A SURVEY ON AWARENESS OF CALCIUM & VITAMIN D AMONG WOMEN IN DHAKA CITY

A Dissertation submitted to the Department of Pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy

Submitted by

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Declaration by the Research Candidate

I, **Monika Hossain Khan**, **ID: 2013-1-70-010** hereby declare that the dissertation entitled-- **Awareness of Calcium & Vitamin D among Women in Dhaka City.** Submitted by me to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of degree of Bachelor of Pharmacy is a record of research work under the supervision and guidance of **Farah Shahjin**, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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<u>Certificate by the Supervisor</u>

This is to certify that the thesis entitled **“Awareness of Calcium and Vitamin D among Women in Dhaka City”** submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of degree of Bachelor of Pharmacy is a Bona Fide record of original and genuine research work carried out by **Monika Hossain Khan**, **ID: 2013-1-70-010** in 2016 of her research in the Department of Pharmacy, East West University, under the supervision and guidance of me.

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Certificate by the Chairperson

This is to certify that the thesis entitled **"Awareness of Calcium and Vitamin D among Women in Dhaka City"** submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of degree of Bachelor of Pharmacy is a Bona Fide record of original and genuine research work carried out by **Monika Hossain Khan**, **ID: 2013-1-70-010** in 2016.

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Dedication

This research work is dedicated to my beloved parents,

Who are my biggest Inspirations and to

My Research Supervisor,

Honorable faculties and loving friends.

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Abbreviation

AI	Adequate Intake
AV node	Atrioventricular node
Ca	Calcium
CaR	Calcium Receptor
cAMP	cyclic Adenosine monophosohate
CKD	Chronic Kidney Disease
CCB	Calcium Channel Blocker
DV	Daily Value
EDTA	Ethylenediaminetetraacetic acid
ECF	Extra Cellular Fluid
GNAS1	Guanine Nucleotide binding protein Alpha Stimulating gene
GFR	Glomerular Filtration Rate
ICF	Intra Cellular Fluid
IU	International Unit
PTH	Para Thyroid Hormone
RDA	Recommended Dietary Allowance
SA node	Sinoatrial node
UV	Ultra Violet

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. The aim of the study is to aware women about Calcium and Vitamin D, to aware them about the diseases that occur due to Calcium and Vitamin D deficiency and to make people conscious about their dietary health. The present study was designed and conducted to establish a basic understanding on the level of gap of knowledge and awareness among women in Bangladesh. In this study purposive sampling technique was followed. After collecting, the data were checked and analyzed with the help of Microsoft Excel 2007. The result was shown in bar, pie and column chart and calculated the percentage of the knowledge attitude and perception regarding awareness of calcium and vitamin D. Majority of the women have not been prescribed calcium supplement for bone disorder. Lack of awareness and insufficient knowledge of the essentiality of these two nutrients are assumed to cause this problem in Bangladesh. From the survey it was found that about the 90% & 92% women know Calcium & Vitamin D as a food supplement while 10% & 8% do not know about the Calcium & Vitamin D. They have come to largely know about milk (50%), Egg (19%) as Calcium containing food. On the basis of drinking milk is response mainly daily (40%). 37% and 35% ever been prescribed any Calcium & Vitamin D supplement by a physician while 63% and 65% ever not been prescribed. most of the women answered that they first knew about calcium and vitamin D from either from textbooks (58%) and their family (56%) or from doctor (40%). The term of "Osteoporosis" is known to 35% of women while 65% do not know about it. From this survey, we have come to know that the women who are non science background do not have adequate knowledge of essential nutrients, minerals, vitamins etc. If they have gap of knowledge about calcium and vitamin D, their children 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.

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

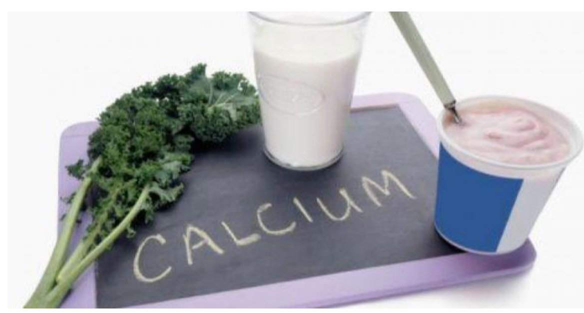
Chapter One

Introduction

1. INTRODUCTION

1.1 Calcium

Calcium (Ca^{2+}), the most abundant mineral in the body, is found in some foods, added to others, available as a dietary supplement, and present in some medicines (such as antacids). Calcium is required for vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signaling and hormonal secretion, though less than 1% of total body calcium is needed to support these critical metabolic functions. Serum calcium is very tightly regulated and does not fluctuate with changes in dietary intakes; the body uses bone tissue as a reservoir for, and source of calcium, to maintain constant concentrations of calcium in blood, muscle, and intercellular fluids.



The remaining 99% of the body's calcium supply is stored in the bones and teeth where it supports their structure and function. Bone itself undergoes continuous remodeling, with constant resorption and deposition of calcium into new bone. The balance between bone resorption and deposition changes with age. Bone formation exceeds resorption in periods of growth in children and adolescents, whereas in early and middle adulthood both processes are relatively equal. In aging adults, particularly among postmenopausal women, bone breakdown exceeds formation, resulting in bone loss that increases the risk of osteoporosis over time (National Institutes of Health, 2016).

The normal adult man and women posses about 1300 and 1000 gm of Ca^{2+} . Ca2+ is present in small amount in extracellular fluids and to a minor extent within the cell. (Goodman and Gillman,2002). 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. (Parfitt, 1988).

1.2 Sources of Calcium

The main calcium contenders are milk, yogurt, and cheese, but dairy shouldn't be the only dietary pit stop to fill up on this nutrient. Leafy greens, seafood, legumes, and fruit also contain calcium and many foods and drinks are fortified with the mineral.

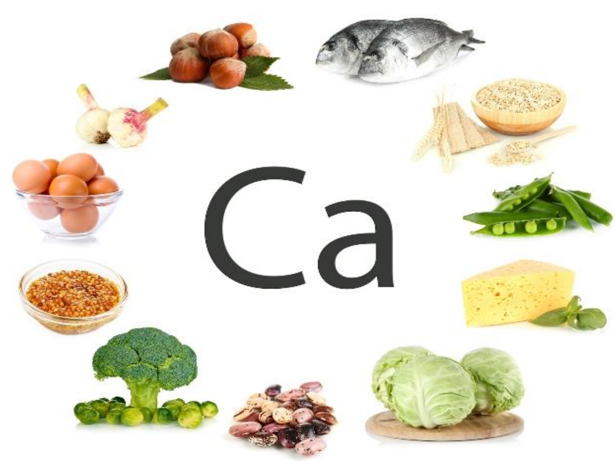


Figure: 1.2.1 Food Sources of calcium (Autajay, 2003).

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).

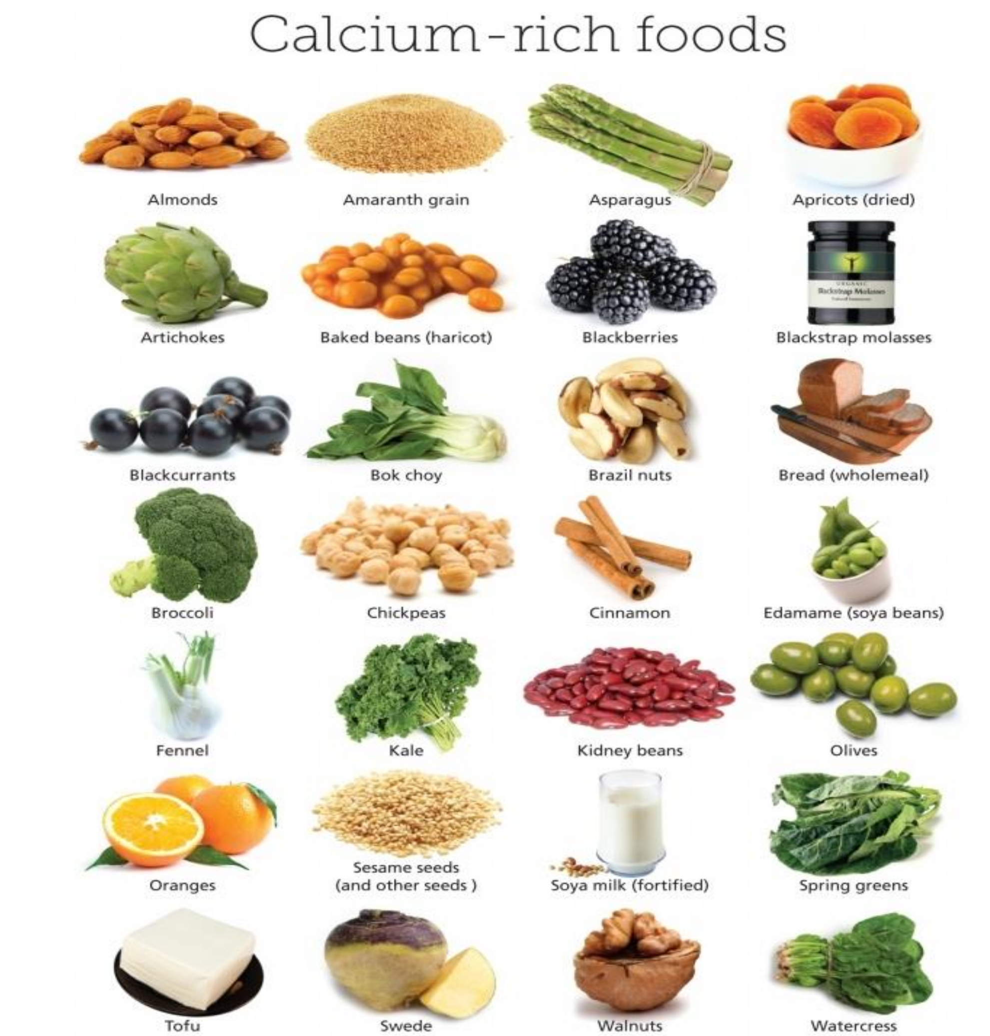


Figure: 1.2.2 Calcium rich foods (Mineravita,2015)

Table 1.2 : Selected Food Sources of Calcium

Food	Milligrams (mg) per serving	Percent DV*
Yogurt, plain, low fat, 8 ounces	415	42
Mozzarella, part skim, 1.5 ounces	333	33
Sardines, canned in oil, with bones, 3 ounces	325	33
Yogurt, fruit, low fat, 8 ounces	313–384	31–38
Cheddar cheese, 1.5 ounces	307	31
Milk, nonfat, 8 ounces**	299	30
Soymilk, calcium-fortified, 8 ounces	299	30

Table 1.2 : Selected Food Sources of Calcium		
Food	**Milligrams (mg) per serving**	**Percent DV***
Milk, reduced-fat (2% milk fat), 8 ounces	293	29
Milk, buttermilk, lowfat, 8 ounces	284	28
Milk, whole (3.25% milk fat), 8 ounces	276	28
Orange juice, calcium-fortified, 6 ounces	261	26
Tofu, firm, made with calcium sulfate, ½ cup***	253	25
Salmon, pink, canned, solids with bone, 3 ounces	181	18
Cottage cheese, 1% milk fat, 1 cup	138	14
Tofu, soft, made with calcium sulfate, ½ cup***	138	14
Ready-to-eat cereal, calcium-fortified, 1 cup	100–1,000	10–100
Frozen yogurt, vanilla, soft serve, ½ cup	103	10
Turnip greens, fresh, boiled, ½ cup	99	10
Kale, raw, chopped, 1 cup	100	10
Kale, fresh, cooked, 1 cup	94	9
Ice cream, vanilla, ½ cup	84	8
Chinese cabbage, bok choi, raw, shredded, 1 cup	74	7
Bread, white, 1 slice	73	7
Pudding, chocolate, ready to eat, refrigerated, 4 ounces	55	6
Tortilla, corn, ready-to-bake/fry, one 6" diameter	46	5
Tortilla, flour, ready-to-bake/fry, one 6" diameter	32	3
Sour cream, reduced fat, cultured, 2 tablespoons	31	3
Bread, whole-wheat, 1 slice	30	3
Broccoli, raw, ½ cup	21	2
Cheese, cream, regular, 1 tablespoon	14	1

* DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet.

1.3 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, Ca2+, 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 Ca2+ from bone, reabsorption in the kidney back into circulation, and increases in the activation of vitamin D3 to Calcitriol. Calcitriol, the active form of vitamin D3, 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.

1.4 Physiological role of calcium

- **Participates in the structure of bones and teeth**: At least 99% of the total amount of calcium is in the bones and teeth. Calcium in the bones is transformed into a hydroxyapatite - $Ca_{10}(PO_4)_6(OH)_2$ but the bones also contain significant amounts of calcium phosphate, carbonate, citrate, fluoride, magnesium, strontium, trace and minor amounts of other salts. Minerals account about 50% of the total bone mass. The rest is organic matrix in which are proteins, glycoproteins and proteoglycans that bind calcium salts. Every day in the bones can be exchanged up to 700 mg of calcium. The immediate source of calcium for bones is calcium from the body fluids and cells. Although the this amount of calcium is small (<10 g) compared to the amount of bone it is critically important for the regulation surprisingly large number of cellular activities.
- **Metabolic regulation**: This is one of the main roles of calcium. Protein kinases, which modulate the activity of key enzymes as a response to hormone binding to the surface of cells, are calcium activated - either directly, or binding to a protein that binds calcium - *calmodulin*.

- **Regulation of cellular activity**: These include nerve and muscle function, hormone action, blood coagulation, cell motility, and many others. Regulates muscle contraction by regulating the contractility of *actin* and *myosin*. Since it participate in such a large number of cellular regulation it is also called the "*second messenger*".
- **Intermediates in the reaction of cells to various stimuli**: The way of this action is analogous to the regulatory actions of cyclic nucleotides. Effect of calcium is mediated by an intracellular receptor protein - *calmodulin*, which binds calcium ions when their concentration in the reaction to the stimulus increases. Calmodulin has been found in every studied cell that contains the nucleus. When Ca^{2+} binds to calmodulin it activity many enzymes, and among them are those who participate in the metabolism of cyclic nucleotides, protein phosphorylation, secretory function, muscle contraction, the formation of microtubules, glycogen metabolism and calcium flux. It were found that potent inhibitors of calmodulin activity are phenothiazine drugs that relax the smooth muscles of several peptides that are found in poisonous insects.
- **It is the part of many metalloenzyme**: For example. α-amylase and phospholipase contain calcium as an essential part of the catalytic. *Osteocalcin* is a protein from the bones which is important for normal bone mineral crystallization. Calbindin D is essential for intestinal absorption of calcium, the translation of calcium into the cells and the absorption of calcium from the glomerular filtrate in the kidney. Some of the blood proteins must bind calcium for their activity. Many anticoagulants bind calcium chelate structures (such as EDTA and citrate).

In the calcium-binding proteins calcium effect on

- **Secretion of hormones and neurotransmitters**: *Annexin* protein must bind to calcium tu bind to a phospholipid membrane. On this case it initiate cellular secretory vesicles to fuse with the surface of membrane and then exocytosis.
- **Cell adhesion**: *Kaderine* are calcium-dependent proteins that regulate cell adhesion and normal contact inhibition of cell replication. Defect in the function of kaderine is linked to the development of malignancy.
- **Cytoskeleton proteins**: The importance of Ca^{2+} in these activities is reflected in the precision which regulates the concentration of Ca^{2+} concentrations. Normal plasma

contains 9-11 mg of calcium per 100 mL. Daily variations are rarely greater than ±3%. These narrow limits reflect the complex regulatory action of vitamin D, parathyroid hormone, calcitonin and other hormones. (Mineravita,2015)

1.5 Calcium Homeostasis

- Calcium homeostasis refers to the regulation of the concentration of calcium ions in the extracellular fluid $[Ca^{++}]_{ECF}$. This parameter is tightly controlled because the calcium ions have a stabilizing effect on voltage-gated ion channels. For instance, when $[Ca^{++}]_{ECF}$ is too low (hypocalcemia), voltage-gated ion channels start opening spontaneously, causing nerve and muscle cells to become hyperactive. The syndrome of involuntary muscle spasms due to low $[Ca^{++}]_{ECF}$ is called hypocalcemic tetany. Conversely, when $[Ca^{++}]_{ECF}$ is too high (hypercalcemia), voltage-gated ion channels don't open as easily, and there is depressed nervous system function. Another problem of hypercalcemia is that calcium can combine with phosphate ions, forming deposits of calcium phosphate (stones) in blood vessels and in the kidneys.

1.5.1 Endocrine Regulation of $[Ca^{++}]_{ECF}$

The two most important hormones for maintaining calcium levels in the body are parathyroid hormone (PTH) and $1,25(OH)_2D$ (the active form of vitamin D). The major regulator is PTH, which is part of a negative feedback loop to maintain $[Ca^{++}]_{ECF}$ (see Humoral regulation). PTH secretion is stimulated by hypocalcemia, and it works through three mechanisms to increase Ca^{++} levels:

- PTH stimulates the release of Ca^{++} from bone, in part by stimulating bone resorption.

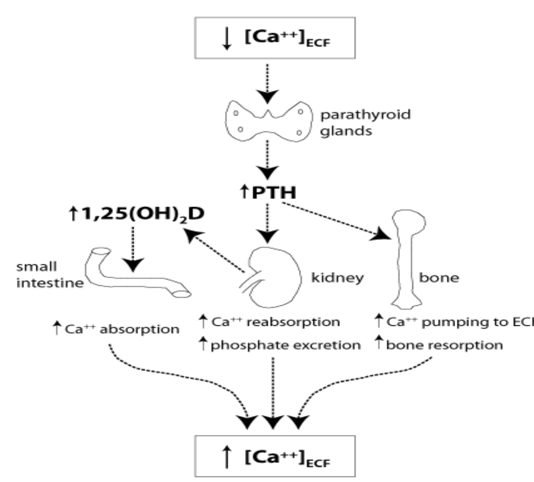


Figure: 1.5.1 Endocrine Regulation of $[Ca^{++}]_{ECF}$

- PTH decreases urinary loss of Ca^{++} by stimulating Ca^{++} reabsorption.

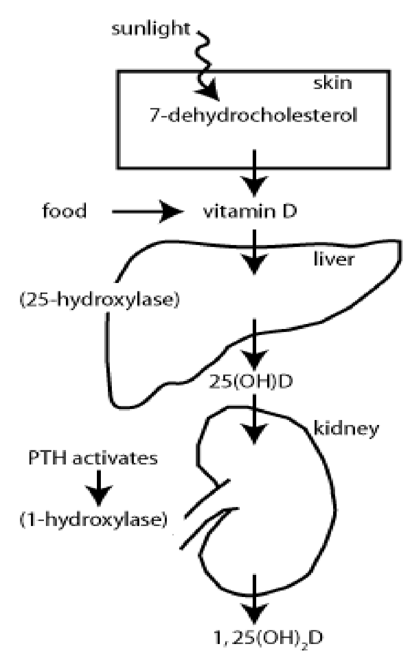
- PTH indirectly stimulates Ca^{++} absorption in the small intestine by stimulating synthesis of $1,25(OH)_2D$ in the kidney.

1.5.2 PTH Effects on Bone

- PTH has a rapid effect (occurring within minutes), whereby it stimulates osteoblasts to pump Ca^{++} ions out of the fluid surrounding the bone (which has a higher Ca^{++} concentration) and into the ECF. Over a longer time course, PTH stimulates bone resorption by stimulating osteoclastogenesis. Although PTH stimulates bone resorption, it is actually the **osteoblasts** that express PTH receptors. PTH stimulation of osteoblasts causes them to express a signaling molecule that activates osteoclasts. For more details, see the page on bone remodeling.

1.5.3 PTH Effects on Kidney

- PTH has two important effects on the kidney that work to increase $[Ca^{++}]_{ECF}$. First, it decreases the loss of Ca^{++} ions in the urine by stimulating Ca^{++} reabsorption. "Reabsorption" is the term used to describe the transfer of substances from the forming urine back into the ECF. Filtration, the first step in urine formation, is a nonspecific process, whereby water and low molecular weight substances move by bulk flow from the plasma and into the forming urine. Reabsorption, which is performed by the cells of the kidney tubules, allows the recovery of those useful small molecules such as glucose, amino acids, and Ca^{++} ions. As well as stimulating Ca^{++} reabsorption, PTH also inhibits phosphate reabsorption in the kidney.



- The other key effect of PTH on the kidney is to stimulate production of $1,25(OH)_2D$, the active form of vitamin D. A precursor (known specifically as vitamin D_3 or cholecalciferol) is synthesized in a photochemical reaction in the skin, in response to sunlight. Cholecalciferol (and a similar compound that is present in foods) is then chemically modified in the liver to form 25-(OH)D. The enzyme in the liver is *constitutively active*, meaning it is always working. By contrast, the kidney enzyme is *regulated*. The role of PTH is to stimulate the regulated kidney enzyme, resulting in the production of $1,25(OH)_2D$. This is extremely important for bone health and Ca^{++} homeostasis because $1,25(OH)_2D$ works in the small intestine to promote Ca^{++} absorption.

- In kidney disease, inadequate amounts of $1,25(OH)_2D$ are made. What happens is that Ca^{++} homeostasis is maintained at the expense of bone. $[Ca^{++}]_{ECF}$ drops because of a lack of Ca^{++} absorption from the diet. Hypocalcemia stimulates high levels of PTH secretion; this is termed secondary hyperparathyroidism because the problem that causes the hyperparathyroidism is in the kidney, not at the parathyroid gland. Secondary hyperparathyroidism is treated by administering vitamin D and Ca^{++} supplements. The drug cinacalcet is approved for the treatment of secondary hyperparathyroidism. Cinacalcet is a calcimimetic drug that binds to the Ca^{++} receptor on cells in the parathyroid gland, inhibiting the secretion of PTH.

1.6 Hypocalcemia and Hypercalcemia

Hypocalcemia and hypercalcemia are terms used clinically to refer to abnormally low and high serum calcium concentrations. It should be noted that, because about one half of serum calcium is protein bound, abnormal serum calcium, as measured by total serum calcium, may occur secondary to disorders of serum proteins rather than as a consequence of changes in ionized calcium. Hypercalcemia and hypocalcemia indicate serious disruption of calcium homeostasis but do not on their own reflect calcium balance. They can be classified by the main organ responsible for the disruption of calcium homeostasis, although clinically more than one mechanism is invariably involved.

1.7 Intestinal Calcium Absorption

Dietary intake and absorption are essential to provide sufficient calcium to maintain healthy body stores. Approximately 30% of dietary calcium ingested in a healthy adult is absorbed by the small intestine. Calcium absorption is a function of active transport that is controlled by $1,25(OH)_2D$, which is particularly important at low calcium intakes, and passive diffusion, which dominates at high calcium intakes. Typically, at normal calcium intake, $1,25(OH)_2D$-dependent transport accounts for the majority of absorption, whereas as little as 8 to 23% of overall calcium absorption is caused by passive diffusion.

Because almost all dietary calcium intake is absorbed from the upper intestine, frequent meals or oral supplements promote net calcium absorption. The bioavailability of dietary calcium can be enhanced. Aluminum hydroxide, which binds dietary phosphate , when taken in excess leads to hypercalciuria from increased calcium absorption. On the other hand, calcium absorption is lowered if the bioavailability of dietary calcium is lowered by calcium-binding agents such as cellulose, phosphate, and oxalate. A variety of diseases of the small bowel, including sprue and short bowel syndrome, can result in severe calcium malabsorption.

Absorptive hypercalcemia occurs from conditions that produce increased serum $1,25(OH)_2D$ levels as occurs in sarcoidosis, increased serum 25(OH)D levels from vitamin D poisoning, or excessive intake of calcitriol or its analogs. Absorptive hypercalcemia readily develops in children and patients with chronic kidney disease (CKD) when they receive amounts of dietary calcium that exceed the ability of their kidneys to filter and excrete the calcium load.

Absorptive hypocalcemia caused solely by a low dietary calcium intake is rare, because the homeostatic mechanisms are highly efficient and maintain serum calcium in the low physiologic range at the expense of calcium stores in bone. However, absorptive hypocalcemia is common in states of low, or inappropriately low, serum $1,25(OH)_2D$ as occurs in chronic vitamin D deficiency, osteomalacia, and rickets or in impaired $1,25(OH)_2D$ production as occurs in CKD.

1.8 Bone Calcium Remodeling

Bone continuously remodels by coordinated cellular mechanisms to adapt its strength to the changing needs of growth and physical exercise. Old, damaged, and unneeded bone is removed by resorption, and new bone is subsequently deposited by formation. Diseases affecting either or both of these processes lead to disturbed calcium homeostasis.

Remodeling hypercalcemia results from increased net bone resorption as occurs in osteoclastic metastatic bone cancer, primary hyperparathyroidism, and vitamin D poisoning. In CKD patients with adynamic bone disease, hypercalcemia is readily produced because the bone is unable to take up calcium by formation.

Remodeling hypocalcemia results from increased net bone formation as occurs in postparathyroidectomy “hungry bone syndrome” and osteoblastic metastatic bone cancer. It has been hypothesized that bone can release to, and remove calcium from, the circulation by active mechanisms separate from the remodeling system . However, although bone acts as a temporary buffer to take up and release serum calcium, the mechanism is largely passive and driven by the serum calcium concentration itself. (CJASN, 2016)

1.9 Factors that decrease calcium absorption

1.9.1 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).

1.9.2 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).

1.9.3 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).

1.9.4 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).

1.9.5 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).

1.9.6 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).

1.9.7 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).

1.10 Calcium Distribution

Calcium plays a key role in a wide range of biologic functions, either in the form of its free ion or bound complexes. One of the most important functions as bound calcium is in skeletal mineralization. The vast majority of total body calcium (>99%) is present in the skeleton as calcium-phosphate complexes, primarily as hydroxyapatite, which is responsible for much of the material properties of bone. In bone, calcium serves two main purposes: it provides skeletal strength and, concurrently, provides a dynamic store to maintain the intra- and extracellular calcium pools.

Nonbone calcium represents <1% of total body calcium (∼10 g in an adult). However, it is in constant and rapid exchange within the various calcium pools and is responsible for a wide range of essential functions, including extra- and intracellular signaling, nerve impulse transmission, and muscle contraction. Serum calcium ranges from ∼8.8 to 10.4 mg/dl (2.2 to 2.6 mM) in healthy subjects. It comprises free ions (∼51%), protein-bound complexes (∼40%), and ionic complexes (∼9%). To avoid calcium toxicity, the concentration of serum ionized calcium is tightly maintained within a physiologic range of 4.4 to 5.4 mg/dl (1.10 to 1.35 mM). Nonionized calcium is bound to a variety of proteins and anions in both the extra- and intracellular pools. The main calcium-binding proteins include albumin and globulin in serum and calmodulin and other calcium-binding proteins in the cell. The major ionic complexes in serum are calcium phosphate, calcium carbonate, and calcium oxalate. (CJASN, 2016)

1.11 Metabolism of calcium

The extracellular fluid (ECF) ionized calcium (1 mmol/L) concentration is 104 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) PH 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: 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).

1.12 Renal Calcium Excretion

Renal calcium excretion is regulated by two main mechanisms: tubular calcium reabsorption and filtered calcium load. Disruption of either or both of these mechanisms leads to abnormal calcium homeostasis. In CKD, disturbances in calcium homeostasis are common and, as GFR decreases, disturbances in calcium homeostasis increase.

<u>1.12.1 Tubular reabsorptive hypercalcemia</u> arises from a sustained increase in tubular calcium reabsorption as occurs in primary hyperparathyroidism, sodium depletion, thiazide medications, and inactivating mutations in the CaR.

<u>1.12.2 Tubular reabsorptive hypocalcemia</u> arises from a sustained decrease in tubular calcium reabsorption as occurs in postsurgical hypoparathyroidism, abnormalities in the PTHR complex, and activating CaR mutations.

<u>1.12.3 GFR hypercalcemia</u> develops when the input of calcium to the circulation exceeds its removal by the kidney's filtration rate independent of the tubular calcium reabsorption rate. This readily occurs in children and patients with CKD. In states of reduced GFR, even a normal input of calcium into the circulation from gut or bone can result in hypercalcemia. It is also important to note that hypercalcemia itself is deleterious to kidney function, and reduced GFR is often an important component of any hypercalcemia. (CJASN, 2016)

1.13 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. Ca2+ 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: 1.13 Effect of calcium on cell

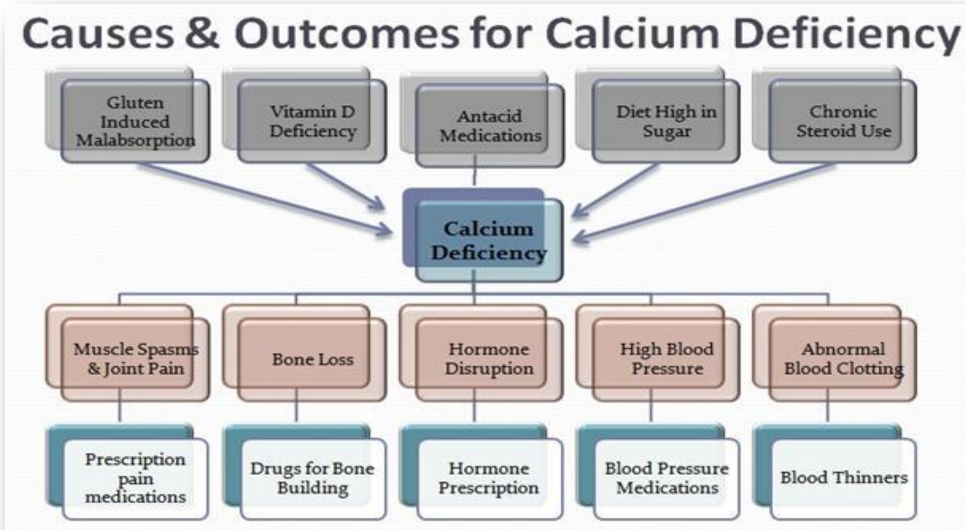
Cell Type	Effect
Secretory cells	Increase secretion
Juxtaglomerular cell	Decrease secretion
Parathyroid chief cell	Decrease secretion
Neurons	Transmission
T-cells	Response to antigen presentation
Myocytes	Contraction
Various	Activation and function of protein kinase C

1.14 Calcium Deficiency

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.

Inadequate intakes of dietary calcium from food and supplements produce no obvious symptoms in the short term. Circulating blood levels of calcium are tightly regulated. Hypocalcemia results primarily from medical problems or treatments, including renal failure, surgical removal of the stomach, and use of certain medications (such as diuretics). Symptoms of hypocalcemia include numbness and tingling in the fingers, muscle cramps, convulsions, lethargy, poor appetite, and abnormal heart rhythms. If left untreated, calcium deficiency leads to death.

Over the long term, inadequate calcium intake causes osteopenia which if untreated can lead to osteoporosis. The risk of bone fractures also increases, especially in older individuals. Calcium deficiency can also cause rickets, though it is more commonly associated with vitamin D deficiency. (National Institutes of Health, 2016)



1.15 Symptoms of Calcium Deficiency

- Brittle, weak bones
- Bone fractures
- Osteoporosis
- Problems with proper blood clotting
- Weakness and fatigue
- Delays in children's growth and development
- Heart problems involving blood pressure and heart rhythms (Dr. Axe, 2016)

1.16 Symptoms of Excess Calcium

- Unquenchable thirst
- Excesive urination
- Nausea
- Abnormal pain (one-sided)
- Constipation
- Vomiting
- Lack of apetite
- Weakness
- Depression

- Irritability
- Memory loss (Sunflower press, 2015)

1.17 Pharmacological action of Calcium regulating drugs

1.17.1 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).

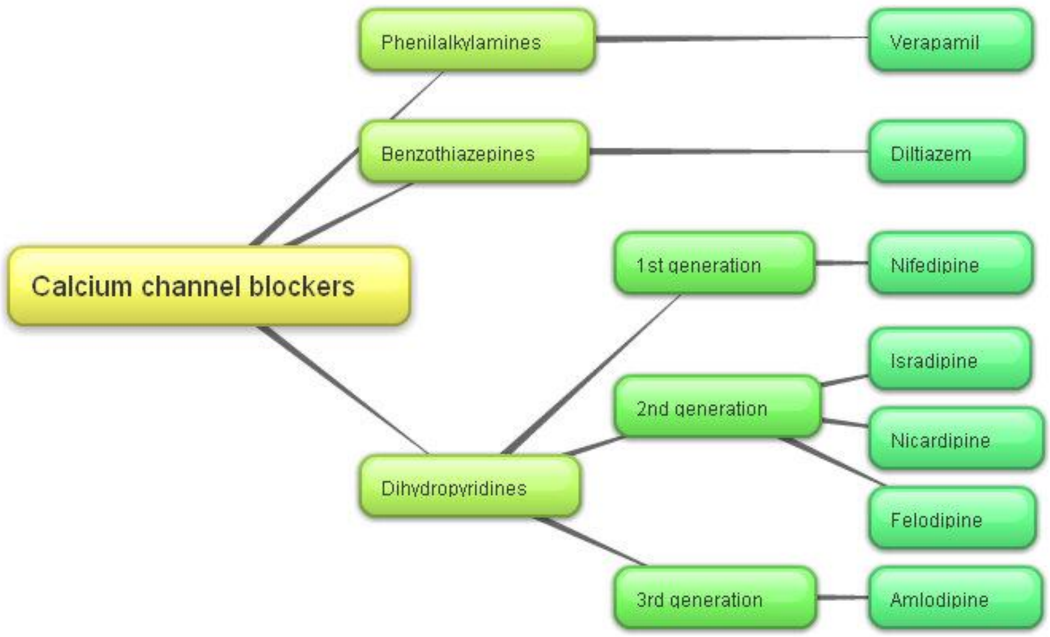


Figure: 1.17.1 Classification of calcium channel blockers (Yousef *et al.*, 2005).

1.17.2 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).

1.17.3 Mechanism of action and pharmacological effects of drugs

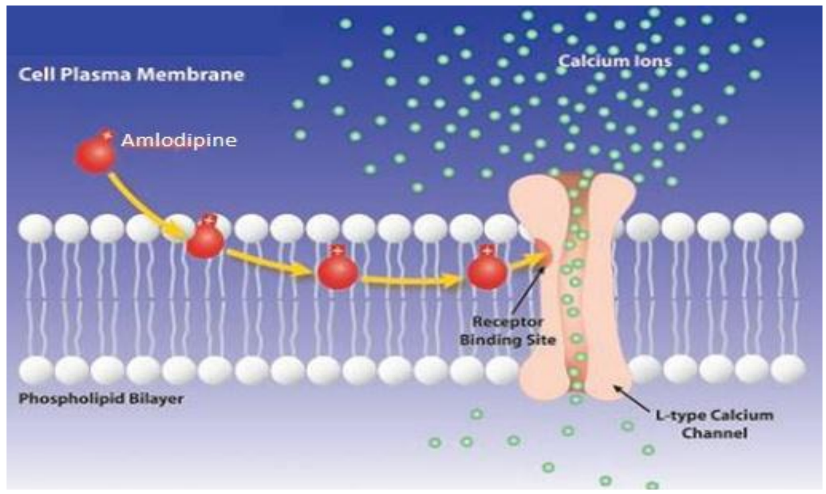


Figure: 1.17.3.1 Mechanism of action of Amlodipine on calcium channel (Joseph and Pasco, 2000)

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)

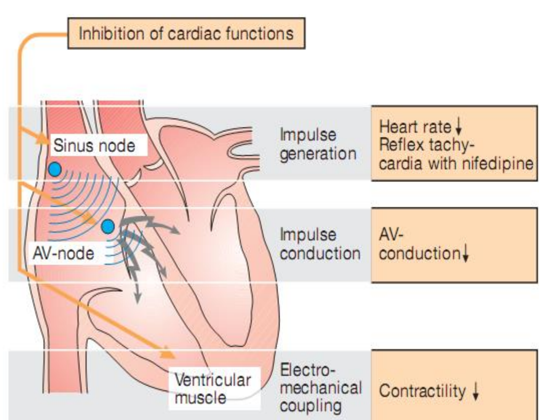


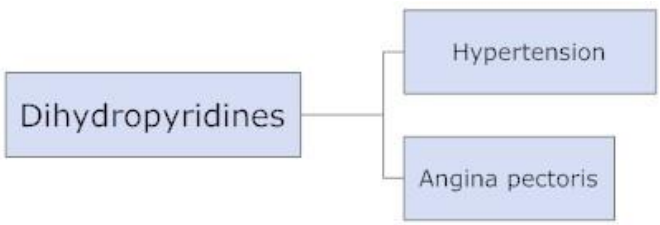
Figure: 1.17.3.2 Influence of Nifedipine on control of cardiac impulse conduction and contractility (Joseph and Pasco, 2000)

1.17.4 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)

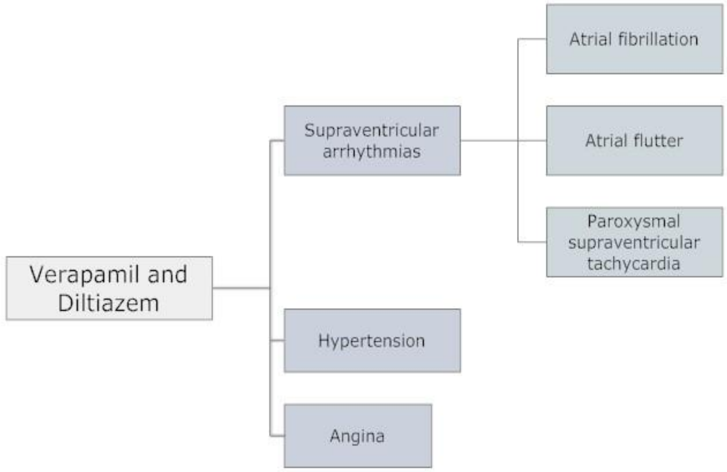
1.18 Indications of drugs

1.18.1 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.



1.19 Disorder related with Calcium

1.19.1 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).

1.19.2 Hypercalcemia

Moderate elevations of the concentration of Ca2+ 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 Ca2+ 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 Ca2+ 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 Ca2+ 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 Ca2+ 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 Ca2+-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.

1.19.3 Hypocalcemia

Mild hypocalcemia [i.e., reduction in ionized serum Ca2+ concentrations from normal to concentrations above 3.2 mg/dl (0.8 ml), approximately equal to a total serum Ca2+ 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 Ca2+ 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. Mg2+ deficiency may accentuate the hypocalcemia by diminishing the secretion and action of PTH. In infants with malabsorption or inadequate calcium intake, Ca2+ 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 Gsa (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.

1.20 Minimum Dose of Calcium

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

Table: 1.20 Minimum Dose of Calcium. (Calcium Dosing Guidelines For General Supplementation)

Age	Adequate Intake
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.

1.21 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.

1.22 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.

1.23 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.

1.24 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).

1.25 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)

1.26 Vitamin D

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol.

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis.

Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many cells have vitamin D receptors, and some convert 25(OH)D to $1,25(OH)_2D$.

Serum concentration of 25(OH)D is the best indicator of vitamin D status. It reflects vitamin D produced cutaneously and that obtained from food and supplements and has a fairly long circulating half-life of 15 days. 25(OH)D functions as a biomarker of exposure, but it is not clear to what extent 25(OH)D levels also serve as a biomarker of effect (i.e., relating to health status or outcomes). Serum 25(OH)D levels do not indicate the amount of vitamin D stored in body tissues.

In contrast to 25(OH)D, circulating $1,25(OH)_2D$ is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate. Levels of $1,25(OH)_2D$ do not typically decrease until vitamin D deficiency is severe.

There is considerable discussion of the serum concentrations of 25(OH)D associated with deficiency (e.g., rickets), adequacy for bone health, and optimal overall health, and cut points have not been developed by a scientific consensus process. Based on its review of data of vitamin D needs, a committee of the Institute of Medicine concluded that persons are at risk of vitamin D deficiency at serum 25(OH)D concentrations <30 nmol/L (<12 ng/mL). Some are potentially at risk for inadequacy at levels ranging from 30–50 nmol/L (12–20 ng/mL). Practically all people are sufficient at levels ≥ 50 nmol/L (≥ 20 ng/mL); the committee stated that 50 nmol/L is the serum 25(OH)D level that covers the needs of 97.5% of the population. Serum concentrations >125 nmol/L (>50 ng/mL) are associated with potential adverse effects. (NIH, 2016)

Table: 1.26 Recommended Dietary Allowances (RDAs) for Vitamin D

Age	Male	Female	Pregnancy	Lactation
0–12 months	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

1.27 Physiological Roles of Vitamin D

- Absorb calcium. Vitamin D, along with calcium, helps build bones and keep bones strong and healthy.
- Block the release of parathyroid hormone. This hormone reabsorbs bone tissue, which makes bones thin and brittle.
- Vitamin D may also play a role in muscle function and the immune system.
- There have been studies to suggest that it might help prevent colon, prostate, and breast cancers.
- There is also some research that it might help prevent and treat diabetes, heart disease, high blood pressure, and multiple sclerosis. (Cleveland Clinic, 2016)
- Research has shown that vitamin D might play an important role in regulating mood and warding off depression.
- Pregnant women who take an adequate amount of vitamin D during gestation may experience positive immune effects.
- Promotes the absorption of phosphate.
- Helps in development of normal teeth.

1.28 Sources of Vitamin D

1.28.1 Food

Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks. Vitamin D in these foods is primarily in the form of vitamin D_3 and its metabolite 25(OH)D_3. Some mushrooms provide vitamin D_2 in variable amounts. Mushrooms with enhanced levels of vitamin D_2 from being exposed to ultraviolet light under controlled conditions are also available.

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 supplemen**t.**

Other dairy products made from milk, such as cheese and ice cream, are generally not fortified. Ready-to-eat breakfast cereals often contain added vitamin D, as do some brands of orange juice, yogurt, margarine and other food products.

Table: 1.28.1 Selected food sources of vitamin D

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Swordfish, cooked, 3 ounces	566	142
Salmon (sockeye), cooked, 3 ounces	447	112
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 ounces	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D,	40	10

Food	IUs per serving*	Percent DV**
0.75-1 cup (more heavily fortified cereals might provide more of the DV)		
Cheese, Swiss, 1 ounce	6	2

* IUs = International Units.

** DV = Daily Value.

Figure: 1.28.1 Vitamin D containing foods (NIH, 2016)

1.28.2 Sun exposure

Most people meet at least some of their vitamin D needs through exposure to sunlight. Ultraviolet (UV) B radiation with a wavelength of 290–320 nanometers penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to previtamin D_3, which in turn becomes vitamin D_3. Season, time of day, length of day, cloud cover, smog, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D synthesis. Perhaps surprisingly, geographic latitude does not consistently predict average serum 25(OH)D levels in a population. Ample opportunities exist to form vitamin D (and store it in the liver and fat) from exposure to sunlight during the spring, summer, and fall months even in the far north latitudes.

Complete cloud cover reduces UV energy by 50%; shade (including that produced by severe pollution) reduces it by 60%. UVB radiation does not penetrate glass, so exposure to sunshine indoors through a window does not produce vitamin D. Sunscreens with a sun protection factor (SPF) of 8 or more appear to block vitamin D-producing UV rays, although in practice people generally do not apply sufficient amounts, cover all sun-exposed skin, or reapply sunscreen regularly. Therefore, skin likely synthesizes some vitamin D even when it is protected by sunscreen as typically applied.

The factors that affect UV radiation exposure and research to date on the amount of sun exposure needed to maintain adequate vitamin D levels make it difficult to provide general guidelines. It has been suggested by some vitamin D researchers, for example, that approximately 5–30 minutes of sun exposure between 10 AM and 3 PM at least twice a week to the face, arms, legs, or back without sunscreen usually lead to sufficient vitamin D synthesis and that the moderate use of commercial tanning beds that emit 2%–6% UVB radiation is also effective. Individuals with limited sun exposure need to include good sources of vitamin D in their diet or take a supplement to achieve recommended levels of intake.

Despite the importance of the sun for vitamin D synthesis, it is prudent to limit exposure of skin to sunlight and UV radiation from tanning beds. UV radiation is a carcinogen responsible for most of the estimated 1.5 million skin cancers and the 8,000 deaths due to metastatic melanoma that occur annually in the United States. Lifetime cumulative UV damage to skin is also largely responsible for some age-associated dryness and other cosmetic changes. The American Academy of Dermatology advises that photoprotective measures be taken, including the use of sunscreen, whenever one is exposed to the sun. Assessment of vitamin D requirements cannot address the level of sun exposure because of these public health concerns about skin cancer, and there are no studies to determine whether UVB-induced synthesis of vitamin D can occur without increased risk of skin cancer.

1.29 Vitamin D Intakes and Status

The National Health and Nutrition Examination Survey (NHANES), 2005–2006, estimated vitamin D intakes from both food and dietary supplements. Average intake levels for males from foods alone ranged from 204 to 288 IU/day depending on life stage group; for females the range was 144 to 276 IU/day. When use of dietary supplements was considered, these mean values were substantially increased (37% of the U.S. population used a dietary supplement containing vitamin D.) The most marked increase was among older women. For women aged 51–70 years, mean intake of vitamin D from foods alone was 156 IU/day, but 404 IU/day with supplements. For women >70 years, the corresponding figures were 180 IU/day to 400 IU/day.

Comparing vitamin D intake estimates from foods and dietary supplements to serum 25(OH)D concentrations is problematic. One reason is that comparisons can only be made on group means rather than on data linked to individuals. Another is the fact that sun exposure affects vitamin D status; serum 25(OH)D levels are generally higher than would be predicted on the basis of vitamin D intakes alone. The NHANES 2005–2006 survey found mean 25(OH)D levels exceeding 56 nmol/L (22.4 ng/mL) for all age-gender groups in the U.S. population. (The highest mean was 71.4 nmol/L [28.6 ng/mL] for girls aged 1–3 years, and the lowest mean was 56.5 nmol/L [22.6 ng/mL] for women aged 71 and older. Generally, younger people had higher levels than older people, and males had slightly higher levels than females.) 25(OH)D levels of approximately 50 nmol/L (20 ng/mL) are consistent with an intake of vitamin D from foods and dietary supplements equivalent to the RDA.

Over the past 20 years, mean serum 25(OH)D concentrations in the United States have slightly declined among males but not females. This decline is likely due to simultaneous increases in body weight, reduced milk intake, and greater use of sun protection when outside.

1.30 Vitamin D Deficiency

Nutrient deficiencies are usually the result of dietary inadequacy, impaired absorption and use, increased requirement, or increased excretion. A vitamin D deficiency can occur when usual intake is lower than recommended levels over time, exposure to sunlight is limited, the kidneys cannot convert 25(OH)D to its active form, or absorption of vitamin D from the digestive tract is inadequate. Vitamin D-deficient diets are associated with milk allergy, lactose intolerance, ovo-vegetarianism, and veganism.

Rickets and osteomalacia are the classical vitamin D deficiency diseases. In children, vitamin D deficiency causes rickets, a disease characterized by a failure of bone tissue to properly mineralize, resulting in soft bones and skeletal deformities. Rickets was first described in the mid-17th century by British researchers. In the late 19th and early 20th centuries, German physicians noted that consuming 1–3 teaspoons/day of cod liver oil could reverse rickets. The fortification of milk with vitamin D beginning in the 1930s has made rickets a rare disease in the United States, although it is still reported periodically, particularly among African American infants and children.

Prolonged exclusive breastfeeding without the AAP-recommended vitamin D supplementation is a significant cause of rickets, particularly in dark-skinned infants breastfed by mothers who are not vitamin D replete. Additional causes of rickets include extensive use of sunscreens and placement of children in daycare programs, where they often have less outdoor activity and sun exposure. Rickets is also more prevalent among immigrants from Asia, Africa, and the Middle East, possibly because of genetic differences in vitamin D metabolism and behavioral differences that lead to less sun exposure.

In adults, vitamin D deficiency can lead to osteomalacia, resulting in weak bones. Symptoms of bone pain and muscle weakness can indicate inadequate vitamin D levels, but such symptoms can be subtle and go undetected in the initial stages.

1.31 Groups at Risk of Vitamin D Inadequacy

Obtaining sufficient vitamin D from natural food sources alone is difficult. For many people, consuming vitamin D-fortified foods and, arguably, being exposed to some sunlight are essential for maintaining a healthy vitamin D status. In some groups, dietary supplements might be required to meet the daily need for vitamin D.

1.31.1 Breastfed infants

Vitamin D requirements cannot ordinarily be met by human milk alone, which provides <25 IU/L to 78 IU/L. (The vitamin D content of human milk is related to the mother's vitamin D status, so mothers who supplement with high doses of vitamin D may have correspondingly high levels of this nutrient in their milk.) A review of reports of nutritional rickets found that a majority of cases occurred among young, breastfed African Americans. A survey of Canadian pediatricians found the incidence of rickets in their patients to be 2.9 per 100,000; almost all those with rickets had been breast fed. While the sun is a potential source of vitamin D, the AAP advises keeping infants out of direct sunlight and having them wear protective clothing and sunscreen. As noted earlier, the AAP recommends that exclusively and partially breastfed infants be supplemented with 400 IU of vitamin D per day, the RDA for this nutrient during infancy.

1.31.2 Older adults

Older adults are at increased risk of developing vitamin D insufficiency in part because, as they age, skin cannot synthesize vitamin D as efficiently, they are likely to spend more time indoors, and they may have inadequate intakes of the vitamin. As many as half of older adults in the United States with hip fractures could have serum 25(OH)D levels <30 nmol/L (<12 ng/mL).

1.31.3 People with limited sun exposure

Homebound individuals, women who wear long robes and head coverings for religious reasons, and people with occupations that limit sun exposure are unlikely to obtain adequate vitamin D from sunlight. Because the extent and frequency of use of sunscreen are unknown, the significance of the role that sunscreen may play in reducing vitamin D synthesis is unclear. Ingesting RDA levels of vitamin D from foods and/or supplements will provide these individuals with adequate amounts of this nutrient.

1.31.4 People with dark skin

Greater amounts of the pigment melanin in the epidermal layer result in darker skin and reduce the skin's ability to produce vitamin D from sunlight. Various reports consistently show lower serum 25(OH)D levels in persons identified as black compared with those identified as white. It is not clear that lower levels of 25(OH)D for persons with dark skin have significant health consequences. Those of African American ancestry, for example, have reduced rates of fracture and osteoporosis compared with Caucasians (see section below on osteoporosis). Ingesting RDA levels of vitamin D from foods and/or supplements will provide these individuals with adequate amounts of this nutrient.

1.31.5 People with inflammatory bowel disease and other conditions causing fat malabsorption

Because vitamin D is a fat-soluble vitamin, its absorption depends on the gut's ability to absorb dietary fat. Individuals who have a reduced ability to absorb dietary fat might require vitamin D supplementation. Fat malabsorption is associated with a variety of medical conditions, including some forms of liver disease, cystic fibrosis, celiac disease, and Crohn's disease, as well as ulcerative colitis when the terminal ileum is inflamed. In addition, people with some of these conditions might have lower intakes of certain foods, such as dairy products fortified with vitamin D.

1.31.6 People who are obese or who have undergone gastric bypass surgery

A body mass index $\geq$30 is associated with lower serum 25(OH)D levels compared with non-obese individuals; people who are obese may need larger than usual intakes of vitamin D to achieve 25(OH)D levels comparable to those of normal weight. Obesity does not affect skin's capacity to synthesize vitamin D, but greater amounts of subcutaneous fat sequester more of the vitamin and alter its release into the circulation. Obese individuals who have undergone gastric bypass surgery may become vitamin D deficient over time without a sufficient intake of this nutrient from food or supplements, since part of the upper small intestine where vitamin D is absorbed is bypassed and vitamin D mobilized into the serum from fat stores may not compensate over time.

1.32 Vitamin D and Health

Optimal serum concentrations of 25(OH)D for bone and general health have not been established; they are likely to vary at each stage of life, depending on the physiological measures selected. Also, as stated earlier, while serum 25(OH)D functions as a biomarker of exposure to vitamin D (from sun, food, and dietary supplements), the extent to which such levels serve as a biomarker of effect (i.e., health outcomes) is not clearly established.

Furthermore, while serum 25(OH)D levels increase in response to increased vitamin D intake, the relationship is non-linear for reasons that are not entirely clear. The increase varies, for example, by baseline serum levels and duration of supplementation. Increasing serum 25(OH)D to >50 nmol/L requires more vitamin D than increasing levels from a baseline <50 nmol/L. There is a steeper rise in serum 25(OH)D when the dose of vitamin D is <1,000 IU/day; a lower, more flattened response is seen at higher daily doses. When the dose is ≥1,000 IU/day, the rise in serum 25(OH)D is approximately 1 nmol/L for each 40 IU of intake. In studies with a dose ≤600 IU/day, the rise is serum 25(OH)D was approximately 2.3 nmol/L for each 40 IU of vitamin D consumed.

In 2011, The Endocrine Society issued clinical practice guidelines for vitamin D, stating that the desirable serum concentration of 25(OH)D is >75 nmol/L (>30 ng/ml) to maximize the effect of this vitamin on calcium, bone, and muscle metabolism. It also reported that to consistently raise serum levels of 25(OH)D above 75 nmol/L (30 ng/ml), at least 1,500-2,000 IU/day of supplemental vitamin D might be required in adults, and at least 1,000 IU/day in children and adolescents.

However, the FNB committee that established DRIs for vitamin D extensively reviewed a long list of potential health relationships on which recommendations for vitamin D intake might be based. These health relationships included resistance to chronic diseases (such as cancer and cardiovascular diseases), physiological parameters (such as immune response or levels of parathyroid hormone), and functional measures (such as skeletal health and physical performance and falls). With the exception of measures related to bone health, the health relationships examined were either not supported by adequate evidence to establish cause and effect, or the conflicting nature of the available evidence could not be used to link health benefits to particular levels of intake of vitamin D or serum measures of 25(OH)D with any level of confidence. This overall conclusion was confirmed by a more recent report on vitamin D and calcium from the Agency for Healthcare Research and Quality, which reviewed data from nearly 250 new studies published between 2009 and 2013. The report concluded that it is still not possible to specify a relationship between vitamin D and health outcomes other than bone health.

1.33 Osteoporosis

More than 40 million adults in the United States have or are at risk of developing osteoporosis, a disease characterized by low bone mass and structural deterioration of bone tissue that increases bone fragility and significantly increases the risk of bone fractures. Osteoporosis is most often associated with inadequate calcium intakes, but insufficient vitamin D contributes to osteoporosis by reducing calcium absorption. Although rickets and osteomalacia are extreme examples of the effects of vitamin D deficiency, osteoporosis is an example of a long-term effect of calcium and vitamin D insufficiency. Adequate storage levels of vitamin D maintain bone strength and might help prevent osteoporosis in older adults, non-ambulatory individuals who have difficulty exercising, postmenopausal women, and individuals on chronic steroid therapy.

Normal bone is constantly being remodeled. During menopause, the balance between these processes changes, resulting in more bone being resorbed than rebuilt. Hormone therapy with estrogen and progesterone might be able to delay the onset of osteoporosis. Several medical groups and professional societies support the use of HRT as an option for women who are at increased risk of osteoporosis or fractures. Such women should discuss this matter with their health care providers.

Most supplementation trials of the effects of vitamin D on bone health also include calcium, so it is difficult to isolate the effects of each nutrient. Among postmenopausal women and older men, supplements of both vitamin D and calcium result in small increases in bone mineral density throughout the skeleton. They also help to reduce fractures in institutionalized older populations, although the benefit is inconsistent in community-dwelling individuals. Vitamin D supplementation alone appears to have no effect on risk reduction for fractures nor does it appear to reduce falls among the elderly; one widely-cited meta-analysis suggesting a protective benefit of supplemental vitamin D against falls has been severely critiqued. However, a large study of women aged ≥69 years followed for an average of 4.5 years found both lower (<50 nmol/L [<20 ng/mL]) and higher(≥75 nmol/L [≥30 ng/mL]) 25(OH)D levels at baseline to be associated with a greater risk of frailty. Women should consult their healthcare providers about their needs for vitamin D (and calcium) as part of an overall plan to prevent or treat osteoporosis.

1.34 Cancer

Laboratory and animal evidence as well as epidemiologic data suggest that vitamin D status could affect cancer risk. Strong biological and mechanistic bases indicate that vitamin D plays a role in the prevention of colon, prostate, and breast cancers. Emerging epidemiologic data suggest that vitamin D may have a protective effect against colon cancer, but the data are not as strong for a protective effect against prostate and breast cancer, and are variable for cancers at other sites. Studies do not consistently show a protective or no effect, however. One study of Finnish smokers, for example, found that subjects in the highest quintile of baseline vitamin D status had a threefold higher risk of developing pancreatic cancer. A recent review found an increased risk of pancreatic cancer associated with high levels of serum 25(OH)D (≥100 nmol/L or ≥40 ng/mL).

Vitamin D emerged as a protective factor in a prospective, cross-sectional study of 3,121 adults aged ≥50 years (96% men) who underwent a colonoscopy. The study found that 10% had at least one advanced cancerous lesion. Those with the highest vitamin D intakes (>645 IU/day) had a significantly lower risk of these lesions. However, the Women's Health Initiative, in which 36,282 postmenopausal women of various races and ethnicities were randomly assigned to receive 400 IU vitamin D plus 1,000 mg calcium daily or a placebo, found no significant differences between the groups in the incidence of colorectal cancers over 7 years. More recently, a clinical trial focused on bone health in 1,179 postmenopausal women residing in rural Nebraska found that subjects supplemented daily with calcium (1,400–1,500 mg) and vitamin D_3 (1,100 IU) had a significantly lower incidence of cancer over 4 years compared with women taking a placebo. The small number of cancers (50) precludes generalizing about a protective effect from either or both nutrients or for cancers at different sites. This caution is supported by an analysis of 16,618 participants in NHANES III (1988–1994), in which total cancer mortality was found to be unrelated to baseline vitamin D status. However, colorectal cancer mortality was inversely related to serum 25(OH)D concentrations. A large observational study with participants from 10 western European countries also found a strong inverse association between prediagnostic 25(OH)D concentrations and risk of colorectal cancer.

Further research is needed to determine whether vitamin D inadequacy in particular increases cancer risk, whether greater exposure to the nutrient is protective, and whether some individuals could be at increased risk of cancer because of vitamin D exposure. Taken together, however, studies to date do not support a role for vitamin D, with or without calcium, in reducing the risk of cancer.

1.35 Other conditions

A growing body of research suggests that vitamin D might play some role in the prevention and treatment of type 1 and type 2 diabetes, hypertension, glucose intolerance, multiple sclerosis, and other medical conditions. However, most evidence for these roles comes from in vitro, animal, and epidemiological studies, not the randomized clinical trials considered to be more definitive. Until such trials are conducted, the implications of the available evidence for public health and patient care will be debated. One meta-analysis found use of vitamin D supplements to be associated with a statistically significant reduction in overall mortality from any cause, but a reanalysis of the data found no association. A systematic review of these and other health outcomes related to vitamin D and calcium intakes, both alone and in combination, was published in August 2009.

1.36 Health Risks from Excessive Vitamin D

Vitamin D toxicity can cause non-specific symptoms such as anorexia, weight loss, polyuria, and heart arrhythmias. More seriously, it can also raise blood levels of calcium which leads to vascular and tissue calcification, with subsequent damage to the heart, blood vessels, and kidneys. The use of supplements of both calcium (1,000 mg/day) and vitamin D (400 IU) by postmenopausal women was associated with a 17% increase in the risk of kidney stones over

7 years in the Women's Health Initiative. A serum 25(OH)D concentration consistently >500 nmol/L (>200 ng/mL) is considered to be potentially toxic.

Excessive sun exposure does not result in vitamin D toxicity because the sustained heat on the skin is thought to photodegrade previtamin D_3 and vitamin D_3 as it is formed. In addition, thermal activation of previtamin D_3 in the skin gives rise to various non-vitamin D forms that limit formation of vitamin D_3 itself. Some vitamin D_3 is also converted to nonactive forms. Intakes of vitamin D from food that are high enough to cause toxicity are very unlikely. Toxicity is much more likely to occur from high intakes of dietary supplements containing vitamin D.

Long-term intakes above the UL increase the risk of adverse health effects. Most reports suggest a toxicity threshold for vitamin D of 10,000 to 40,000 IU/day and serum 25(OH)D levels of 500–600 nmol/L (200–240 ng/mL). While symptoms of toxicity are unlikely at daily intakes below 10,000 IU/day, the FNB pointed to emerging science from national survey data, observational studies, and clinical trials suggesting that even lower vitamin D intakes and serum 25(OH)D levels might have adverse health effects over time. The FNB concluded that serum 25(OH)D levels above approximately 125–150 nmol/L (50–60 ng/mL) should be avoided, as even lower serum levels (approximately 75–120 nmol/L or 30–48 ng/mL) are associated with increases in all-cause mortality, greater risk of cancer at some sites like the pancreas, greater risk of cardiovascular events, and more falls and fractures among the elderly. The FNB committee cited research which found that vitamin D intakes of 5,000 IU/day achieved serum 25(OH)D concentrations between 100–150 nmol/L (40–60 ng/mL), but no greater. Applying an uncertainty factor of 20% to this intake value gave a UL of 4,000 IU which the FNB applied to children aged 9 and older, with corresponding lower amounts for younger children.

Table: 1.36 Tolerable Upper Intake Levels (ULs) for vitamin D

Age	Male	Female	Pregnancy	Lactation
0–6 months	1,000 IU (25 mcg)	1,000 IU (25 mcg)		
7–12 months	1,500 IU (38 mcg)	1,500 IU (38 mcg)		
1–3 years	2,500 IU (63 mcg)	2,500 IU (63 mcg)		
4–8 years	3,000 IU (75 mcg)	3,000 IU (75 mcg)		
≥9 years	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)

1.37 Interactions with Medications

Vitamin D supplements have the potential to interact with several types of medications. A few examples are provided below. Individuals taking these medications on a regular basis should discuss vitamin D intakes with their healthcare providers.

1.37.1 Steroids

Corticosteroid medications such as prednisone, often prescribed to reduce inflammation, can reduce calcium absorption and impair vitamin D metabolism. These effects can further contribute to the loss of bone and the development of osteoporosis associated with their long-term use.

1.37.2 Other medications

Both the weight-loss drug orlistat and the cholesterol-lowering drug cholestyramine can reduce the absorption of vitamin D and other fat-soluble vitamins. Both phenobarbital and phenytoin, used to prevent and control epileptic seizures, increase the hepatic metabolism of vitamin D to inactive compounds and reduce calcium absorption.

1.38 Vitamin D and Healthful Diets

The federal government's 2015-2020 *Dietary Guidelines for Americans* notes that "Nutritional needs should be met primarily from foods. ... Foods in nutrient-dense forms contain essential vitamins and minerals and also dietary fiber and other naturally occurring substances that may have positive health effects. In some cases, fortified foods and dietary supplements may be useful in providing one or more nutrients that otherwise may be consumed in less-than-recommended amounts."

The *Dietary Guidelines for Americans* describes a healthy eating pattern as one that:

- Includes a variety of vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, and oils.
- Milk is fortified with vitamin D, as are many ready-to-eat cereals and some brands of yogurt and orange juice. Cheese naturally contains small amounts of vitamin D.
- Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.
- Fatty fish such as salmon, tuna, and mackerel are very good sources of vitamin D. Small amounts of vitamin D are also found in beef liver and egg yolks.
- Limits saturated and *trans* fats, added sugars, and sodium. Vitamin D is added to some margarines. Stays within our daily calorie needs. (NIH, 2016)

Chapter Two

Literature Review

2. LITERATURE REVIEW

2.1 Awareness regarding the importance of calcium and vitamin D among the undergraduate pharmacy students in Bangladesh

Riaz Uddin,corresponding author1 Naz Hasan Huda et al

Calcium and vitamin D are two important micronutrients required for maintaining proper bone health. 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 pharmacy students at undergraduate level in Bangladesh. A total of 713 students of Bachelor of Pharmacy course participated in the study. The students were asked about basic idea related to calcium and vitamin D and the disorders due to their deficiency, name of common foods containing calcium and vitamin D, their perception regarding the essentiality of the said nutrients etc. It was found that most of the students were familiar with the importance of calcium (98.9%) and vitamin D (99.3%) in bone health. 82.2% students know about the term osteoporosis. Unfortunately, 10.7% and 18.8% students failed to mention at least one food that is rich in calcium and vitamin D, respectively. Most of the students got familiar about the nutrients from their teachers (48.9%) and textbooks (32.8%). (BMC Research Notes, 6(1), p.134.)

2.2 Calcium and Vitamin D Related Knowledge in 16-18 Years Old Adolescents: Does Living in Urban or Rural Areas

MatterDewan Taslima Akhter, Riaz Uddin et al

Vitamin D deficiency is very common in Bangladesh. However, there is scanty of literature available about the knowledge of calcium and vitamin D in 16-18 years old adolescents. The present study has been conducted to determine whether a lack of knowledge exists in this age group about these nutrients and to find out the correlation between students' living in urban or rural areas. We conducted a cross sectional survey in 2992 students living in urban (62.6%) and rural (37.4%) areas aged between 16-18 years. We followed a 2 step sampling technique. 6 colleges from both urban and rural areas were selected by convenience of the interviewers and then required sample size was calculated from the number of students of each college. The students filled up a questionnaire after a detailed briefing about the study by the interviewer. We found that many of the students, both from urban and rural settings have lack of knowledge and awareness of calcium and vitamin D. Our data suggest that though the rural students are less familiar with vitamin D ($p<0.001$) and osteoporosis ($p=0.0056$) than urban students, they exercise a healthy diet in terms of milk consumption ($p<0.0001$) and engage themselves more in outdoor activities, spend more time in sunlight ($p<0.0001$) than the urban students. Thus the rural students may require less supplemental support of calcium and/or vitamin D than the urban students ($p<0.0001$).(Riaz Uddin et al)

2.3 Knowledge Regarding Vitamin D Among Private University Students in Malaysia

Audrey Sharmaine A/P Rajaretnam1, Mohammed A Abdalqader et al

Vitamin D is known as the sunlight vitamin which mainly helps in bone metabolism and calcium homeostasis. It is estimated that one billion people have vitamin D deficiency and it is considered as a public health problem. The purpose of this study is to explore the knowledge among students regarding vitamin D and its associated factors. A cross sectional study was conducted among 360 private university students using selfadministered questionnaires regarding vitamin D Knowledge on aspects of vitamin D sources, health benefits, factors of vitamin D deficiency and recommended intakes and some others. Females were more predominant in this study (69.4 %). Most students are aware and have good knowledge regarding vitamin D with male having a higher knowledge compared to female. Besides that, 69% of them agreed that vitamin D main source is the sun. Only 11.1 % know the correct answer regarding the recommended daily dosage of vit. D which is 600 IU per day.(Mohammed A Abdalqader et al)

2.4 Vitamin D Supplementation Among Women of Childbearing Age: Prevalence and Disparities

Deborah Gardner, MPHc University of Washington – Health Services, Maternal and
Child Health Committee Chair: Janice Bell PhD, MPH, MN, BScN Committee Members:
Mario Kratz et al

Maternal vitamin D deficiency is associated with numerous adverse health conditions. However, most women of childbearing age are vitamin D deficient. Although scientific and public awareness about vitamin D deficiency's role in health has increased in recent years, current data are not available to assess whether there have been concomitant increases of supplementation among women of childbearing age. We assessed prevalence and significant associations of vitamin D supplementation among childbearing-age women (16–49 years) in the most recently available.

Sampling weights were applied to account for the complex survey design and ensure generalizability to women of childbearing age among the noninstitutionalized population in the US. 2 Analyses were conducted using Stata versions 11 and 12 (College Station, TX). Of 1749 women, 459 (33%) had taken supplements containing vitamin D during the past 30 days. We observed low supplementation prevalence (range 12%–27%) among teenagers, those with high body mass index (BMI), low socio-economic status (low-income, low education, ethnicity other than white, food insecurity, or no/government insurance), as well as parous women who had never breastfed, and women with no history of vigorous or moderate exercise. In the fully adjusted regression models, 2 Mexican-American race/ethnic identity (OR: .53, 95% CI .33–.86), low food security (OR: .65, 95% CI .44–.95), no health insurance (OR .65, 95% CI .42–1.00), government/other health insurance (OR: .66, 95% CI .45–.96), and parity without breastfeeding (OR: .63, 95% CI .40–.99) were associated with lower likelihood of vitamin D supplement use compared with the reference groups.(BScN Committee Members: Mario Kratz et al)

Chapter Three

Methodology

3. METHODOLOGY

3.1 Type of the study

The study was performed on a cross sectional observation which was attempted to find out the awareness of calcium and vitamin D among women in Dhaka city.

3.2 Study Area

East West University, Shahabuddin Medical College & Hospital, Ahsanullah University, City College, Viqarunnisa Noon School & College, Dhaka City.

3.3 Study Population

In this study, a total number of 310 girls and women were surveyed with a questionnaire in order to assess the knowledge, perception and attitude regarding awareness of calcium and vitamin D. Informed consent was obtained from the eligible participants before interviewed and participants who agreed to join the study provided required information for the studies.

3.4 Study Period

The duration of the study was about six months from July to December in 2016.

3.5 Questionnaire Development

The pre-tested questionnaire was specially designed to collect the simple background data and the needed information. The questionnaire was written in simple English in order to avoid unnecessary semantic misunderstanding. The questionnaire was pilot tested to ensure it was understandable by the participants.

3.6 Sampling Techniques

In this study purposive sampling technique was followed.

3.7 Data Analysis

After collecting, the data were checked and analyzed with the help of Microsoft Excel 2007. The result was shown in bar, pie and column chart and calculated the percentage of the knowledge attitude and perception regarding awareness of calcium and vitamin D.

Chapter Four

Result

4. RESULT

4.1 Age Ranges of the Participants

Table: 4.1 Age Ranges of the Participants

Age Ranges of Women Responded	Percentages
10-20	13%
21-30	39%
31-40	28%
41-50	15%
51-60	5%

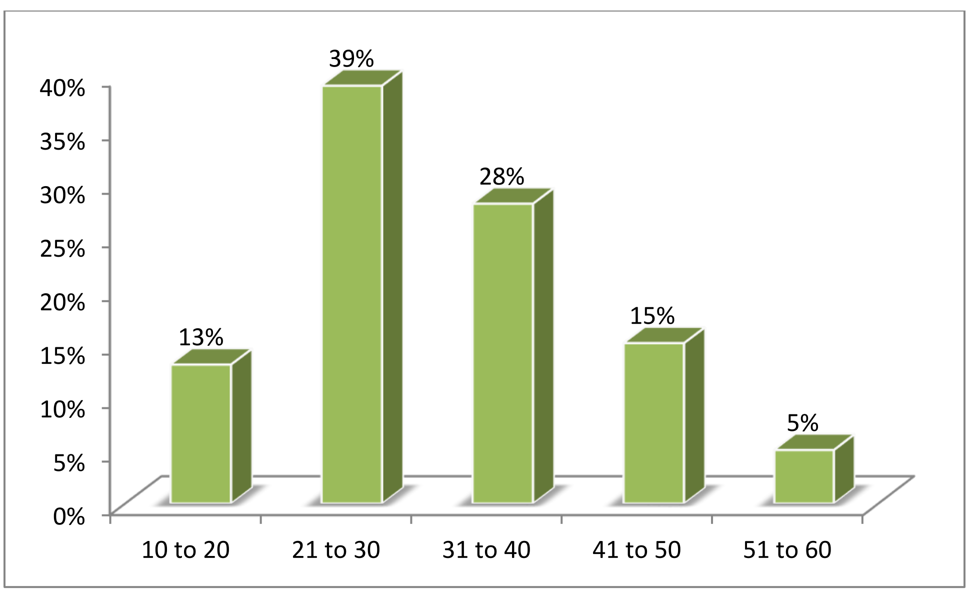


Figure 4.1: Age ranges of responded women

4.2 Respondents who have children

Table: 4.2 Number of respondents who have children

Responded women having children	Total number of women	Yes	No
Number	310	171	139
Percentage		55%	45%

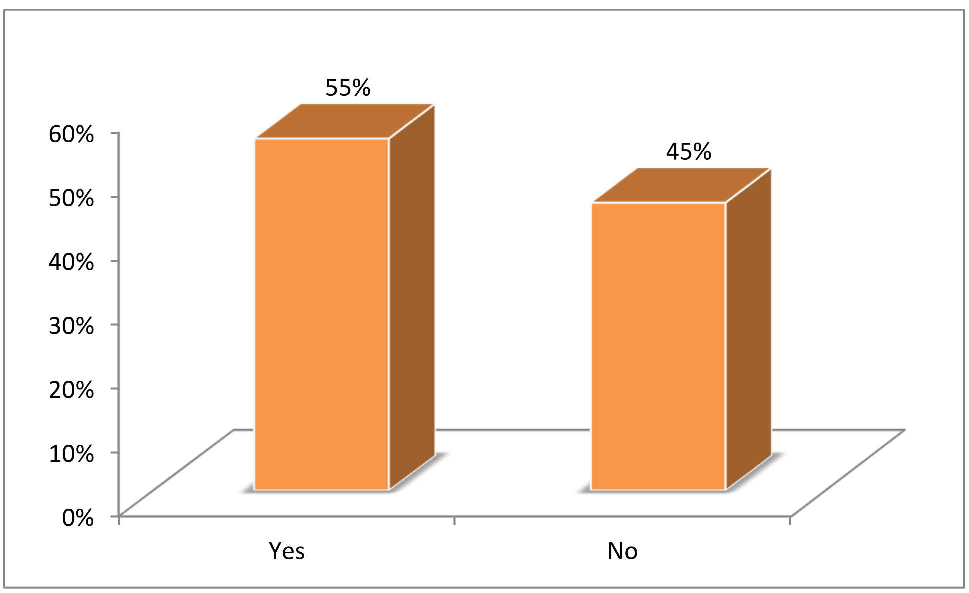


Figure 4.2: Number of respondents who have children

4.3 Respondents suffering from bone disorder

Table: 4.3 Number of respondents suffering from bone disorder

Responded women having bone disorder	Total number of women	Yes	No
Number	310	88	222
Percentage		28%	72%

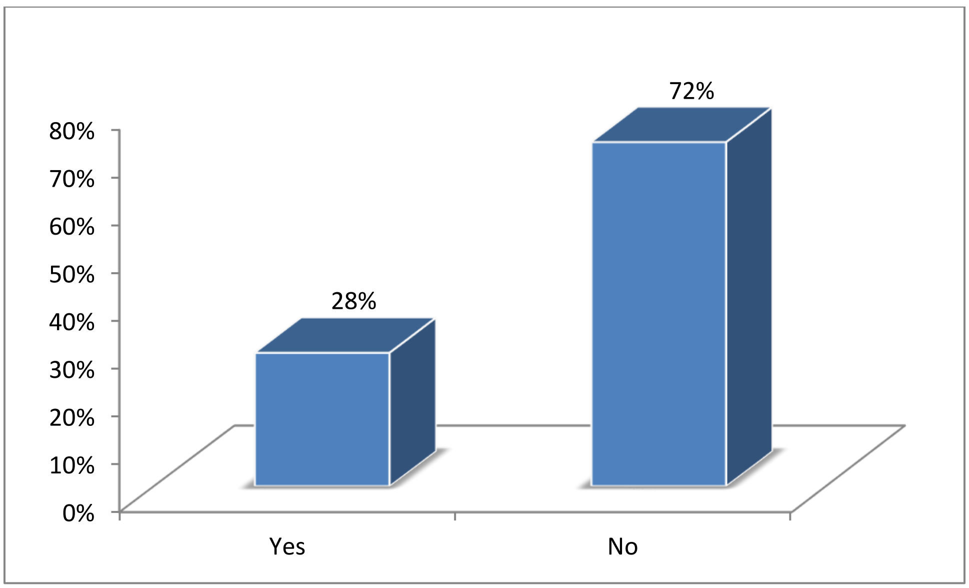


Figure: 4.3 Number of respondents suffering from bone disorder

4.4 Respondents who have been prescribed calcium supplement

Table: 4.4 Number of respondents who have been prescribed calcium supplement

Responded women who have been prescribed calcium supplement	Total number of women	Yes	No
Number	310	114	194
Percentage		37%	63%

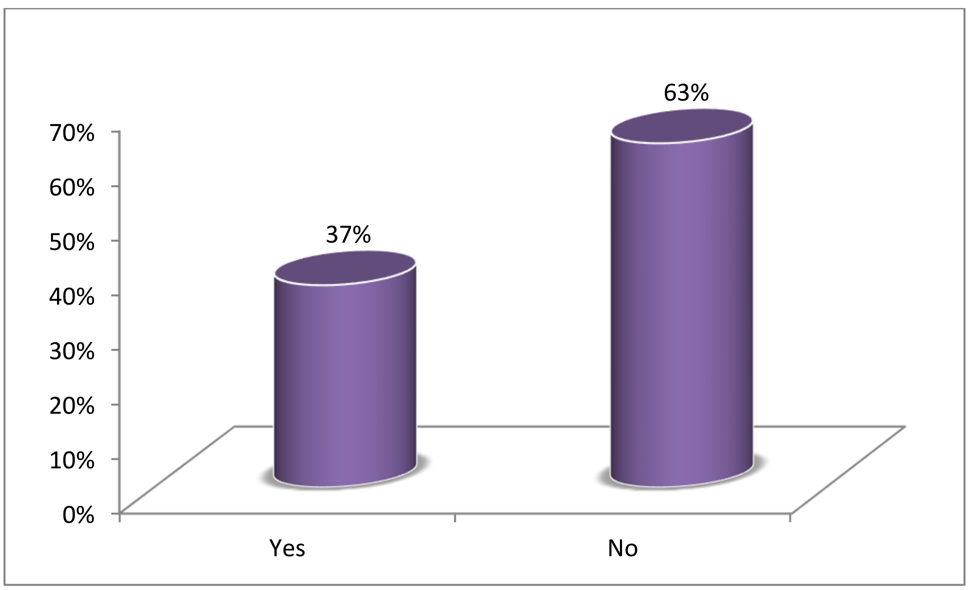


Figure: 4.4 Number of respondents who have been prescribed calcium supplement

4.5 Respondents who have been prescribed vitamin D

Table: 4.5 Number of respondents who have been prescribed vitamin D

Respondents who have been prescribed vitamin D	Total number of women	Yes	No
Number	310	107	200
Percentage		35%	65%

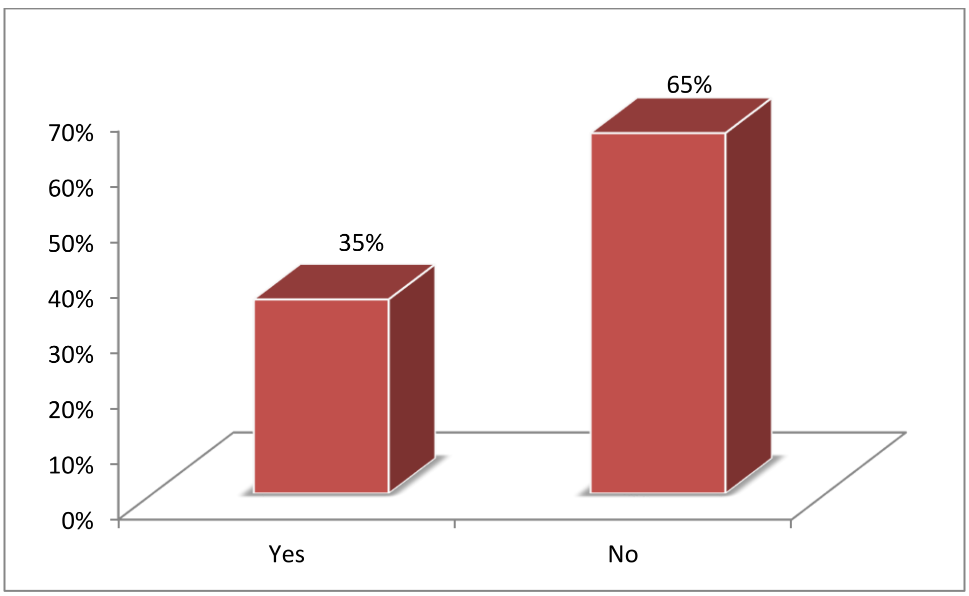


Figure: 4.5 Number of respondents who have been prescribed vitamin D

4.6 Respondents asked if calcium is an important mineral

Table: 4.6 Respondents asked if calcium is an important mineral

Respondents asked if calcium is an important mineral	Total number of women	Yes	No
Number	310	277	31
Percentage		90%	10%

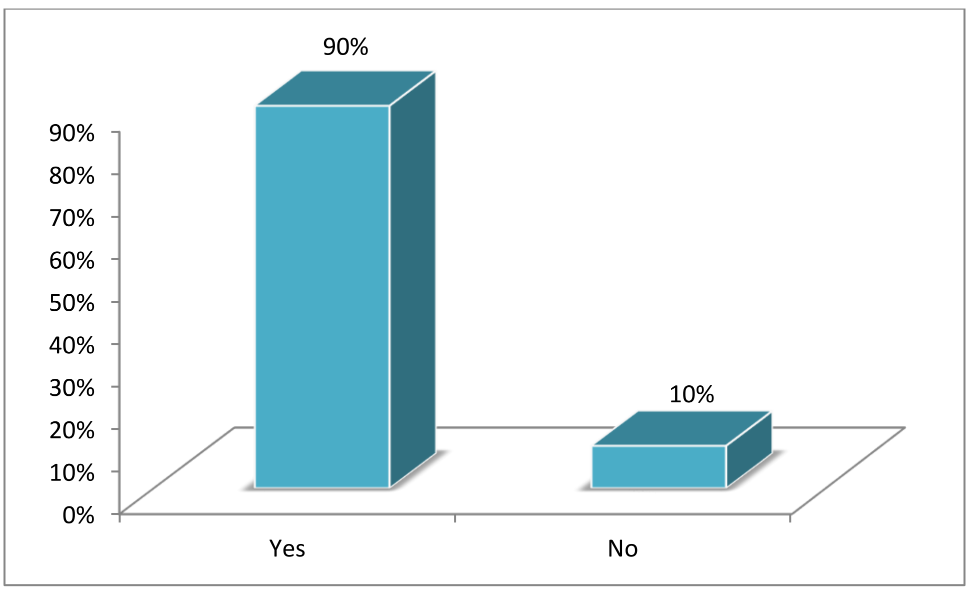


Figure: 4.6 Respondents asked if calcium is an important mineral

4.7 Responses about calcium sources

Table: 4.7 Responses about calcium sources

Responses about calcium sources	Milk	Yogurt	Cheese	Butter	Vegetables	Egg
Number	157	31	28	17	33	59
Percentage	50%	10%	9%	5%	11%	19%

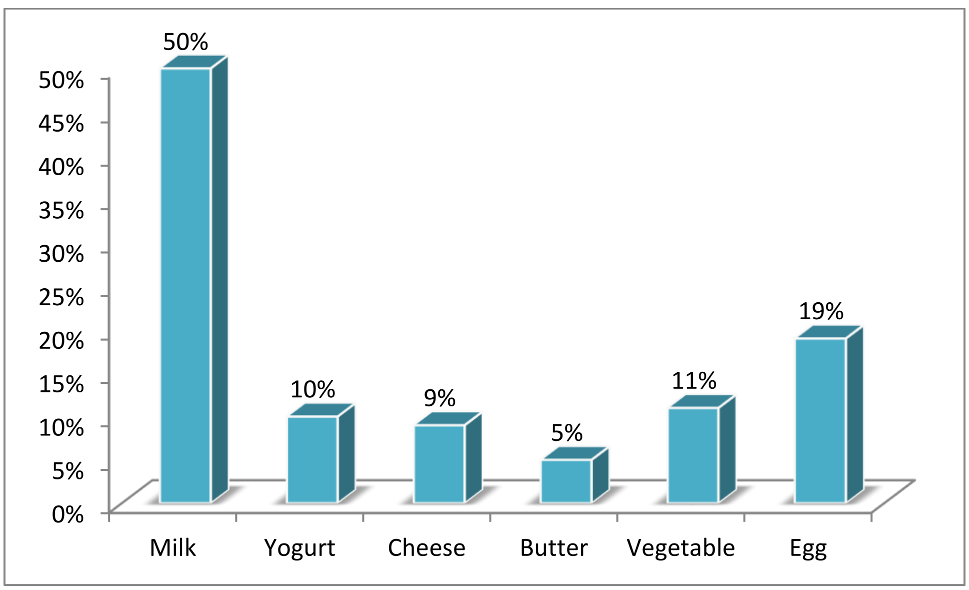


Figure: 4.7 Responses about calcium sources

4.8 Responded women asked if vitamin D is essential

Table: 4.8 Responded women asked if vitamin D is essential

Responded women asked if vitamin D is essential	Total number of women	Yes	No
Number	310	285	24
Percentage		92%	8%

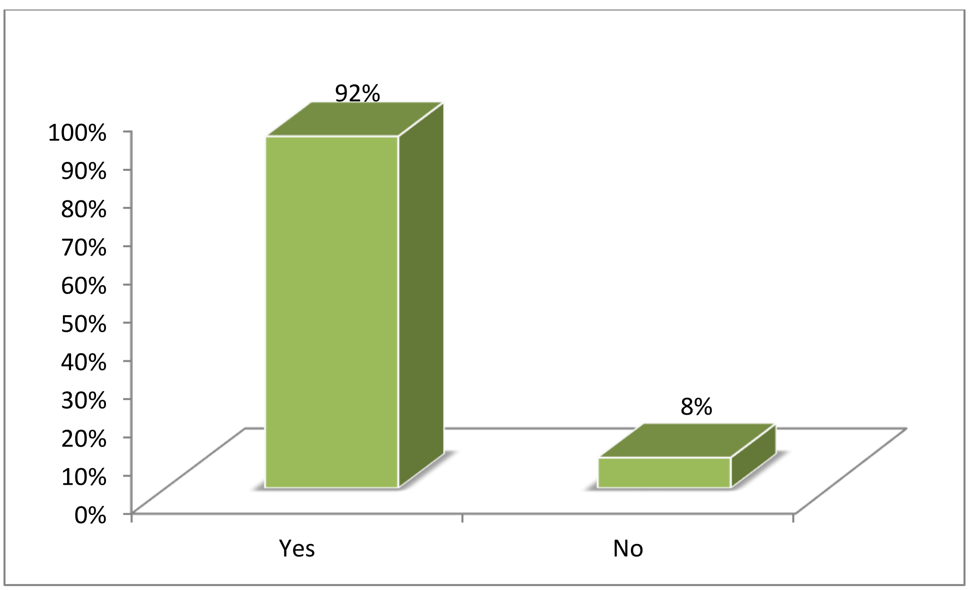


Figure: 4.8 Responded women asked if vitamin D is essential

4.9 Responses about Vitamin D sources

Table: 4.9 Responses about Vitamin D sources

Responses about Vitamin D sources	Liver	Sunlight	Fish	Sea food	Egg yolk	Vegetables
Number	35	75	34	17	22	55
Percentage	11%	24%	11%	5%	7%	18%

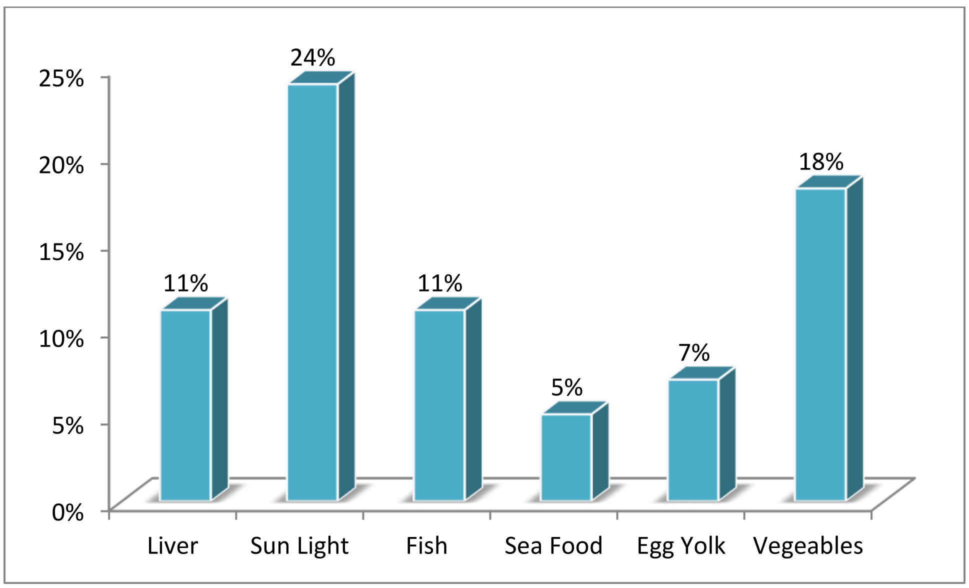


Figure: 4.9 Responses about Vitamin D sources

4.10 Sources for learning about calcium

Table: 4.10 Sources for learning about calcium

Sources for learning about calcium	Percentage	Number	Total
Books	58%	179	310
Family	56%	172	
Internet	25%	79	
Teacher	39%	121	
Media	24%	74	
Doctor	40%	124	
Others	6%	17	

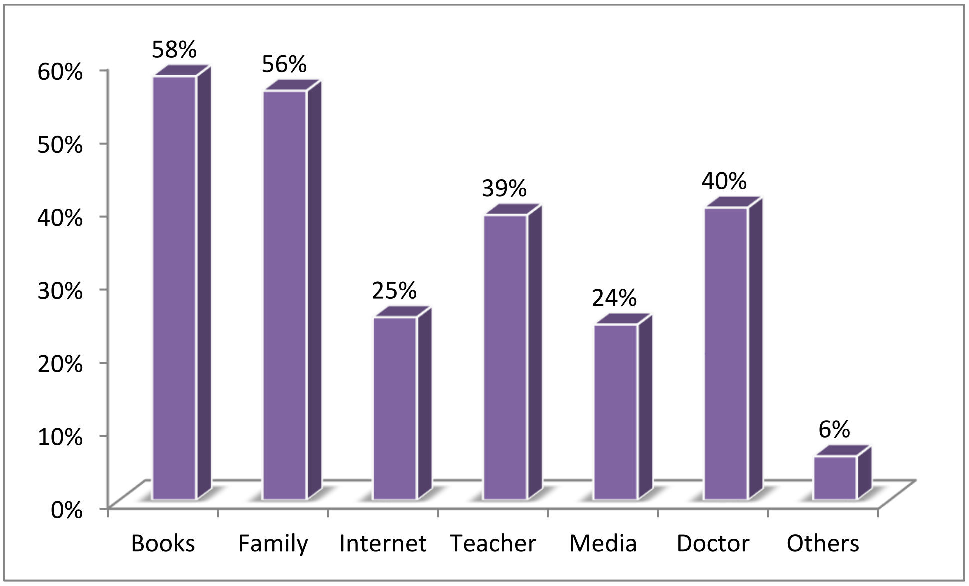


Figure: 4.10 Sources for learning about calcium

4.11 Number of respondents who correctly stated the dietary intake of calcium

Table: 4.11 Number of respondents who correctly stated the dietary intake of calcium

Respondents who correctly stated the dietary intake of calcium	Total number of women	Yes	No
Number	310	28	282
Percentage		9%	91%

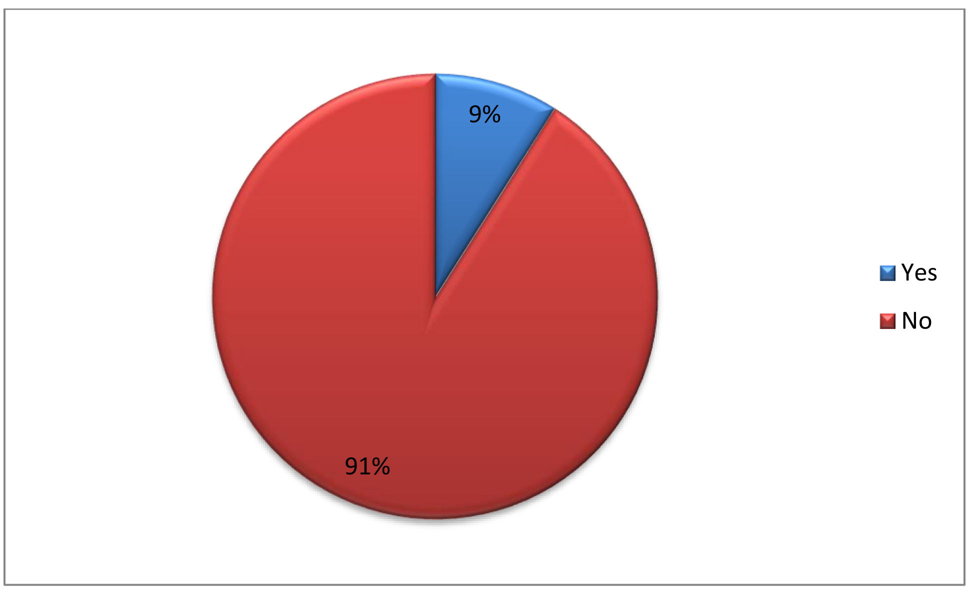


Figure: 4.11 Number of respondents who correctly stated the dietary intake of calcium

4.12 Respondents who correctly stated the dietary intake of vitamin D

Table: 4.12 Number of respondents who correctly stated the dietary intake of vitamin D

Responded women who correctly stated the dietary intake of Vitamin D	Total number of women	Yes	No
Number	310	16	294
Percentage		5%	95%

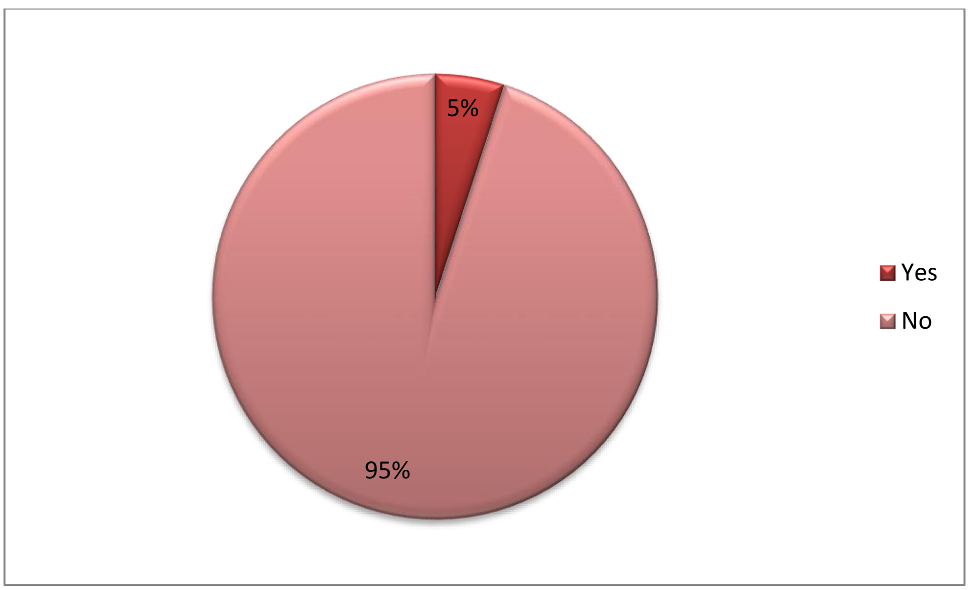


Figure: 4.12 Number of respondents who correctly stated the dietary intake of vitamin D

4.13 Respondents who knew about osteoporosis

Table: 4.13 Number of respondents who knew about osteoporosis

Respondents who knew about osteoporosis	Total number of women	Yes	Don't Know
Number	310	108	202
Percentage		35%	65%

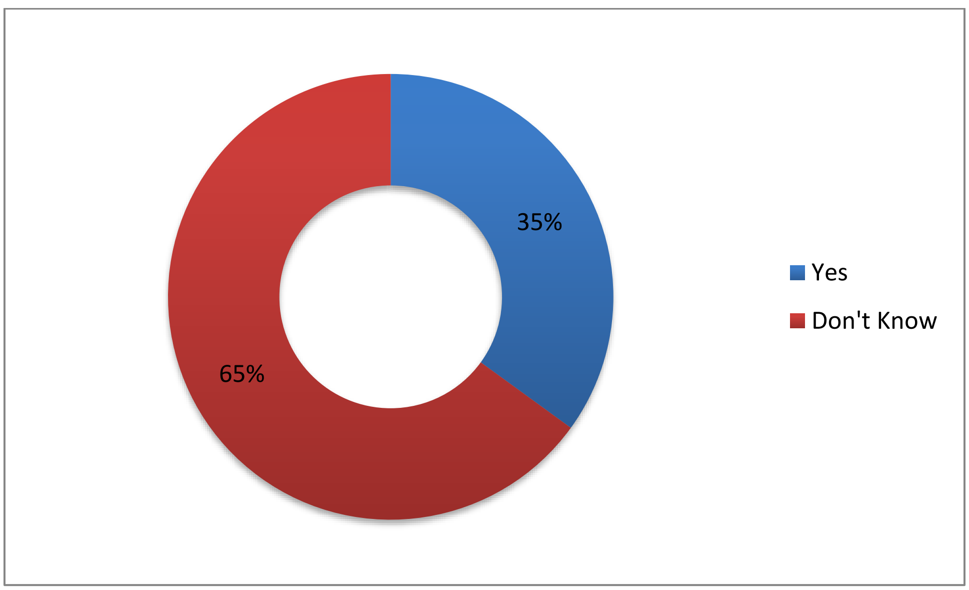


Figure: 4.13 Number of respondents who knew about osteoporosis

4.14 Respondents who were asked if women are more affected by osteoporosis than men

Table: 4.14 Respondents who were asked if women are more affected by osteoporosis than men

Respondents who were asked if women are more affected by osteoporosis than men	Total number of women	Yes	No
Number	310	230	80
Percentage		74%	26%

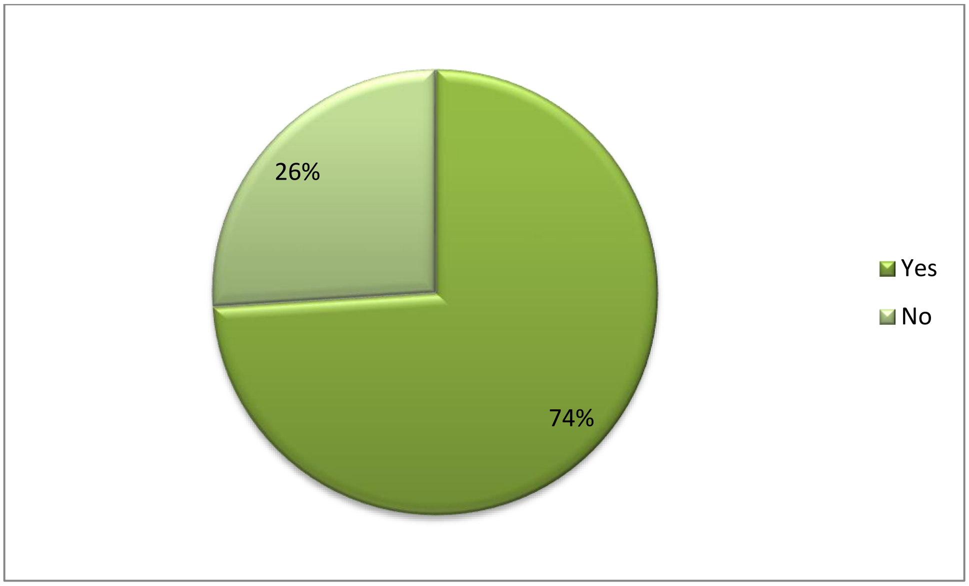


Figure: 4.14 Respondents who were asked if women are more affected by osteoporosis than men

4.15 Respondents who knew about calcium deficiency disease of children

Table: 4.15 Respondents who knew about calcium deficiency disease of children

Respondents who knew about calcium deficiency disease of children	Total number of women	Yes	Don't Know
Number	310	65	245
Percentage		21%	79%

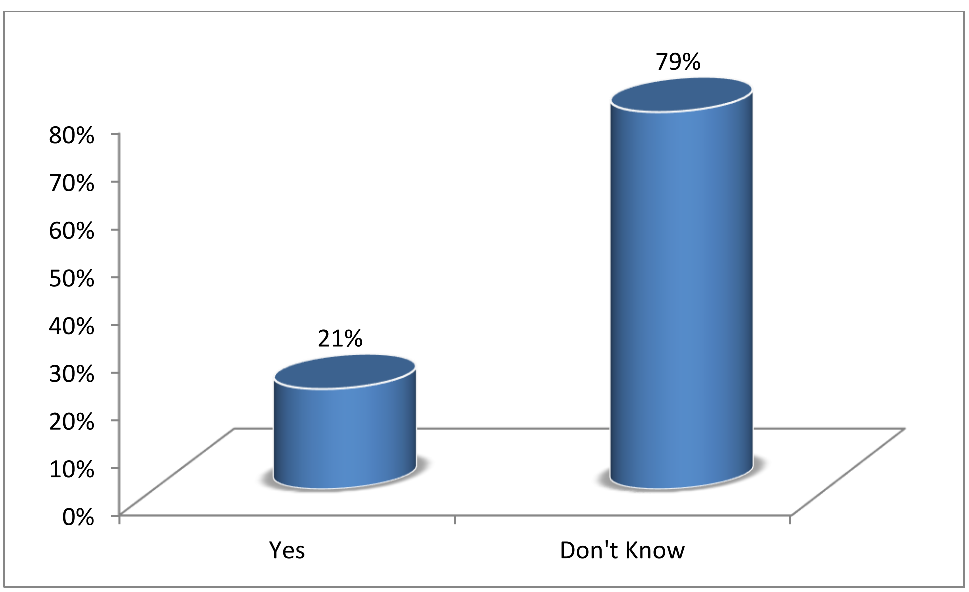


Figure: 4.15 Respondents who knew about calcium deficiency disease of children

4.16 Respondents who knew about frequency of milk consumption

Table: 4.16 Respondents who knew about frequency of milk consumption

Respondents who knew about frequency of milk consumption	Percentage	Number	Total
Daily	40%	124	310
Weekly	15%	45	
Monthly	4%	12	
Yearly	4%	13	
Never	20%	61	
Others	17%	54	

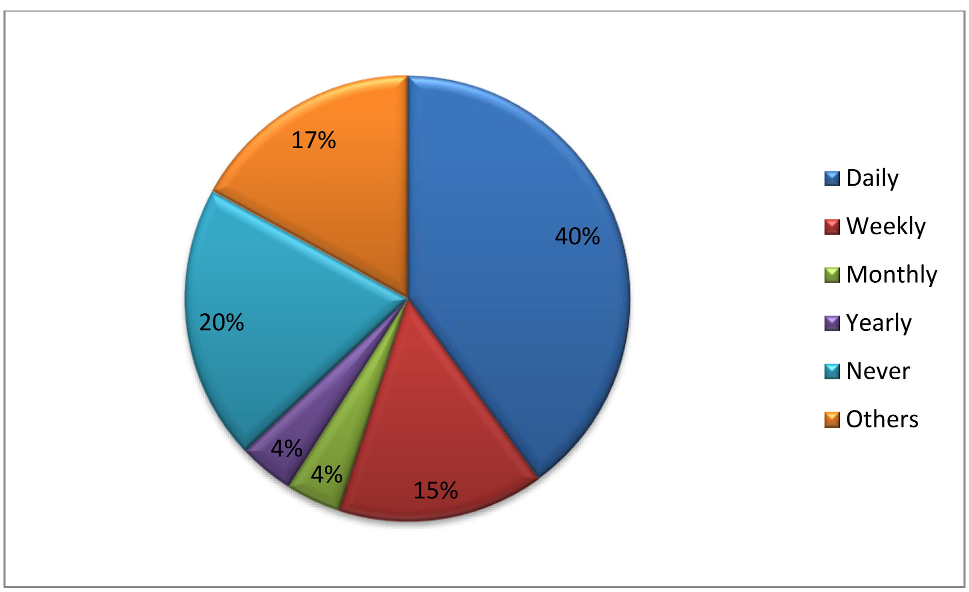


Figure: 4.16 Respondents who knew about frequency of milk consumption

4.17 Respondents stated about sunlight exposure

Table: 4.17 Respondents stated about sunlight exposure

Respondents stated about sunlight exposure	Percentage	Number	Total
Less than 1hr	25%	77	310
Greater than 1hr	29%	90	
Greater than 2hr	26%	81	
Greater than 3hr	10%	30	
Greater than 4hr	2%	5	
Do not know	7%	23	
Others	1%	4	

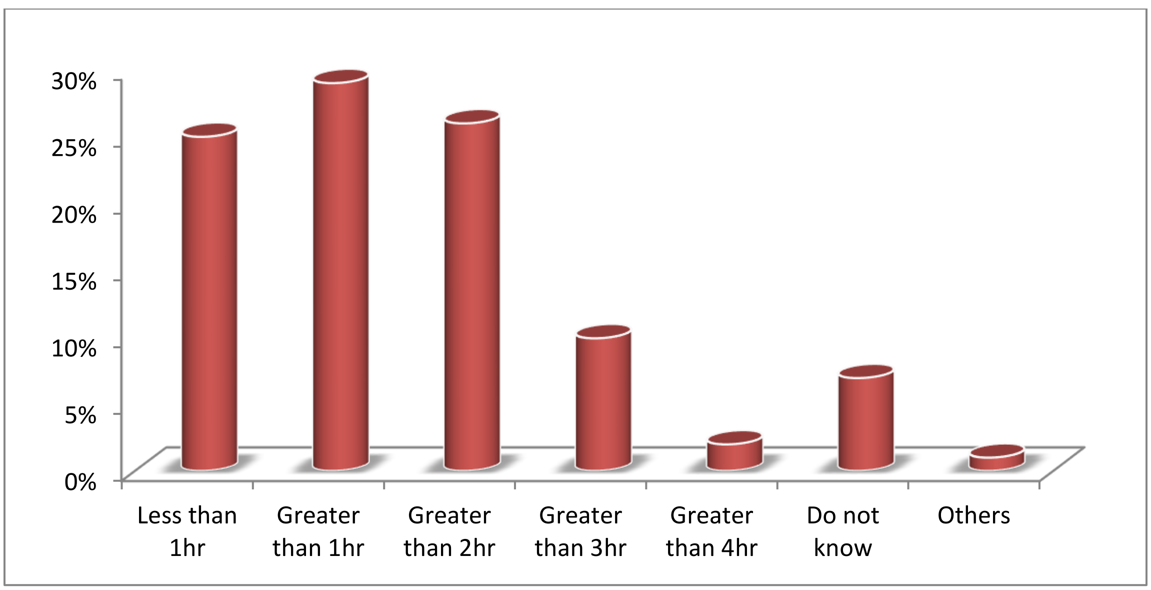


Figure: 4.17 Respondents stated about sunlight exposure

Chapter Five

Discussion

5. DISCUSSION

In this study some women were asked to mention name of three foods containing calcium and vitamin D. From the survey it was found that about the 90% & 92% women know Calcium & Vitamin D as a food supplement while 10% & 8% do not know about the Calcium & Vitamin D. They have come to largely know about milk (50%), Egg (19%), Vegetable (11%), Yogurt (10%) and Cheese (9%) as Calcium containing food.

They also know about Liver (11%), Fish (12%), Vegetable (18%), Eggs (7%), Others (24%) as Vitamin D containing food. On the basis of drinking milk is response mainly daily (40%). They remain in the high sun exposure per day like <1hr (29%). 37% and 35% ever been prescribed any Calcium & Vitamin D supplement by a physician while 63% and 65% ever not been prescribed.

Women were asked about the source of their knowledge and information they know about calcium and vitamin D. Interestingly most of the women answered that they first knew about calcium and vitamin D from either from textbooks (58%) and their family (56%), from doctor (40%), their teacher (39%), from internet (25%), from media (24%) and other sources (6%).

From the responses it was observed that both calcium and vitamin D are equally known among the women. They are not that much familiar with the term ‘osteoporosis’. The term of “Osteoporosis” is known to 35% of women while 65% do not know about it.

The women who have science background 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 women were not that much 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.

The rural women are less familiar with vitamin D ($p<0.001$) and osteoporosis ($p=0.0056$) than urban women, they exercise a healthy diet in terms of milk consumption ($p<0.0001$) and engage themselves more in outdoor activities, spend more time in sunlight ($p<0.001$) than urban women. Thus the rural women may require less supplemental support of calcium and/or vitamin D than urban women ($p<0.0001$).

A study was performed in Vietnam A total of 1,536 individuals aged 14 to 85 years participated in the study. Fifty three percent of participants did not like being exposed to sunlight. On the average, most reported approximately 14 hours per week under the sun. Majority (81%) reported that they had heard of vitamin D from newspapers (32%), friends (20%) or radio and television (13%). However, their knowledge about the source of vitamin D was inadequate: 37% thought that vitamin D comes from the sun, 28% from foodstuff and the sun, while 17% did not know the source of vitamin D. Analysis of the determinants of knowledge of vitamin D suggested that only educational level was a significant predictor of vitamin D knowledge.

One interesting finding of my study is that, most of the women first heard about calcium and / vitamin D from family and academic sources (from their teacher and textbooks). In Bangladesh women also know about calcium and vitamin D from doctor. But illiterate women were not aware of Calcium and vitamin D. My study mainly represented the literate women.

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 Six

Conclusion

6. 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 women and children in Bangladesh.

From this survey, we have come to know that the women who are non science background do not have adequate knowledge of essential nutrients, minerals, vitamins etc. If they have gap of knowledge about calcium and vitamin D, their children 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 Seven

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