergocalciferol. Calciferol occurs naturally in fish oils and egg yolk. In the United States, it's added to margarines and milk. Cholecalciferzl is created when sunlight hits our skin and ultraviolet rays react with steroid chemicals in body fat just underneath. Ergocalciferol is synthesized in plants exposed to sunlight. Cholecalciferol and ergocalciferol justify vitamin D's nickname: the Sunshine Vitamin.

1.2.13 Vitamin D Deficiency

Vitamin D deficiency is characterized by inadequate mineralization or by demineralization of the skeleton. Among children, vitamin D deficiency is a common cause of bone deformities known as rickets. Vitamin D deficiency in adults leads to a mineralization defect in the skeleton, causing osteomalacia, and induces secondary hyperparathyroidism with consequent bone loss and

osteoporosis. Potential roles for vitamin D beyond bone health, such as effects on muscle strength, the risk for cancer and for type 2 diabetes, are currently being studied. The Agency for Healthcare Research and Quality recently reviewed the effectiveness and safety of vitamin D on outcomes related to bone health (Cranney *et al,* 2007).

1.2.13.1 Risk factors for vitamin D deficiency include:

• Black & ethnic minority patients with darker skin

• Elderly patients in residential care, housebound or institutionalised patients

• Older people aged 65 years and over

• Infants and young children under 5 years of age

• Intestinal malabsorption e.g. coeliac disease, crohns disease, gastrectomy, cholestatic liver disease

• Routine covering of face or body e.g. habitual sunscreen use factor 15 or above

• Vegan/vegetarian diet

• Liver or renal disease

• Medications including certain anticonvulsants, cholestyramine, colestipol, liquid paraffin,

sucralfate, rifampicin, glucocorticoids, highly active antiretrovirals

• Obesity (BMI >30)

• All pregnant and breast feeding women, especially teenagers and young women

• Short interval pregnancies

• Patients with persistently low calcium, low phosphate or raised Alkaline Phosphatase

• Low vitamin D dietary intake

• Cystic fibrosis

• If one family member is Vitamin D deficient it is likely others in the family may also be deficient, unless that person has a specific medical condition

Research indicates vitamin D deficiency is a causal factor in all facets of human health, as shown below (Sievenpiper et al, 2008).

Brain and Mind

Alzheimer's	Depression	Insomnia
Anxiety	Insomnia	Irritability
Autism	Multiple Sclerosis	Reduced IQ
Brain birth-defects	Fatigue and malaise	Schizophrenia
Dementia	Parkinson's	Psychosis

Body

Aneurysm	Hypertension	Muscle wasting
Arthritis and pain	Hip fractures	Osteoarthritis
Asthma	Hypothyroid	Osteoporosis
Chronic pain	Hemorrhoids	Periodontal disease
Diabetes	Migraines	Rickets
Fibromyalgia	Multiple sclerosis	Seizure
Heart disease	Muscle weakness	Stroke

Immune System

varieties of cancer Common colds Common flues & H1N1

Once foods were fortified with vitamin d and rickets appeared to have been conquered, many health care professionals thought the majorhealth problems resulting from vitamin D deficiency had been resolved. However,rickets can be considered the tip of the vitamin D–deficiency iceberg. In fact, vitamin D deficiency remains common in children and adults. In uteri and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia andmuscle weakness, and increase the risk of fracture.The discovery that most tissues and cells in the body have a vitamin D

receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease. (Pearce and Cheetham, 2010)

1.2.13.2 Cancer

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic,prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes.55‑65Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 mg per milliliter are associated with a30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers**.** (Holick,2004)

1.2.13.3 Autoimmune Diseases, Osteoarthritis, and Diabetes

Living at higher latitudes increases the risk of type 1 diabetes, multiple sclerosis, and Crown's disease.68,69 Living below 35 degrees latitude for the first 10 years of life reduces the risk of multiple sclerosis by approximately 50%.69,70 Among white men and women, the risk of multiple sclerosis decreased by 41% for every increase of 20 ng per milliliter in 25-hydroxyvitamin D above approximately24 mg per milliliter(60 mol per liter) Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing multiple sclerosis.72 Similar observations have been made for rheumatoid arthritis73 and osteoarthritis.74 Several studies suggest that vitamin D supplementation in children reduces the risk of type

1diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet auto antibodies in offspring.53 For 10,366 children in Finland who were given 2000 IU of vitamin D_3 per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80%.75 Among children with vitamin D deficiency the risk was increased by approximately 200%. In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome.53 Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D. (Holick,2004)

1.2.13.4 Cardiovascular Disease

Living at higher latitudes increases the risk of hypertension and cardiovascular disease.54,77 In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25-hydroxyvitamin D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mm Hg).78 Vitamin D deficiency is associated with congestive heart failure54 and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.54,79 Vitamin D Deficiency and Other Disorders. (Holick, 2004)

1.2.13.5 Schizophrenia and Depression

Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression. 80,81 Maintaining vitamin D sufficiency in uteri and during early life, to satisfy the vitamin D receptor transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.

1.2.13.6 Lung Function and Wheezing Illnesses

Men and women with a 25-hydroxyvitamin D level above 35 ng per milliliter (87 mol per liter) had the Children of women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for wheezing illnesses.

1.2.14 Mal absorption and Medication of vitamin D

Patients with mild or moderate hepatic failure or intestinal fat-mal absorption syndromes, as well as patients who are taking anticonvulsant medications, glucocorticoids, or other drugs that

activate steroid and xenobiotic receptor, require higher doses of vitamin D .Exposure to sunlight or ultraviolet B radiation from a tanning bed or other ultraviolet B–emitting device is also effective. Sunlight and Artificial Ultraviolet B Radiation Sensible sun exposure can provide an adequate amount of vitamin D_3, which is stored in body fat and released during the winter.

1.2.15 Vitamin D Toxicity

Too much vitamin D can be harmful, it certainly can - though anything can be toxic in excess, even water. As one of the safest substances known to man, vitamin D toxicity is very rare. In fact, people are at far greater risk of vitamin D deficiency than they are of vitamin D toxicity. Vitamin D toxicity is a condition where blood serum concentrations of vitamin D's storage form, 25(OH)D or calcidiol, become too high, causing adverse systemic effects.

1.2.15.1 Toxic doses

What exactly constitutes a toxic dose of vitamin D has yet to be determined, though it is possible this amount may vary with the individual. Published cases of toxicity, for which serum levels and dose are known, all involve intake of ≥ 40000 IU (1000 mcg) per day. Two different cases involved intake of over 2,000,000 IU per day - both men survived.

1.2.15.2 Serum levels

Upper limit and toxicity threshold Upper limit for a substance is the amount up to which is considered safe and without risk of adverse effects in the majority of the population. Toxicity threshold for a substance is the amount beyond which over-saturation occurs and symptoms of toxicity manifest. These values for 25(OH)D are as follows: Toxicity threshold level - 200-250 mg/mol (500-750 mol/L) Upper limit - 100 mg/mL (250 mol/L)

1.2.15.3 Symptoms: toxicity and overdose

Signs of vitamin D toxicity are high urine and blood calcium

The first sign of vitamin D toxicity is hypercalciuria (excess calcimine the urine) followed by hypercalcemia (high bloodcalcium). The following symptoms may present :

- vomiting
- poor appetite
- constipation (possibly alternating with diarrhea)
- weakness
- weight loss
- tingling sensations in the mouth
- confusion
- heart rhythm abnormalities
- The immediate symptoms of vitamin D overdose are:
- abdominal cramps
- nausea and vomiting

It is fairly difficult to become toxic using vitamin D3. If we think we may be toxic because we

are having an adverse reaction to vitamin D but we have not been using excessive amounts like those described above, or symptoms could be due to reasons other than toxicity.

If the results show a serum 25(OH)D level of 200-250 ng/mol (500-750 mol/L) or more, it could be toxic. The following measures should be taken until vitamin D levels return to normal:

- avoidance of direct sunlight exposure
- avoidance of foods and supplements containing vitamin D
- restriction of calcium intake
- drinking 8 glasses of water daily

In most cases, vitamin D toxicity can be corrected without lasting problems, provided the body has not remained in a hypercalcemia state for too long. Hypocalcaemia has the potential to cause soft tissue calcification, resulting in deposits of calcium crystals in the heart, lungs, and/or

kidneys. With prolonged hypercalcemia, permanent damage is possible if calcification is severe enough.

1.2.16 Use of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism

During exposure to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol in the skin is converted to previtamin D3, which is immediately converted to vitamin D3 in a heat-dependent process. Excessive exposure to sunlight degrades previtamin D3 and vitamin D3 intoInactive photoproducts. Vitamin D2 and vitamin D3 from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D (hereafter "D" represents D2 or D3) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D–binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to25-hydroxyvitamin D. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status.

1.2.17 Analogs of Calcitriol

Several vitamin D analogs suppress PTH secretion by the parathyroid glands but have less or negligible hypercalcemic activity. They therefore offer a safer and more effective means of controlling secondary hyperparathyroidism.

Calcipotriol (calcipotriene) is a synthetic derivative of calcitriol with a modified side chain that contains a 22-23 double bond, a 24(S)-hydroxy functional group, and carbons 25 to 27 incorporated into a cyclopropane ring. Calcipotriol has comparable affinity with calcitriol for the vitamin D receptor, but it is less than 1% as active as calcitriol in regulating calcium metabolism. This reduced calcemic activity largely reflects the pharmacokinetics of calcipotriol (Kissmeyer and Binderup, 1991). Calcipotriol has been studied extensively as a treatment for psoriasis (see Chapter 62), although its mode of action is not known; a topical preparation (DOVONEX) is available for that purpose. In clinical trials, topical calcipotriol has been found to be slightly more effective than glucocorticoids with a good safety profile.

Paricalcitol (1,25-dihydroxy-19-norvitamin D_2, ZEMPLAR) is a synthetic calcitriol derivative that lacks the exocyclic C19 and has a vitamin D_2 rather than vitamin D_3 side chain. It reduces serum PTH levels without producing hypercalcemia or altering serum phosphorus (Martin et al., 1998). In an animal model, paricalcitol prevented or reversed PTH-induced high-turnover bone disease (Slatopolsky et al., 2003). Paricalcitol administered intravenously is FDA approved for treating secondary hyperparathyroidism in patients with chronic renal failure.

22-Oxacalcitriol (1,25-dihydroxy-22-oxavitamin D_3, OCT, maxicalcitol, OXAROL) differs from calcitriol only in the substitution of C-22 with an oxygen atom. Oxacalcitriol has a low affinity for vitamin D-binding protein; as a result, more of the drug circulates in the free (unbound) form, allowing it to be metabolized more rapidly than calcitriol with a consequent shorter half-life. Oxacalcitriol is a potent suppressor of PTH gene expression and shows very limited activity on intestine and bone. It is a useful compound in patients with overproduction of PTH in chronic renal failure or even with primary hyperparathyroidism (Cunningham, 2004).

1.2.18 Indications for Therapy with Vitamin D

The major therapeutic uses of vitamin D may be divided into four categories: (1) prophylaxis and cure of nutritional rickets; (2) treatment of metabolic rickets and osteomalacia, particularly in the setting of chronic renal failure; (3) treatment of hypoparathyroidism; and (4) prevention and treatment of osteoporosis (discussed in the section on osteoporosis).

1.2.18.1 Nutritional Rickets

Nutritional rickets results from inadequate exposure to sunlight or deficiency of dietary vitamin D. The condition, once extremely rare in the United States and other countries where food fortification with the vitamin is practiced, is now increasing. Infants and children receiving adequate amounts of vitamin D-fortified food do not require additional vitamin D; however, breast-fed infants or those fed unfortified formula should receive 400 units of vitamin D daily as a supplement. The usual practice is to administer vitamin A in combination with vitamin D. A number of balanced vitamin A and D preparations are available for this purpose. Since the fetus acquires more than 85% of its calcium stores during the third trimester, premature infants are especially susceptible to rickets and may require supplemental vitamin D.

Treatment of fully developed rickets requires a larger dose of vitamin D than that used prophylactically. One thousand units daily will normalize plasma Ca^{2+} and phosphate concentrations in approximately 10 days, with radiographic evidence of healing within about 3 weeks. However, a larger dose of 3000 to 4000 units daily often is prescribed for more rapid healing, particularly when respiration is compromised by severe thoracic rickets.

Vitamin D may be given prophylactically in conditions that impair its absorption (e.g., diarrhea, steatorrhea, and biliary obstruction). Parenteral administration also may be used in such cases.

1.2.18.2 Treatment of Osteomalacia and Renal Osteodystrophy

Osteomalacia, distinguished by undermineralization of bone matrix, occurs commonly during sustained phosphate depletion. Patients with chronic renal disease are at risk for developing osteomalacia but also may develop a complex bone disease called renal osteodystrophy. In this setting, bone metabolism is stimulated by an increase in PTH and by a delay in bone mineralization that is due to decreased renal synthesis of calcitriol. In renal osteodystrophy, low bone mineral density may be accompanied by high-turnover bone lesions typically seen in patients with uncontrolled hyperparathyroidism or by low bone remodeling activity seen in patients with adynamic bone disease. The therapeutic approach to the patient with renal osteodystrophy depends on its specific type. In high-turnover (hyperparathyroid) or mixed high-turnover disease with deficient mineralization, dietary phosphate restriction, generally in combination with a phosphate binder, is recommended because phosphate restriction is limited by the need to provide adequate protein intake to maintain nitrogen balance. Although highly effective, aluminum is no longer used as a phosphate binder because it promotes adynamic bone disease, anemia, myopathy, and occasionally dementia. Calcium-containing phosphate binders along with calcitriol administration may contribute to oversuppression of PTH secretion and likewise result in adynamic bone disease and an increased incidence of vascular calcification. Highly effective non-calcium-containing phosphate binders have been developed. Sevelamer hydrochloride (RENAGEL), a nonabsorbable phosphate-binding polymer, effectively lowers serum phosphate concentration in hemodialysis patients, with a corresponding reduction in the calcium× phosphate product. Sevelamer hydrochloride consists of cross-linked poly[allylamine hydrochloride] that is resistant to digestive degradation. Partially protonated amines spaced one carbon from the polymer backbone chelate phosphate ions by ionic and hydrogen bonding. Side

effects of sevelamer include vomiting, nausea, diarrhea, and dyspepsia. Sevelamer does not affect the bioavailability of digoxin, warfarin, enalapril, or metoprolol. (Monier-Faugere *et al.*, 2001)

Renal osteodystrophy associated with low bone turnover (adynamic bone disease) is increasingly common and may be due to oversuppression of PTH with aggressive use of either calcitriol or other vitamin D analogs. While PTH levels generally are low (<100 pg/ml), a high PTH level does not exclude the presence of adynamic bone disease, especially with PTH assays that do not distinguish between biologically active and inactive PTH fragments. Current guidelines suggest that treatment with an active vitamin D preparation is indicated if serum 25-OHD levels are less than 30 ng/ml and serum calcium is less than 9.5 mg/dl (2.37 mM). However, if 25-OHD and serum calcium levels are elevated, vitamin D supplementation should be discontinued. If the serum calcium level is less than 9.5 mg/dl, treatment with a vitamin D analog is warranted irrespective of the 25-OHD level (Eknoyan *et al*., 2003).

1.2.18.3 Hypoparathyroidism

Vitamin D and its analogs are a mainstay of the therapy of hypoparathyroidism. Dihydrotachysterol (DHT) has a faster onset, shorter duration of action, and a greater effect on bone mobilization than does vitamin D and traditionally has been a preferred agent. Calcitriol also is effective in the management of hypoparathyroidism and certain forms of pseudohypoparathyroidism in which endogenous levels of calcitriol are abnormally low. However, most hypoparathyroid patients respond to any form of vitamin D. Calcitriol may be preferred for temporary treatment of hypocalcemia while awaiting effects of a slower-acting form of vitamin D.

1.2.19 Miscellaneous uses of Vitamin D

Vitamin D is used to treat hypophosphatemia associated with Fanconi syndrome. Large doses of vitamin D (over 10,000 units/day) are not useful in patients with osteoporosis and even can be dangerous. However, administration of 400 to 800 units/day of vitamin D to frail, elderly men and women has been shown to suppress bone remodeling, protect bone mass, and reduce fracture incidence (see later section on osteoporosis). Clinical trials suggest that calcitriol may become an important agent for the treatment of psoriasis. As such nontraditional uses of vitamin D are

discovered, it will become important to develop noncalcemic analogs of calcitriol that achieve effects on cellular differentiation without the risk of hypercalcemia **(Kowalzick, 2001).**

1.2.20 Adverse Effects of Vitamin D Therapy

The primary toxicity associated with calcitriol reflects its potent effect to increase intestinal calcium and phosphate absorption, along with the potential to mobilize osseous calcium and phosphate. Hypercalcemia, with or without hyperphosphatemia, commonly complicates calcitriol therapy and may limit its use at doses that effectively suppress PTH secretion. As described earlier, noncalcemic vitamin D analogs provide alternative interventions, although they do not obviate the need to monitor serum calcium and phosphorus concentrations.

Hypervitaminosis D is treated by immediate withdrawal of the vitamin, a low-calcium diet, administration of glucocorticoids, and vigorous fluid support. As noted earlier under hypercalcemia, forced saline diuresis with loop diuretics is also useful. With this regimen, the plasma Ca^{2+} concentration falls to normal, and Ca^{2+} in soft tissue tends to be mobilized. Conspicuous improvement in renal function occurs unless renal damage has been severe. (Goodman and Gillman, 2002)

Chapter 2

Methodology

2 Methodology

2.1 Type of the study

The present study was performed on a cross sectional observation which was attempted to find out the awareness of college going student in Dhaka and out of Dhaka.

2.2 Place of study

2.2.1 Holy cross college

Figure 2.1: Holy Cross College

2.2.2 Govt. Biggan College

Figure 2.2: Govt. Biggan College

2.2.3 Dhaka City College

Figure 2.3: Dhaka City College

2.3 Study Population

In the present study, the survey conducted as cross-selection at the different colleges in Dhaka. At the colleges my survey sample was drawn from the target college students & the information is obtained from the sample once by questioning them & collecting the information provided by them.

2.4 Study period

Study period was 2 months commencing from October 2013 to November 2013. To complete the study in time, a work schedule was prepared depending on different tasks of the study. One month were spent for selection of topic, development of the protocol. One month were spent on official correspondence, data collection, data analysis, report writing and submission of report.

2.5 Sample size and Sampling Technique

In the present study, I was provided with questionnaires sheet as a representative of the survey which was going nationwide. A total of 10 questions were processed for students of different colleges. In this survey only the students were included. Total of 693 questionnaires sheet were processed from the students of different colleges of Dhaka.

2.6 Data collection method

This paper & pencil survey consisted of multiple choice questions. An English language survey was developed based on information drawn from relevant literatures pertaining to general awareness of Calcium & Vitamin D at the college level students. Questionnaires for students covered their tendency to take Calcium & Vitamin D prescription in terms of diseases severity, deficiency, food sources, and other relevant information. Questionnaires were given only to the spontaneously interested candidates during the survey. The participants were requested to respond to the question and then the questionnaires were filled up by the representatives.

2.7 Data analysis

All the data were checked after collection. Then data were entered into computer and results were calculated with Microsoft® Excel 2007. The results were shown in Column and Pie diagrams.

2.8 Sample of questionnaire

QUESTIONNAIRE

Questionnaire about the awareness of Calcium & Vitamin D among college going students in Bangladesh

01. Have you ever heard the name of calcium as a food supplement?

Yes	No

02. Have you ever heard about vitamin D?

Yes	No

03. Can you mention two (2) calcium containing food's name?

a)
b)

04. Can you mention two (2) vitamin D containing food's name?

a)
b)

05. How often do you drink milk?

	Daily		Weekly		Monthly		Yearly		Never

06. How long do you remain in sun exposure per day?

	Less than 1hr
	Greater than 1hr
	Greater than 2hr
	Greater than 3hr
	Greater than 4hr
	Greater than 5hr

07. Have you ever heard the term "osteoporosis"?

Yes	No

08. Have you ever been prescribed any calcium supplement by a physician?

Yes	No

09. Have you ever been prescribed any vitamin D supplement by a physician?

Yes	No

10. From which source you have come to know about calcium & vitamin D?

	Relatives		Teacher		Physician
	Books		Internet		Others

Chapter 3

Result and Discussion

3. Result:

3.1: Tejgon College:

Total Population	125
Girls	84
Boys	41

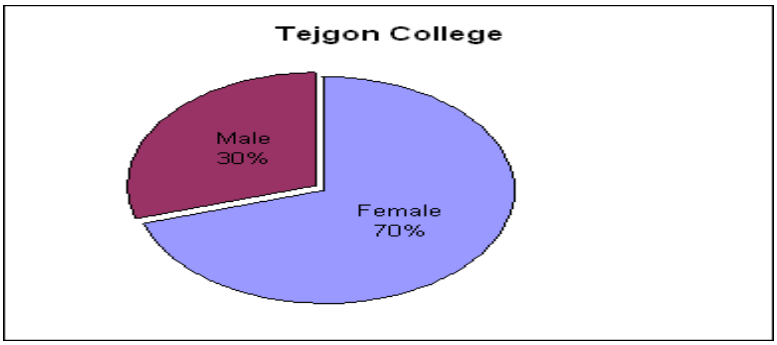


Figure 3.1: Male & Female students (%) of Dhaka Tejgon College.

3.2: City College:

Total Population	147
Girls	94
Boys	53

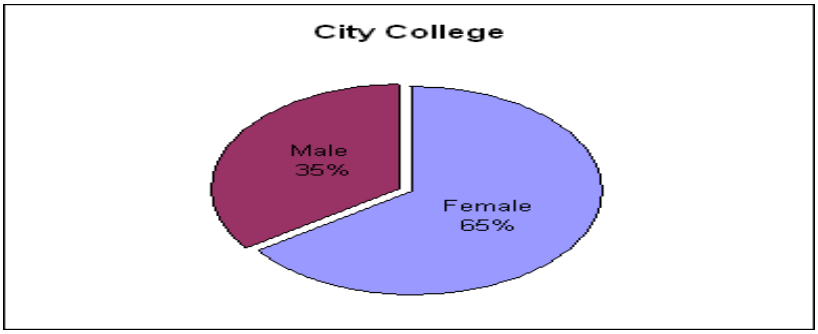


Figure 3.2: Male & Female students (%) of Dhaka City College.

3.3:B. A. F. Shahin College:

Total Population	88
Girls	52
Boys	36

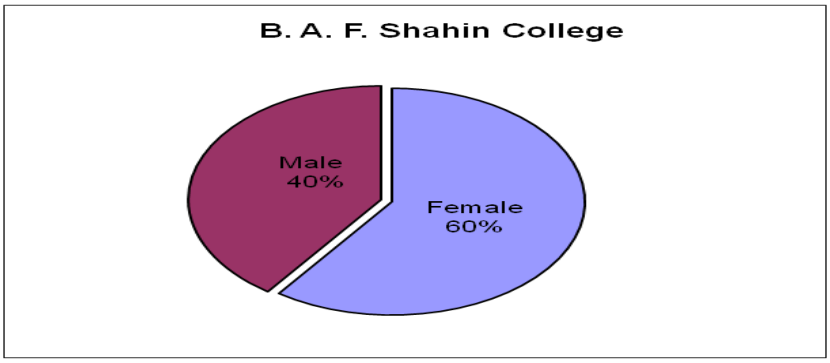


Figure 3.3: Male & Female students (%) of B.A.F. Shahin College.

3.4: B. N. College:

Total Population	125
Girls	84
Boys	41

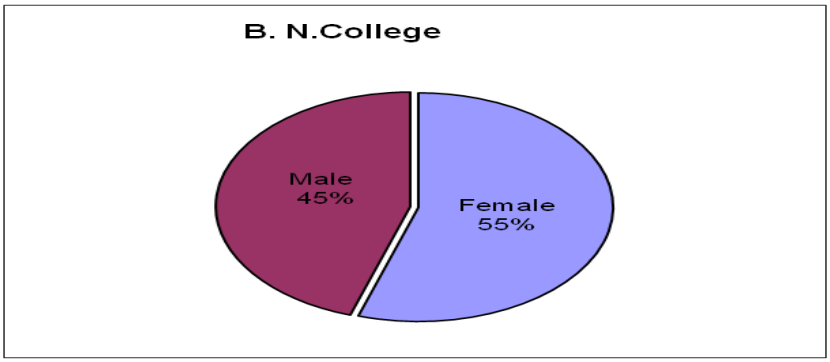


Figure 3.4: Male & Female students (%) of B. N. College.

3.5: Holy Cross College:

Total Population	166
Girls	166
Boys	0

3.6: Govt. Biggan College:

Total Population	58
Girls	0
Boys	58

1. Have you ever heard about Calcium?

Total Population	693
Yes	519
No	174

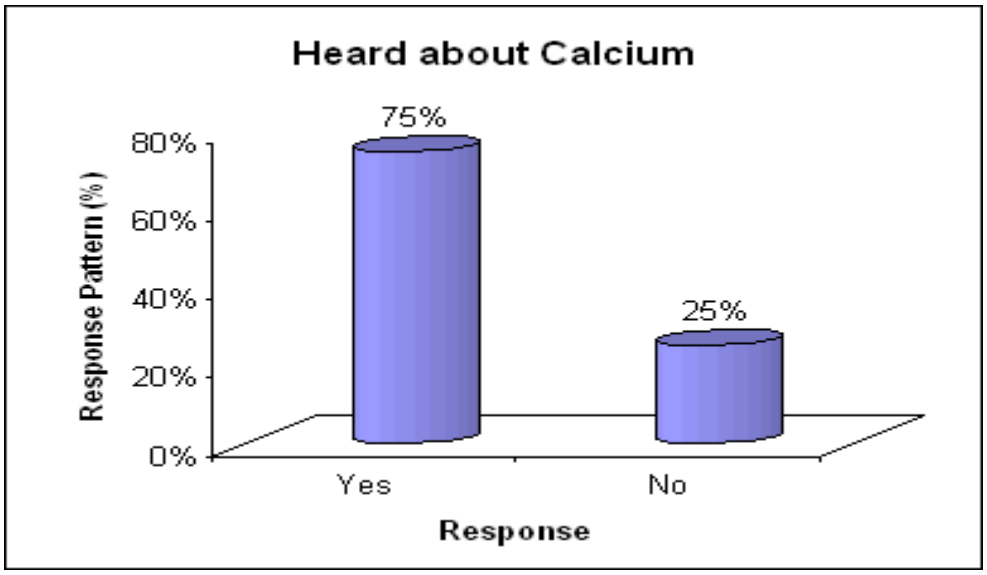


Figure 3.5 : Heard about Calcium response pattern.

2. Have you ever heard about vitamin D?

Total Population	693
Yes	554
No	139

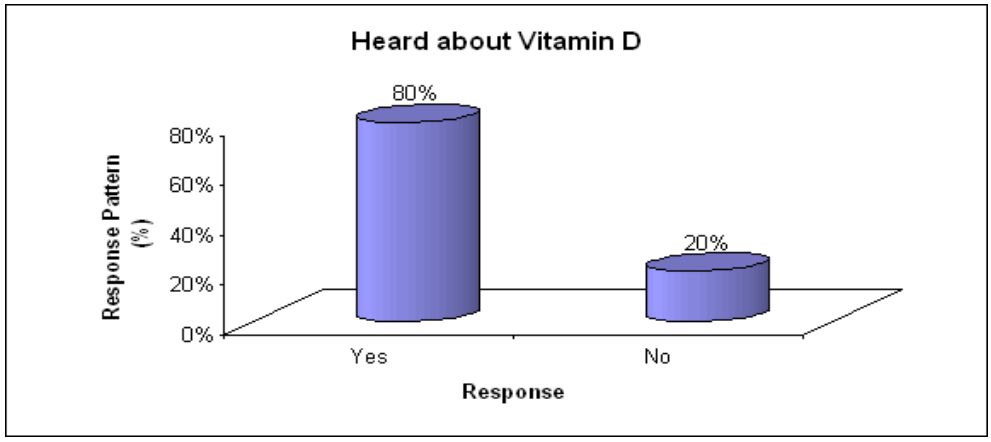


Figure 3.6: Heard about vitamin D response pattern.

3. Can you mention two (2) calcium containing food's name?

Total Population	693
Milk	286
Sea Fish	59
Meat	82
Cheeses	71
Others(Mango, Orange, Vegetable, Ladies finger)	193

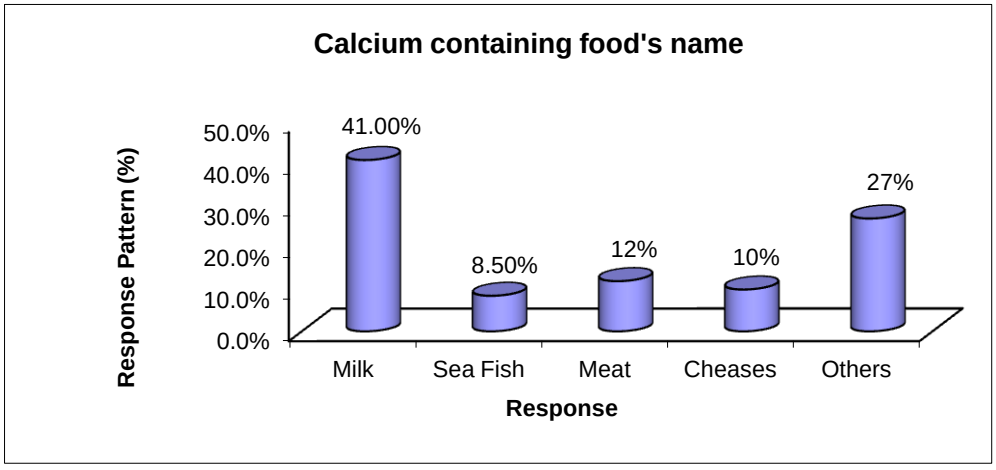


Figure 3.7: Calcium containing food's name

4. Can you mention two (2) vitamin D containing food's name?

Total Population	693
Milk	297
Liver	73
Meat	90
Banana	75
Others (Rice, Horlicks, Ice-cream, Fruits, Vegetable)	76

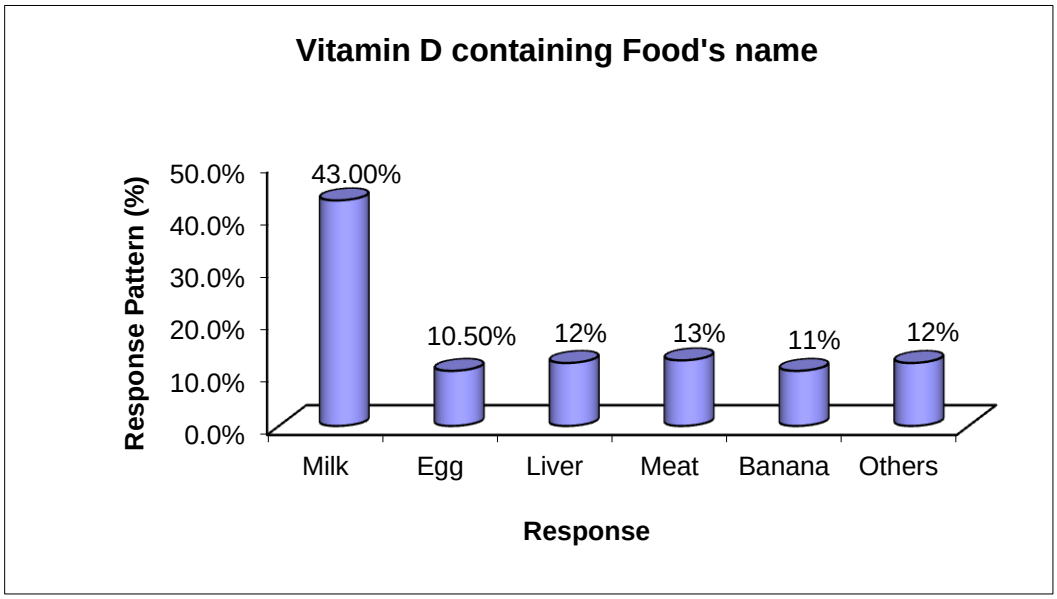


Figure 3.8: Vitamin D containing food's name

5. How often do you drink milk?

Total Population	693
Daily	214
Weekly	151
Monthly	138
Yearly	97
Never	91

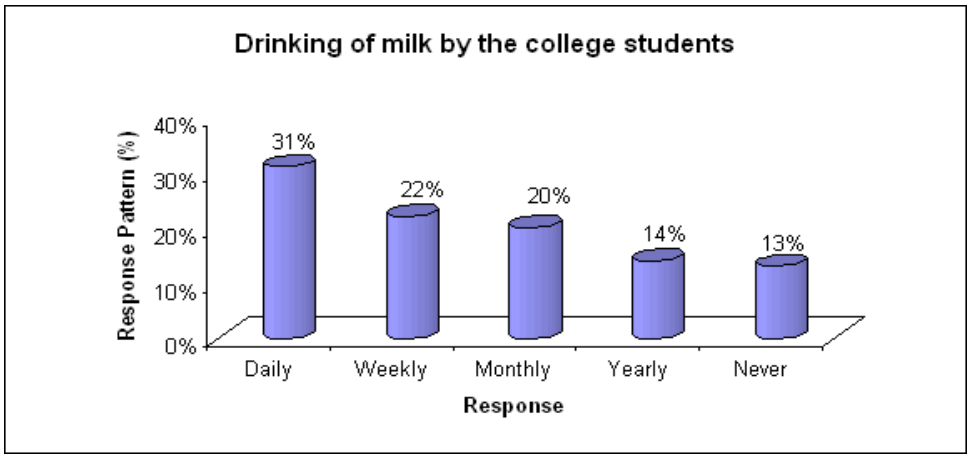


Figure 3.9: Drinking of milk by the college going students.

6. How long do you remain in sun exposure per day?

Total Population	693
Less than 1hr	104
Greater than 1hr	243
Greater than 2hr	174
Greater than 3hr	83
Greater than 4hr	55
Greater than 5hr	34

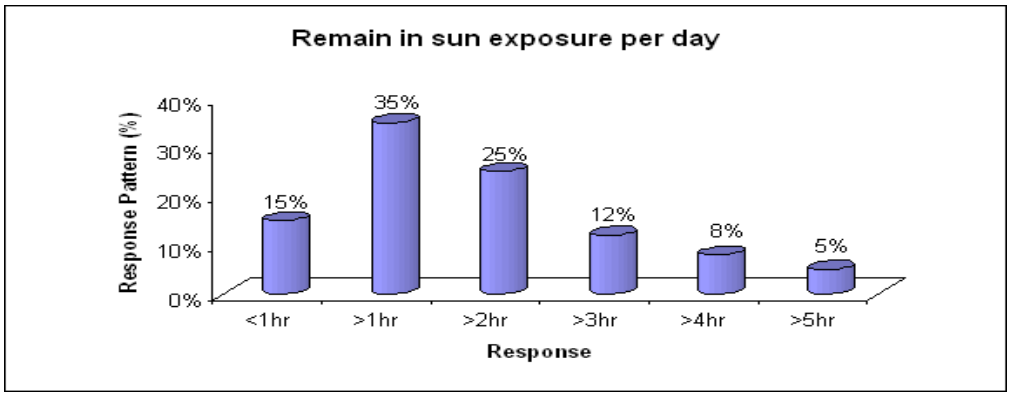


Figure 3.10: Remain in sun exposure per day response pattern.

7. Have you ever heard the term “osteoporosis”?

Total Population	693
Yes	153
No	540

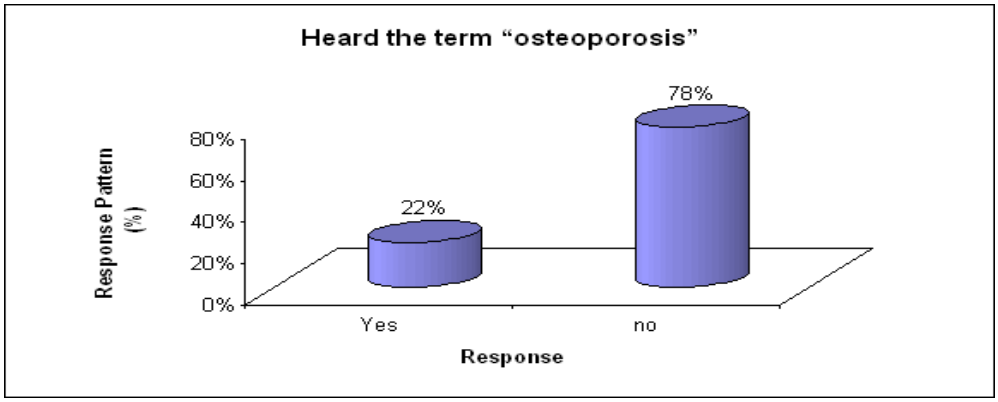


Figure 3.11: Hearing the term of “Osteoporosis”

8. Have you ever been prescribed any calcium supplement by a physician?

Total Population	693
Yes	450
No	243

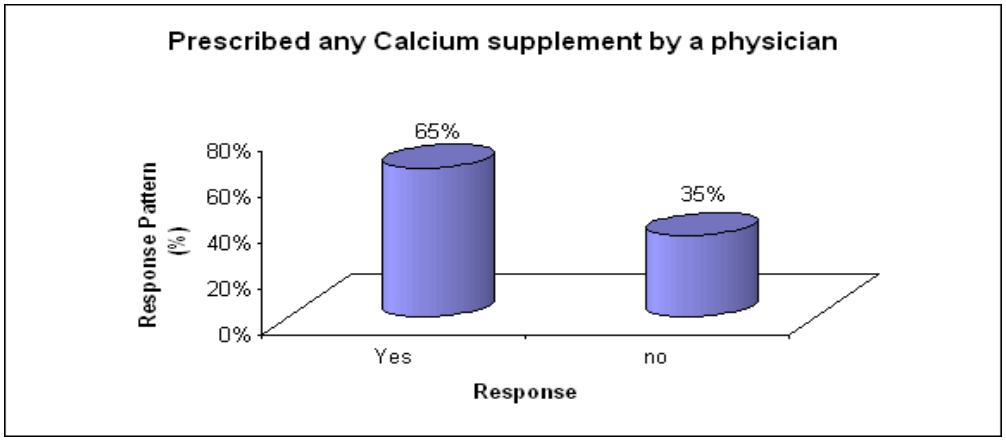


Figure 3.12: Prescribed any Calcium supplement by a physician

9. Have you ever been prescribed any vitamin D supplement by a physician?

Total Population	693
Yes	485
No	208

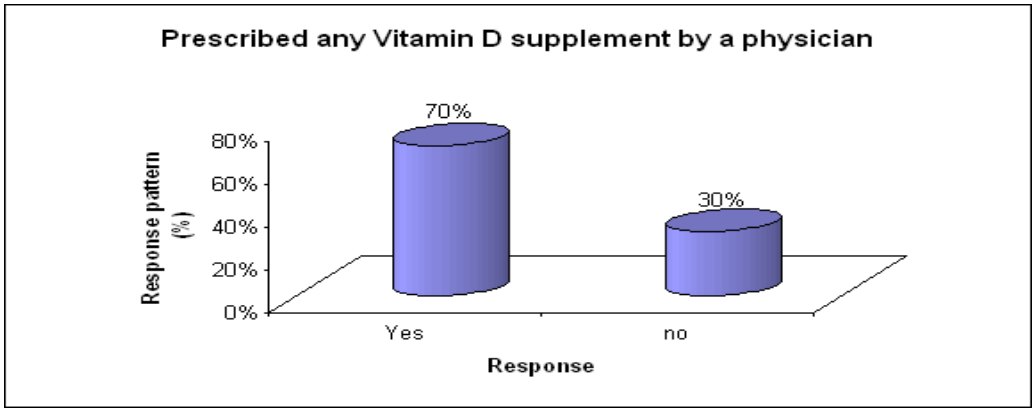


Figure 3.13: Prescribed any Vitamin D supplement by a physician.

10. From which source you have come to know about calcium & or vitamin D?

Total Population	693
Relative	103
Teacher	103
Physician	69
Books	311
Internet	38
Others	69

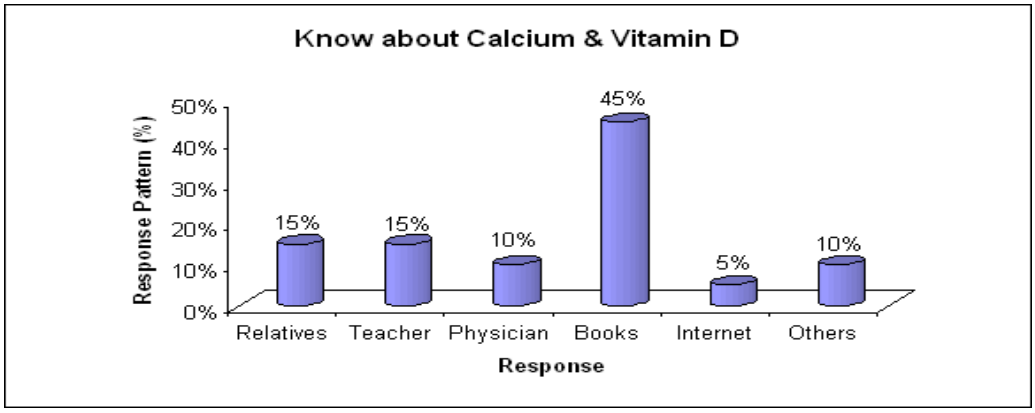


Figure 3.14: know about calcium & or vitamin D

Discussion

The students were asked to mention name of two foods containing calcium. From the survey it was found that about the 75% & 80% college going students know Calcium & Vitamin D as a food supplement while 25% & 20% do not know about the Calcium & Vitamin D. The college going students have come to largely know about milk (41%), Sea fish (8.5%), Meat (12%), Cheeses (10.5%) and others (27%) as Calcium containing food.

They also know about Meat(13%),Liver(12%),Milk(43%),Eggs(10.5%),Banana(10.5%),Others (12%) as a Vitamin D containing food. On the basis of drinking milk is response mainly daily (31%).They remain in the high sun exposure per day like >1hr (35%). (65%) and (70%) ever been prescribed any Calcium & Vitamin D supplement by a physician while (35%) and (30 %) ever not been prescribed.

The students were asked about the source of their knowledge and information they know about calcium and vitamin D. Interestingly most of the students answered that they first knew about calcium and vitamin D from either from textbooks (45%) and their teacher (15%). 15% answered that they first came to know about these mineral and vitamin from their family members and relatives.

From the responses it was observed that both calcium and vitamin D are equally known among the male and female students. Female students are more familiar with the term osteoporosis than the male students. The term of “Osteoporosis” are known (22%) of college going students while (78%) & do not know about it.

The students who are studying college are expected to have adequate knowledge of the essentiality of calcium and vitamin D and the consequences due to lack of calcium and vitamin D. From the current study it was observed that most of the students were familiar with calcium and vitamin D as food supplement. But it seems that they are only familiar to the terminologies, but they do not have sufficient knowledge about the sources from where calcium and vitamin D can be obtained.

One interesting finding of the study is that, most of the students first heard about calcium and/vitamin D from academic sources (from their teachers and textbooks). In Bangladesh the students read a chapter on the vitamins in primary education level. This reflects that the inclusion of such topics in the primary education level is justified and relevant. On the other hand it is alarming that only 15% of students heard the name of calcium and vitamin D from the parents, relatives or from their family. It is expected that the family will be first place for learning for a child.

Vitamin D and calcium deficiency is so common as to represent a major public health problem. It has re-emerged as a global public-health concern and is now linked to a range of infectious, inflammatory and neoplastic diseases throughout the life course and around the world. Country specific sufficient data regarding the use, consumption of calcium and vitamin D for Bangladesh is not available though some studies have been conducted for the determination of vitamin D and calcium status.

Chapter 4

Conclusion

Conclusion

Calcium and Vitamin D are the important component of a healthy diet and a mineral necessary for life. The National foundation says, “Calcium plays an important role in building stronger, denser bones early in life and keeping bones strong and healthy later in life”. Approximately 99% of body’s calcium is stored in the bones & teeth. The rest of the calcium in the body has other important uses, such as some exocytose. The effects of vitamin D supplementation on health are uncertain. A United States Institute of Medicine, (IOM) report states: "Outcomes related to cancer, cardiovascular disease and hypertension, diabetes and metabolic syndrome falls and physical performance, immune functioning & autoimmune disorders, infections, neuropsychological functioning, and preeclampsia could not be linked reliably with calcium or vitamin D intake and were often conflicting. So the questions regards to safety and efficacy awareness of calcium and vitamin D among college going students in Bangladesh.

From this survey, we have come to know that the students who are studying college do not have adequate knowledge of essential nutrients, minerals, vitamins etc. College students have a long academic background related to general biological science. If they have gap of knowledge about calcium and vitamin D, the general people may know little about these food supplements. The government and policy makers should pay attention about improving this situation by utilizing mass media and print media to increase awareness regarding calcium and vitamin D.

Chapter 5

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