Awareness of Deficiency Diseases of Calcium and Vitamin D Among Bangladeshi Men in Dhaka and Chadpur

A dissertation submitted to Department of Pharmacy, East West University, 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, Sazia Hannan Shara, ID: 2012-1-70-039, hereby declare that the dissertation entitled "Awareness of deficiency diseases of calcium and vitamin D among Bangladeshi men in Dhaka and Chadpur" submitted by me to the Department of Pharmacy, East West University and in the partial fulfillment of the requirement for the degree Bachelor of Pharmacy, under the supervision and guidance Ms. Farah Shahjin, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

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Certificate by the Supervisor

This is to certify that the thesis entitled " Awareness of deficiency diseases of calcium and vitamin D among Bangladeshi men in Dhaka and Chadpur " submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the degree Bachelor of Pharmacy is a record of original and genuine research work carried out by Sazia Hannan Shara, ID: 2012-1- 70-039during the period 2016 of his 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 deficiency diseases of calcium and vitamin D among Bangladeshi men in Dhaka and Chadpur" submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the degree Bachelor of Pharmacy is a record of original and genuine research work carried out by Sazia Hannan Shara, ID: 2012-1- 70-039 during the period 2016 of his research in the Department of Pharmacy, East West University.

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Dedication

This research work is dedicated to my husband, parents, honorable faculties and loving friends.

Abstract

Calcium is essential in maintaining total body health, normal growth and development, metabolizing iron, helping blood clotting & regulating blood pressure, keeping bones & teeth strong over lifetime, activity in a number of hormones, cell structure etc. Vitamin D is required for regulation of cell growth, bone formation, immune function, muscle strength, hair growth, reducing autoimmune disease, fighting infection etc. Previous works intended to determine the status of these micronutrients in local population have reported that the people in Bangladesh are at high risk of calcium insufficiency and hypovitaminosis D related health complications. Lack of awareness and insufficient knowledge of the essentiality of these two nutrients are assumed to cause this problem in Bangladesh. The present study was designed and conducted to establish a basic understanding on the level of gap of knowledge and awareness among the deficiency diseases of calcium and vitamin D among Bangladeshi men in Dhaka and Chadpur in Bangladesh. Bangladesh is a one of the most overpopulated country in the world. That's why the most important part in living is to be as healthy as possible avoiding all the diseases. This was a survey based study with male respondents from Dhaka city and Chadpur. They were interviewed with a questionnaire, and 200 male respondents participated in this survey. The age of the male respondents were from 17-35 and they were not from the biological sciences background. From the survey it was found that the majority of men respondents know calcium & vitamin D is essential for normal body physiological function. The male respondent of this study largely know about milk, meat, cheese, fish, egg and others as calcium containing food sources. They also know about meat, liver, milk, eggs, banana, sunlight, fish oil, vegetables oil and others as a vitamin D containing food sources. They also learned about calcium from the sources of books, teachers, doctors, family and others. Most of the participants on this study do not know about the daily intake of Calcium and vitamin D. The men respondents were mostly aware of calcium and vitamin D deficiency diseases that occur in children. Most of the population on this study thought that women are more affected by osteoporosis than men. They also give a good response about the daily sunlight exposure which is less than 1 hour daily. So according to the Bangladesh perspective majority of the population do not know about the importance of calcium and vitamin D. We need to take adequate step to teach more about the importance of calcium and vitamin D in their day to day life.

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List of Abbreviation

Abbreviation	Full form
AI	Adequate Intake
CVD	cardiovascular disease
Ca2+	calcium
DRIs	Dietary Reference Intakes
DHT	Dihydrotachysterol
D2	Ergocalciferol
D3	Cholecalciferol
DASH	Dietary Approaches to Stop Hypertension
EAR	Estimated Average Requirement
FNB	Food and Nutrition Board
HRT	Hormone replacement therapy
IU	International Units
mg	miligrams
mm	Mili miter
mol/L	Mole per litre
mM	Mili mole
OZ	Ounce
PTH	Para thyroid hormone
PHEX	Phosphate regulating gene with homologies to endopeptidases on the X chromosome
RDA	Recommended Dietary Allowance
RXR	Retinoid X receptor
TRPV6	Transient receptor potential cation channel
UL	Tolerable Upper Intake Level
ULs	Upper Intake Levels
USP	United States Pharmacopoeia
UV	Ultraviolet

VDR	vitamin D receptor
XLH	X-linked disorder

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CHAPTER 1
INTRODUCTION

1. Overview

1.1 Calcium

Calcium as a nutrient is most commonly associated with the formation and metabolism of bone. It is 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 (Gennari, 2001)

1.1.1 Physiological Roles of calcium

- Control excitability of nerves and muscles and regulate permeability of cell membrane.
- Maintain integrity of cell membrane and regulate cell adhesion.
- Calcium ions are essential for excitation-contraction of all type of muscle.
- Calcium ions are essential for excitation-secretion coupling in exocrine and endocrine glands.
- Calcium ions releases of transmitter from nerve ending.
- Act as intracellular messenger for hormones and autacoids.
- Generate impulse in heart and determine level automatically.
- Help in coagulation of blood.
- Structural function of bone and teeth.

1.1.2 Recommended Intakes

Intake recommendations for calcium and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences). DRI is the general term for a set of reference values used for planning and assessing the nutrient intakes of healthy people. These values, which vary by age and gender, include:

- Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals.
- Adequate Intake (AI): established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.
- Estimated Average Requirement (EAR): average daily level of intake estimated to meet the requirements of 50% of healthy individuals. It is usually used to assess the adequacy of nutrient intakes in populations but not individuals.
- Tolerable Upper Intake Level (UL): maximum daily intake unlikely to cause adverse health effects .

The FNB established RDAs for the amounts of calcium required for bone health and to maintain adequate rates of calcium retention in healthy people. They are listed in Table 1 in milligrams (mg) per day.

Table 1.1: Recommended Dietary Allowances (RDAs) for Calcium

Age	Male	Female	Pregnant	Lactating
0–6 months	200 mg	200 mg		
7–12 months	260 mg	260 mg		
1–3 years	700 mg	700 mg		
4–8 years	1,000 mg	1,000 mg		
9–13 years	1,300 mg	1,300 mg		

14–18 years	1,300 mg	1,300 mg	1,300 mg	1,300 mg
19–50 years	1,000 mg	1,000 mg	1,000 mg	1,000 mg
51–70 years	1,000 mg	1,200 mg		
71+ years	1,200 mg	1,200 mg		

(KH and JT, 1994)

1.1.3 Sources of Calcium

Food

Milk, yogurt, and cheese are rich natural sources of calcium and are the major food contributors of this nutrient to people in the United States. Nondairy sources include vegetables, such as Chinese cabbage, kale, and broccoli. Spinach provides calcium, but its bioavailability is poor. Most grains do not have high amounts of calcium unless they are fortified; however, they contribute calcium to the diet because they contain small amounts of calcium and people consume them frequently. Foods fortified with calcium include many fruit juices and drinks, tofu, and cereals. Selected food sources of calcium are listed in Table 2.

Table 1.2: Food sources of calcium

Food Source	Serving Size	Calcium (mg)
Milk & yogurt	8 oz	300-450
Cheese	3 oz	300-450
Bones in canned sardines and salmon	3 oz	181-325
Calcium fortified foods (i.e., orange juice, soy milk)	8 oz	200-300
Dark green, leafy vegetables	1 cup	100-200

(KH and JT, 1994)

1.1.3.1 Dietary supplements

The two main forms of calcium in supplements are carbonate and citrate. Calcium carbonate is more commonly available and is both inexpensive and convenient. Due to its dependence on stomach acid for absorption, calcium carbonate is absorbed most efficiently when taken with food, whereas calcium citrate is absorbed equally well when taken with or without food (Struab, 2007).

Calcium citrate is also useful for people with achlorhydria, inflammatory bowel disease, or absorption disorders. Other calcium forms in supplements or fortified foods include gluconate, lactate, and phosphate. Calcium citrate malate is a well-absorbed form of calcium found in some fortified juices (Andon , 2016)

Calcium supplements contain varying amounts of elemental calcium. For example, calcium carbonate is 40% calcium by weight, whereas calcium citrate is 21% calcium. Fortunately, elemental calcium is listed in the Supplement Facts panel, so consumers do not need to calculate the amount of calcium supplied by various forms of calcium supplements (KH & JT, 1994).

The percentage of calcium absorbed depends on the total amount of elemental calcium consumed at one time; as the amount increases, the percentage absorption decreases. Absorption is highest in doses ≤500 mg. So, for example, one who takes 1,000 mg/day of calcium from supplements might split the dose and take 500 mg at two separate times during the day.

Some individuals who take calcium supplements might experience gastrointestinal side effects including gas, bloating, constipation, or a combination of these symptoms. Calcium carbonate appears to cause more of these side effects than calcium citrate, so consideration of the form of calcium supplement is warranted if these side effects are reported. Other strategies to alleviate symptoms include spreading out the calcium dose throughout the day and/or taking the supplement with meals.

1.1.3.2Medicines

Because of its ability to neutralize stomach acid, calcium carbonate is found in some over-the-counter antacid products, such as Tums® and Rolaids®. Depending on its strength, each chewable pill provides 200 to 400 mg of elemental calcium. As noted above, calcium carbonate

is an acceptable form of supplemental calcium, especially for individuals who have normal levels of stomach acid (Ross *et al.,* 2011).

1.1.4 Calcium absorption

Calcium is absorbed by active transport (transcellularly) and by passive diffusion (paracellularly) across the intestinal mucosa. Active transport of calcium is dependent on the action of calcitriol and the intestinal vitamin D receptor (VDR). This transcellular mechanism is activated by calcitriol and accounts for most of the absorption of calcium at low and moderate intake levels. Transcellular transport occurs primarily in the duodenum where the VDR is expressed in the highest concentration, and is dependent on up-regulation of the responsive genes including the calcium transport protein called transient receptor potential cation channel, vanilloid family member 6 or TRPV6. These features up-regulation of VDR and TRPV6 are most obvious during states in which a high efficiency of calcium absorption is required. Passive diffusion or paracellular uptake involves the movement of calcium between mucosal cells and is dependent on luminal serosal electrochemical gradients. Passive diffusion occurs more readily during higher calcium intakes (i.e., when luminal concentrations are high) and can occur throughout the length of the intestine (Ireland and Fordtran, 1973). However, the permeability of each intestinal segment determines passive diffusion rates. The highest diffusion of calcium occurs in the duodenum, jejunum, and ileum. From a recent series of controlled metabolic studies undertaken by the USDA, mean calcium absorption (also referred to as "fractional calcium absorption," which is the percentage of a given dose of calcium that is absorbed) in men and non-pregnant women—across a wide age range—has been demonstrated to be approximately 25 percent of calcium intake. Mean urinary loss averages 22 percent and fecal loss 75 percent of total calcium intake, with minor losses from sweat, skin, hair, etc. In general, mean calcium absorption and calcium intake are directly related (Hunt and Johnson, 2007). However, fractional calcium absorption varies inversely with calcium intake when the intake is very low (Ireland and Fordtran, 1973). For example, when calcium intake was lowered from 2,000 to 300 mg, healthy women increased their fractional whole body retention of ingested calcium, an index of calcium absorption, from 27 percent to about 37 percent. This type of adaptation occurs within 1 to 2 weeks and is accompanied by a decline in serum calcium concentration and a rise in serum PTH and calcitriol concentrations. The fraction of calcium absorbed rises adaptively as intake is

lowered. However, this rise is not sufficient to offset the loss in absorbed calcium that occurs as a result of the lower intake of calcium—however modest that decrease may be—and thus net calcium absorption is reduced. Fractional calcium absorption varies during critical periods of life. In infancy, it is high at approximately 60 percent, although the range is large. Calcium absorption in newborns is largely passive and facilitated by the lactose content of breast milk. As the neonate ages, passive absorption declines and calcitriol-stimulated active intestinal calcium absorption becomes more important (Ireland and Fordtran, 1973).

1.1.5 Factors affecting increasing calcium absorption

The calcium that is consume from diet or as a supplement is absorbed by the body in the small intestine. Not all the calcium that people eat will be absorbed, some will pass through the body and be excreted as waste. How much calcium is absorbed by the body depends on the type of calcium consumption, how well the calcium dissolves in the intestines, and the amount of calcium in body.

1.1.5.1 Acidic conditions in the intestine

Calcium carbonate requires an acidic environment in order to be dissolved in the intestine and absorbed into the blood. Stomach acid production increases in the presence of food, creating an acidic environment. Therefore, calcium carbonate supplements should be taken with a meal. Calcium citrate does not require the presence of extra stomach acid to dissolve and be absorbed and can be taken on an empty or full stomach.

1.1.6 Vitamin D

Calcium absorption is dependent on an adequate level of the active form of vitamin D. Often vitamin D is supplemented, along with calcium. Vitamin D supplements are usually not necessary because vitamin D is available from vitamin D fortified milk, foods such as fish and egg yolks, and exposure to sunlight by the skin. In general, you only need 10-15 minutes of sunlight exposure to maintain an adequate vitamin D level. However, the amount of sunlight that your skin absorbs is dependent on the weather, latitude, time of year, the amount of skin exposed, and sunscreen use.

1.1.7 Estrogen

Estrogen is a hormone that plays an important role in helping increase calcium absorption. After menopause, estrogen levels drop and so may calcium absorption. Hormone replacement therapy has been shown to increase the production of vitamin D thus increasing calcium absorption. (NA, 1994)

1.1.8 Low calcium intakes

The body absorbs calcium less efficiently as calcium intake increases, therefore it is best to take calcium in smaller doses throughout the day to aid absorption. People should not take more than 500 milligrams of calcium at one time and allow 4 to 6 hours between doses.

1.1.9 Low blood calcium

When the calcium level in blood is low, parathyroid hormone is released and increases the production of vitamin D. The vitamin D helps increase calcium absorption, returns the amount of calcium in the blood to normal levels, and makes calcium available to be deposited in the bones.

1.1.10 Lactose

Lactose, the major carbohydrate in milk, aids calcium absorption, however, how this occurs in the body is still unknown.

1.2 Type of supplements

One factor affecting calcium absorption from supplement tablets is how well the calcium tablet dissolves. People should ensure during taking a supplement that will dissolve in intestine and should take one that meets the U.S. Pharmacopeia's (USP) standards for dissolution. The "USP" letters on the label indicate that the supplement meets the U.S. Pharmacopeia's standards for the amount of elemental calcium in a tablet and how well the tablet dissolves. According to USP standards, a calcium tablet must contain 90-110% of the amount of elemental calcium listed on the supplement label and must dissolve in 30-40 minutes.

1.3 Factors affecting decreasing calcium absorption

1.3.1 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 (Weaver, 2016).

1.3.2Phytates

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 (Weaver, 2016).

1.3.3 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 (Weaver, 2016).

1.3.4 Laxatives or anything that induces diarrhea

Diarrhea can move substances through the intestine very rapidly, not leaving enough time for calcium to be absorbed.

1.3.5 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 (Heaney, 2001).

1.3.6 Caffeine intake

This stimulant in coffee and tea can modestly increase calcium excretion and reduce absorption. One cup of regular brewed coffee, for example, causes a loss of only 2–3 mg of calcium.

Moderate caffeine consumption (1 cup of coffee or 2 cups of tea per day) in young women has no negative effects on bone (Heaney, 2009).

1.3.7 Alcohol intake

Alcohol intake can affect calcium status by reducing its absorption and by inhibiting enzymes in the liver that help convert vitamin D to its active form. However, the amount of alcohol required to affect calcium status and whether moderate alcohol consumption is helpful or harmful to bone is unknown.

1.3.8 Tannins in tea

Tannins are substances found in tea which can bind with calcium in the intestine, therefore decreasing its absorption (Heaney, 2009).

1.3.9 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.

1.4 Calcium Deficiency

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 (KH and JT, 1994).

1.5 Calcium and Health

Many claims are made about calcium's potential benefits in health promotion and disease prevention and treatment. This section focuses on several areas in which calcium is or might be involved: bone health and osteoporosis; cardiovascular disease; blood pressure regulation and hypertension; cancers of the colon, rectum, and prostate; kidney stones; and weight management.

1.6 Bone health and osteoporosis

Bones increase in size and mass during periods of growth in childhood and adolescence, reaching peak bone mass around age 30. The greater the peak bone mass, the longer one can delay serious bone loss with increasing age. Everyone should therefore consume adequate amounts of calcium and vitamin D throughout childhood, adolescence, and early adulthood. Osteoporosis, a disorder characterized by porous and fragile bones, is a serious public health problem for more than 10 million U.S. adults, 80% of whom are women. (Another 34 million have osteopenia, or low bone mass, which precedes osteoporosis.) Osteoporosis is most associated with fractures of the hip, vertebrae, wrist, pelvis, ribs, and other bones (Nordin, 1997). An estimated 1.5 million fractures occur each year in the United States due to osteoporosis (Birge *et al.*, 1967).

When calcium intake is low or ingested calcium is poorly absorbed, bone breakdown occurs as the body uses its stored calcium to maintain normal biological functions. Bone loss also occurs as part of the normal aging process, particularly in postmenopausal women due to decreased amounts of estrogen. Many factors increase the risk of developing osteoporosis, including being

female, thin, inactive, or of advanced age; smoking cigarettes; drinking excessive amounts of alcohol; and having a family history of osteoporosis (Nordin, 1997).

1.7 Cancer of the colon and rectum

Data from observational and experimental studies on the potential role of calcium in preventing colorectal cancer, though somewhat inconsistent, are highly suggestive of a protective effect. Several studies have found that higher intakes of calcium from foods (low-fat dairy sources) and/or supplements are associated with a decreased risk of colon cancer. In a follow-up study to the Calcium Polyp Prevention Study, supplementation with calcium carbonate led to reductions in the risk of adenoma (a nonmalignant tumor) in the colon, a precursor to cancer even as long as 5 years after the subjects stopped taking the supplement. In two large prospective epidemiological trials, men and women who consumed 700–800 mg per day of calcium had a 40%–50% lower risk of developing left-side colon cancer. But other observational studies have found the associations to be inconclusive (Baron *et al.,* 1999).

In the Women's Health Initiative, a clinical trial involving 36,282 postmenopausal women, daily supplementation with 1,000 mg of calcium and 400 International Units (IU) of vitamin D3 for 7 years produced no significant differences in the risk of invasive colorectal cancer compared to placebo. The authors of a Cochrane systematic review concluded that calcium supplementation might moderately help prevent colorectal adenomas, but there is not enough evidence to recommend routine use of calcium supplements to prevent colorectal cancer (Chan, 2016).

1.8 Cancer of the prostate

Several epidemiological studies have found an association between high intakes of calcium, dairy foods or both and an increased risk of developing prostate cancer. However, others have found only a weak relationship, no relationship, or a negative association between calcium intake and prostate cancer risk. The authors of a meta-analysis of prospective studies concluded that high intakes of dairy products and calcium might slightly increase prostate cancer risk (Chan and Giovannucci, 2001).

Interpretation of the available evidence is complicated by the difficulty in separating the effects of dairy products from that of calcium. But overall, results from observational studies suggest that total calcium intakes >1,500 mg/day or >2,000 mg/day may be associated with increased prostate cancer risk (particularly advanced and metastatic cancer) compared with lower amounts of calcium (500–1,000 mg/day. Additional research is needed to clarify the effects of calcium and/or dairy products on prostate cancer risk and elucidate potential biological mechanisms (Giovannucci, 1998).

1.9 Cardiovascular disease

Calcium has been proposed to help reduce cardiovascular disease (CVD) risk by decreasing intestinal absorption of lipids, increasing lipid excretion, lowering cholesterol levels in the blood, and promoting calcium influx into cells. However, data from prospective studies of calcium's effects on CVD risk are inconsistent, and whether dietary calcium has different effects on the cardiovascular system than supplemental calcium is not clear. In the Iowa Women's Health Study, higher calcium intake from diet and/or supplements was associated with reduced ischemic heart disease mortality in postmenopausal women (Bostick *et al.*, 1999).

Conversely, in a cohort of older Swedish women, both total and dietary calcium intakes of 1,400 mg/day and higher were associated with higher rates of death from CVD and ischemic heart disease than intakes of 600–1,000 mg/day. Other prospective studies have shown no significant associations between calcium intake and cardiac events or cardiovascular mortality. Data for stroke are mixed, with some studies linking higher calcium intakes to lower risk of stroke, and others finding no associations or trends in the opposite direction (Michaelsson *et al.*, 2013).

Scientists hypothesize that any adverse effects of calcium supplementation on the cardiovascular system could be mediated through hypercalcemia which can occur when excessively high calcium intakes override normal homeostatic control of serum calcium levels. Hypercalcemia has been associated with increased blood coagulation, vascular calcification, and arterial stiffness, thereby raising CVD risk. High calcium intakes can also increase circulating levels of fibroblast growth factor 23, which is associated with an increased risk of cardiovascular events. Supplemental calcium, in particular, causes an acute increase in serum calcium levels, and some researchers hypothesize that this abrupt change, rather than total calcium load, could be responsible for the observed adverse effects (Bolland et al., 2011).

Many scientists have questioned the strength of the available evidence that links supplemental calcium intake with CVD risk, noting that researchers have only considered CVD outcomes in secondary analyses of trial data and these outcomes have not been the primary endpoint of any calcium supplementation trials to date. In their 2012 review of prospective studies and randomized clinical trials, Wang and colleagues concluded that calcium intake from diet or supplements appears to have little or no effect on CVD risk but the available evidence does not allow for a definitive conclusion (Wang *et al.*, 2012).

1.10 Blood pressure and hypertension

Several clinical trials have demonstrated a relationship between increased calcium intakes and both lower blood pressure and risk of hypertension although the reductions are inconsistent. In the Women's Health Study, calcium intake was inversely associated with risk of hypertension in middle-aged and older women (McCarron and Reusser, 1999).

Other observational and experimental studies suggest that individuals who eat a vegetarian diet high in minerals (such as calcium, magnesium, and potassium) and fiber and low in fat tend to have lower blood pressure (Rouse *et al.*, 1986). The Dietary Approaches to Stop Hypertension (DASH) study was conducted to test the effects of three different eating patterns on blood pressure: a control "typical" American diet; one high in fruits and vegetables; and a third diet high in fruits, vegetables, and low-fat dairy products. The diet containing dairy products resulted in the greatest decrease in blood pressure, although the contribution of calcium to this effect was not evaluated (Appel, 1997).

1.11 Kidney stones

Kidney stones in the urinary tract are most commonly composed of calcium oxalate. Some, but not all, studies suggest a positive association between supplemental calcium intake and the risk of kidney stones, and these findings were used as the basis for setting the calcium UL in adults. In the Women's Health Initiative, postmenopausal women who consumed 1,000 mg of supplemental calcium and 400 IU of vitamin D per day for 7 years had a 17% higher risk of kidney stones than subjects taking a placebo. The Nurses' Health Study also showed a positive association between supplemental calcium intake and kidney stone formation. High intakes of dietary calcium, on the other hand, do not appear to cause kidney stones and may actually protect

against developing them . For most individuals, other risk factors for kidney stones, such as high intakes of oxalates from food and low intakes of fluid, probably play a bigger role than calcium intake (Jackson, 2006)

1.12 Groups at Risk of Calcium Inadequacy

Although frank calcium deficiency is uncommon, dietary intakes of the nutrient below recommended levels might have negative health consequences over the long term. The following groups are among those most likely to need extra calcium (Borghi *et al.*, 2002).

1.13 Postmenopausal women

Menopause leads to bone loss because decreases in estrogen production both increase bone resorption and decrease calcium absorption (NA, 1994). Annual decreases in bone mass of 3%–5% per year frequently occur in the first years of menopause, but the decreases are typically less than 1% per year after age 65. Increased calcium intakes during menopause do not completely offset this bone loss Hormone replacement therapy (HRT) with estrogen and progesterone helps increase calcium levels and prevent osteoporosis and fractures. Estrogen therapy restores postmenopausal bone remodeling to the same levels as at premenopause, leading to lower rates of bone loss, perhaps in part by increasing calcium absorption in the gut (Dawson-Hughes *et al.*, 1991).

1.14 Amenorrheic women and the female athlete triad

Amenorrhea, the condition in which menstrual periods stop or fail to initiate in women of childbearing age, results from reduced circulating estrogen levels that, in turn, have a negative effect on calcium balance. Amenorrheic women with anorexia nervosa have decreased calcium absorption and higher urinary calcium excretion rates, as well as a lower rate of bone formation than healthy women (Abrams *et al.*, 1993). The "female athlete triad" refers to the combination of disordered eating, amenorrhea, and osteoporosis. Exercise-induced amenorrhea generally results in decreased bone mass. In female athletes and active women in the military, low bone-mineral density, menstrual irregularities, certain dietary patterns, and a history of prior stress

fractures are associated with an increased risk of future stress fractures. Such women should be advised to consume adequate amounts of calcium and vitamin D. Supplements of these nutrients have been shown to reduce the risk of stress fractures in female Navy recruits during basic training (Nattiv, 2000).

1.14 Individuals with lactose intolerance or cow's milk allergy

Lactose intolerance refers to symptoms (such as bloating, flatulence, and diarrhea) that occur when one consumes more lactose, the naturally occurring sugar in milk, than the enzyme lactase produced by the small intestine can hydrolyze into its component monosaccharides, glucose and galactose. The symptoms vary, depending on the amount of lactose consumed, history of consumption of lactose-containing foods, and type of meal. Although the prevalence of lactose intolerance is difficult to discern [38], some reports suggest that approximately 25% of U.S. adults have a limited ability to digest lactose, including 85% of Asians, 50% of African Americans, and 10% of Caucasians.

Lactose-intolerant individuals are at risk of calcium inadequacy if they avoid dairy products. Research suggests that most people with lactose intolerance can consume up to 12 grams of lactose, such as that present in 8 ounces of milk, with minimal or no symptoms, especially if consumed with other foods; larger amounts can frequently be consumed if spread over the day and eaten with other foods. Other options to reduce symptoms include eating low-lactose dairy products including aged cheeses (such as Cheddar and Swiss), yogurt, or lactose-reduced or lactose-free milk. Some studies have examined whether it is possible to induce adaptation by consuming increment lactose loads over a period of time but the evidence in support of this strategy is inconsistent.

Cow's milk allergy is less common than lactose intolerance, affecting 0.6% to 0.9% of the population. People with this condition are unable to consume any products containing cow's milk proteins and are therefore at higher risk of obtaining insufficient calcium.

To ensure adequate calcium intakes, lactose-intolerant individuals and those with cow's milk allergy can choose nondairy food sources of the nutrient (such as kale, bok choy, Chinese cabbage, broccoli, collards and fortified foods) or take a calcium supplement.

1.15 Vegetarians

Vegetarians might absorb less calcium than omnivores because they consume more plant products containing oxalic and phytic acids. Lacto-ovo vegetarians (who consume eggs and dairy) and nonvegetarians have similar calcium intakes. However, vegans, who eat no animal products and ovo-vegetarians (who eat eggs but no dairy products), might not obtain sufficient calcium because of their avoidance of dairy foods. In the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition, bone fracture risk was similar in meat eaters, fish eaters and vegetarians, but higher in vegans, likely due to their lower mean calcium intake. It is difficult to assess the impact of vegetarian diets on calcium status because of the wide variety of eating practices and thus should be considered on a case by case basis.

1.16 Health Risks from Excessive Calcium

Excessively high levels of calcium in the blood known as hypercalcemia can cause renal insufficiency, vascular and soft tissue calcification, hypercalciuria (high levels of calcium in the urine) and kidney stones. Although very high calcium intakes have the potential to cause hypercalcemia, it is most commonly associated with primary hyperparathyroidism or malignancy.

High calcium intake can cause constipation. It might also interfere with the absorption of iron and zinc, though this effect is not well established. High intake of calcium from supplements, but not foods, has been associated with increased risk of kidney stones. Some evidence links higher calcium intake with increased risk of prostate cancer, but this effect is not well understood, in part because it is challenging to separate the potential effect of dairy products from that of calcium. Some studies also link high calcium intake, particularly from supplements, with increased risk of cardiovascular disease.

The Tolerable Upper Intake Levels (ULs) for calcium established by the Food and Nutrition Board are listed in Table 3 in milligrams (mg) per day. Getting too much calcium from foods is rare; excess intakes are more likely to be caused by the use of calcium supplements. NHANES data from 2003–2006 indicate that approximately 5% of women older than 50 years have

estimated total calcium intakes (from foods and supplements) that exceed the UL by about 300–365 mg.

Table 1.3: Tolerable Upper Intake Levels (ULs) for Calcium

Age	Male	Female Pregnant	Lactating	Age
0–6 months	1,000 mg	1,000 mg		
7–12 months	1,500 mg	1,500 mg		
1–8 years	2,500 mg	2,500 mg		
9–18 years	3,000 mg	3,000 mg	3,000 mg	3,000 mg
19–50 years	2,500 mg	2,500 mg	2,500 mg	2,500 mg
51+ years	2,000 mg	2,000 mg		

(Nattiv, 2000)

1.16.1 **Interactions with Medications**

Calcium supplements have the potential to interact with several types of medications. This section provides a few examples. Individuals taking these medications on a regular basis should discuss their calcium intake with their healthcare providers.

Calcium can decrease absorption of the following drugs when taken together: biphosphonates (to treat osteoporosis), the fluoroquinolone and tetracycline classes of antibiotics, levothyroxine, phenytoin (an anticonvulsant), and tiludronate disodium (to treat Paget's disease).

Thiazide-type diuretics can interact with calcium carbonate and vitamin D supplements, increasing the risks of hypercalcemia and hypercalciuria.

Both aluminum- and magnesium-containing antacids increase urinary calcium excretion. Mineral oil and stimulant laxatives decrease calcium absorption. Glucocorticoids, such as prednisone, can cause calcium depletion and eventually osteoporosis when they are used for months.

1.16.2 Calcium 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.Many dairy products, such as milk, cheese, and yogurt, are rich sources of calcium. Some vegetables provide significant amounts of calcium, as do some fortified cereals and juices. Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.Tofu made with calcium salts is a good source of calcium (check the label), as are canned sardines and canned salmon with edible bones. Limits saturated and trans fats, added sugars, and sodium. Low-fat and nonfat dairy products provide amounts of calcium that are roughly similar to the amounts in their full-fat versions.

1.17 Vitamin D

Vitamin D is the general name given to a group of fat-soluble compounds that are essential for maintaining the mineral balance in the body. Vitamin D (calciferol) comprises a group of fat soluble seco-sterols found naturally only in a few foods, such as fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. The two major physiologically relevant forms of vitamin D are D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is photosynthesized in the skin of vertebrates by the action of solar ultraviolet (UV) B radiation on 7-dehydrocholesterol (Fieser, 1959).

Vitamin D2 is produced by UV irradiation of ergosterol, which occurs in molds, yeast, and higher-order plants. Under conditions of regular sun exposure, dietary vitamin D intake is of minor importance. However, latitude, season, aging, sunscreen use, and skin pigmentation influence the production of vitamin D3 by the skin (Institute of Medicine 1997). Most of the dietary intake of vitamin D comes from fortified milk products and other fortified foods such as

breakfast cereals and orange juice .Both vitamin D2 and D3 are used in nonprescription vitamin D supplements, but vitamin D2 is the form available by prescription in the United States. As cholecalciferol is synthesized in the skin by the action of ultraviolet light on 7-dehydrocholesterol, a cholesterol derivative, and vitamin D does not fit the classical definition of a vitamin. Nevertheless, because of the numerous factors that influence its synthesis, such as latitude, season, air pollution, area of skin exposed, pigmentation, age, etc., vitamin D is recognized as an essential dietary nutrient (Holick, 2007).

1.18 Role of vitamin D

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

1.19 Food source of vitamin D

Table 1.4: vitamin D containing food

• Salmon, Mackerel and Other Fatty Fish
• Vitamin D3 Fortified Milk or Raw milk
• Butter, Cheese, Egg
• Cod Liver Oil and Other Fish Oils
• Beef Liver, Chicken Liver and Pork Liver
• Mushrooms

(Holick, 2007)

1.19.1 Other source

- sun light exposure

1.19.2 Salmon, Mackerel and Other Fatty Fish

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

1.19.3 Vitamin D3 Fortified Milk or Raw Milk

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

1.19.4 Cod Liver Oil and Other Fish Oils

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

1.19.5 Beef Liver, Chicken Liver and Pork Liver

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

1.19.6 Butter, Cheese and Eggs

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

1.19.7 Other Fortified Foods

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

1.19.8 Sun Exposure

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

vitamin D is essential for the control of normal calcium and phosphate blood levels. It is known to be required for the absorption of calcium and phosphate in the small intestine, their Awareness of Calcium & Vitamin D among college going students in Bangladesh. 26 mobilization from the bones, and their reabsorption in the kidneys. Through these three functions it plays an important role for the proper functioning of muscles, nerves and blood clotting and for normal bone formation and mineralization. It has been suggested that vitamin D also plays an important role in controlling cell proliferation and differentiation, immune responses and insulin secretion.

1.20 Metabolism of Vitamin D

Vitamin D itself does not act upon intestine, kidney and bone but must be bioactivated in the liver and kidney. To be biologically activated at physiologic concentrations, Calcifediol [25(OH)D3] must be converted in the kidneys to 1,25-dihydroxyvitamin D or Calcitriol [1,25(OH)2D] which is thought to be responsible for most, if not all, of the biologic functions of vitamin D. The production of Calcifediol in the liver and of Calcitriol in the kidney is tightly regulated. In the liver, vitamin D-25-hydroxylase is down-regulated by vitamin D and its metabolites, thereby limiting any increase in the circulating concentration of Calcifediol following intakes or following production of vitamin D after exposure to sunlight. In the kidney, in response to serum calcium and phosphorus concentrations, the production of Calcitriol is regulated through the action of parathyroid hormone (DeLuca 1988).

1.21 Metabolic Activation

Whether derived from diet or endogenously synthesized, vitamin D requires modification to become biologically active. The primary active metabolite of the vitamin is calcitriol [1a,25-dihydroxyvitamin D, 1,25(OH)2D], the product of two successive hydroxylation of vitamin .

1.22 Hydroxylation of Vitamin D

The initial step in vitamin D activation occurs in the liver, where cholecalciferol and ergocalciferol are hydroxylated in the 25-position to generate 25-OH-cholecalciferol (25-OHD, or calcifediol) and 25-OH-ergocalciferol, respectively. 25-OHD is the major circulating form of vitamin D3; it has a biological half-life of 19 days, and normal steady-state concentrations are 15 to 50 mg/ml. Reduced extracellular Ca2+ levels stimulate 1a-hydroxylation of 25-OHD, increasing the formation of biologically active 1,25(OH)2D3. In contrast, when Calcium ion concentrations are elevated, 25-OHD is inactivated by 24-hydroxylation. Similar reactions occur with 25-OH-ergocalciferol. Normal steady-state concentrations of 25-OHD in human beings are 15 to 50 mg/ml, although concentrations below 25 mg/ml may be associated with increased circulating PTH and greater bone turnover.

1.23 24-Hydroxylase

Calcitriol and 25-OHD are hydroxylated to 1, 24, 25(OH)2D and 24,25(OH)2D, respectively, by another renal enzyme, 24-hydroxylase, whose expression is induced by calcitriol and suppressed by factors that stimulate the 25-OHD-1a-hydroxylase. Both 24-hydroxylated compounds are less active than calcitriol and presumably represent metabolites destined for excretion Active vitamin D functions as a hormone, and its main biologic function in people is to maintain serum calcium and phosphorus concentrations within the normal range by enhancing the efficiency of the small intestine to absorb these minerals from the diet (DeLuca, 1988).

When dietary calcium intake is inadequate to satisfy the body's calcium requirement, 1,25(OH)2 D, along with PTH, mobilizes calcium stores from the bone. In the kidney, 1,25(OH)2 D increases calcium reabsorption by the distal renal tubules. Apart from these traditional calcium-related actions, 1,25(OH)2 D and its synthetic analogs are increasingly recognized for their potent antiproliferative, prodifferentiative, and immunomodulatory activities (Nagpal *et at.*, 2005)

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

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

1.25 Absorption and Excretion of vitamin D

Both vitamins D2 and D3 are absorbed from the small intestine, although vitamin D3 may be absorbed more efficiently. Most of the vitamin appears first within chylomicrons in lymph. Bile is essential for adequate absorption of vitamin D; deoxycholic acid is the major constituent of bile in this regard. The primary route of vitamin D excretion is the bile; only a small percentage

is found in the urine. Patients who have intestinal bypass surgery or otherwise have severe shortening or inflammation of the small intestine may fail to absorb vitamin D sufficiently to maintain normal levels; hepatic or biliary dysfunction also may seriously impair vitamin D absorption. Absorbed vitamin D circulates in the blood in association with vitamin D-binding protein, a -globulin. The vitamin disappears from plasma with a half-life of 19 to 25 hours but isαspecific stored in fat depots for prolonged periods.

1.26 Production Regulation of Calcitriol

Calcitriol, the active form of vitamin D, is an important player in calcium and bone metabolism, but it also has a physiological role beyond its well-known role in skeletal homeostasis. Receptors for Calcitriol are present in various immune cells, including monocytes, macrophages and dendritic cells, as well as T and B lymphocytes, thus suggesting a role for Calcitriol in both innate and adaptive immune responses. Besides being targets, immune cells express vitamin Dactivating enzymes, allowing local conversion of inactive vitamin D into Calcitriol within the immune system. Data from epidemiological studies are clear: vitamin D deficiency, especially in early life, increases the risk of autoimmune diseases later on and is associated overall with an increased risk of infections. Moreover, higher levels of Calcitriol are associated with relative protection against infections and autoimmune diseases. These association data are corroborated by experiments in preclinical animal models, where data exist that even supplementing with high doses of vitamin D or analogues of Calcitriol can interfere with the course of immune diseases, especially autoimmune diseases like colitis, multiple sclerosis and type 1 diabetes. Vitamin D without a subscript represents either D2 or D3 or both and is biologically inert. Vitamin D from the skin or diet is only short-lived in circulation (with a half-life of 1–2 days), as it is either stored in fat cells or metabolized in the liver (Mawer *et al.,* 1972). In circulation, vitamin D is bound to vitamin D-binding protein and transported to the liver, where it is converted to 25-hydroxyvitamin D [25(OH)D] (DeLuca 1984). This major circulating form of vitamin D is a good reflection of cumulative effects of exposure to sunlight and dietary intake of vitamin D (Haddad 1973) and is therefore used by clinicians to determine vitamin D status.

1.27 Vitamin D Reinvented

An important clue to roles of vitamin D beyond calcium homeostasis came with the finding that the 1,25-dihydroxyvitamin D nuclear receptor is present in most tissues. A reevaluation of the physiological and pharmacological actions of vitamin D produced evidence that vitamin D can regulate the immune system and thereby is implicated in several immune-mediated diseases. In addition the literature contains reports that vitamin D insufficiency may play a role in the development of multiple sclerosis, rheumatoid arthritis, and asthma, and increases the risk of tuberculosis, pneumonia, poor cognitive function, periodontal disease, and reduced muscle tone and lower-extremity function. Several vitamin D supplementation studies have been reported, especially related to individual cancer types, and most show a modest positive effect. However, the most striking recent study based on vitamin D supplementation is the meta analysis of randomized control trials looking at total mortality .The authors identified 18 such trials of vitamin D intake that reported results for total mortality and found a 7% reduction in total mortality from any cause for patients, most taking relatively modest supplements of vitamin D (400–800 IU/day) (Holick 1995).

1.28 Disorders of Vitamin D

1.28.1 Hypervitaminosis D

The acute or long-term administration of excessive amounts of vitamin D or enhanced responsiveness to normal amounts of the vitamin leads to derangements in calcium metabolism. The responses to vitamin D reflect endogenous vitamin D production, tissue reactivity, and vitamin D intake. Some infants may be hyper reactive to small doses of vitamin D. In adults, hypervitaminosis D results from overtreatment of hypoparathyroidism or secondary hyperparathyroidism of renal osteodystrophy and from faddist use of excessive doses. Toxicity in children also may occur following accidental ingestion of adult doses.The amount of vitamin D necessary to cause hypervitaminosis varies widely. As a rough approximation, continued daily ingestion of 50,000 units or more by a person with normal parathyroid function and sensitivity to vitamin D may result in poisoning. Hypervitaminosis D is particularly dangerous in patients who are receiving digoxin because the toxic effects of the cardiac glycosides are enhanced by hypercalcemia. The initial signs and symptoms of vitamin D toxicity are those associated with hypercalcemia. Since hypercalcemia in vitamin D intoxication generally is due to very high

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

Vitamin D deficiency results in inadequate absorption of Calcium ion and phosphate. The consequent decrease of plasma Ca2+concentration stimulates PTH secretion, which acts to restore plasma Calcium ion at the expense of bone. Plasma concentrations of phosphate remain subnormal because of the phosphaturic effect of increased circulating PTH. In children, the result is a failure to mineralize newly formed bone and cartilage matrix, causing the defect in growth known as rickets. As a consequence of inadequate calcification, bones of individuals with rickets are soft, and the stress of weight bearing gives rise to bowing of the long bones. In adults, vitamin D deficiency results in osteomalacia, a disease characterized by generalized accumulation of undermineralized bone matrix. Severe osteomalacia may be associated with extreme bone pain and tenderness. Muscle weakness, particularly of large proximal muscles, is typical and may reflect both hypophosphatemia and inadequate vitamin D action on muscle. Gross deformity of bone occurs only in advanced stages of the disease. Circulating 25-OHD concentrations below 8 ng/ml are highly predictive of osteomalacia.

1.28.2 Metabolic Rickets and Osteomalacia

These disorders are characterized by abnormalities in calcitriol synthesis or response.

1.28.3 Hypophosphatemic vitamin D-resistant rickets

In its most common form, is an X-linked disorder (XLH) of calcium and phosphate metabolism. Calcitriol levels are inappropriately normal for the observed degree of hypophosphatemia. Patients experience clinical improvement when treated with large doses of vitamin D, usually incombination with inorganic phosphate. Even with vitamin D treatment, calcitriol

concentrationsmay remain lower than expected. The genetic basis for XLH hasbeen defined (Consortium, 1995). The affected protein, a phosphate-regulating gene with homologies to endopeptidases onthe X chromosome (PHEX), is a neutral endoprotease. The substrate for this enzyme likely isinvolved in renal phosphate transport. Syndromes closely related to XLH, in which phosphatelevels are altered without significant net changes in serum concentrations of calcium, PTH, or1,25(OH)2D3, includehereditary hypophosphatemic rickets with hypercalciuria and autosomal dominant hypophosphatemic rickets.The latter disorder maps to chromosome12p13.3 and is associated with mutations in the gene encoding fibroblast growth factor 23(Econs *et al*., 1997).

1.28.4 Renal Rickets

It is associated with chronic renal failure and is characterized by decreased conversion of 25-OHD to calcitriol. Phosphate retention decreases plasma Ca2+concentrations, leading to secondary hyperparathyroidism. In addition, calcitriol deficiency impairs intestinal Ca2+absorption and mobilization from bone. Hypocalcemia commonly results (although in some patients, prolonged and severe hyperparathyroidism eventually may lead to hypercalcemia). Aluminum deposition in bone also may play a role in the genesis of the skeletal disease (Goodman and Gillman, 2002).

Hereditary 1,25-dihydroxyvitamin D resistance (also called vitamin D-dependent rickets type II) Is an autosomal recessive disorder that is characterized by hypocalcemia, osteomalacia, rickets, and total alopecia. Mutations of the vitamin D receptor cause vitamin D-dependent rickets type II (Malloy et al., 1999). Absolute hormone resistance results from premature stop mutations or missense mutations in the zinc finger DNA-binding domain. Several missense mutations in the ligand-binding domain also have been described that result in partial or complete hormone resistance. These mutations alter ligand binding or heterodimerization with the retinoid X receptor (RXR). The 25(OH)-vitamin D values are normal, whereas 1,25(OH)2-vitamin D levels are elevated in type II vitamin D-dependent rickets. This clinical feature distinguishes hereditary vitamin Ddependent deficiency (vitamin D-dependent rickets type I), where αrickets type II from CYP1 serum 1,25(OH)2-vitamin D values are depressed. Children affected by vitamin D-dependent rickets type II are refractory even to massive doses of vitamin D and calcitriol, and

they may require prolonged treatment with parenteral Ca2+. Some remission of symptoms has been observed during adolescence, but the basis of remission is unknown.

1.29 Minimum Dose of Vitamin D

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

1.30 Risk factors for vitamin D deficiency

- Black & ethnic minority patients with darker skin
- Elderly patients in residential care, housebound or institutionalised patients
- Older people aged 65 years and over
- Infants and young children under 5 years of age
- Intestinal malabsorption e.g. coeliac disease, crohns disease, gastrectomy, cholestatic liver disease
- Routine covering of face or body e.g. habitual sunscreen use factor 15 or above
- Vegan/vegetarian diet
- Liver or renal disease
- Medications including certain anticonvulsants, cholestyramine, colestipol, liquid paraffin, sucralfate, rifampicin, glucocorticoids, highly active antiretrovirals
- Obesity
- All pregnant and breast feeding women, especially teenagers and young women
- Short interval pregnancies
- Patients with persistently low calcium, low phosphate or raised Alkaline Phosphatase
- Low vitamin D dietary intake
- Cystic fibrosis

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

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

1.31 Factors affect vitamin D status

Sun Exposure

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

Age

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

Dark Skin

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

Weight

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

Chronic illness

The body demands more vitamin D when we`re sick, and is probably using it up faster than we can get it from the sun. In order to achieve consistent and predictable results, it is important to use the proper carrier form of vitamin D supplements. The absolute best form is an oil-based vitamin D preparation. Dry preparations, like tablets and capsules, should be avoided. Vitamin D is fat soluble, and needs to be taken with fat in order to be properly absorbed - hence the oil-based recommendation. There are two common types of vitamin D: Vitamin D3 (cholecalciferol) and Vitamin D2 (ergocalciferol). Will need to avoid supplementing with vitamin D2 which is a synthetic product made by exposing certain plants to ultraviolet radiation. D2 is not what the human body naturally uses, and compared to D3 it falls far short in terms of efficacy.

Our Body Uses Vitamin D

Vitamin D is a fat-soluble vitamin that promotes absorption of calcium and phosphorus. Most people associate the nutrient calcium with healthy bones and teeth, but no matter how much calcium we have in your diet, without vitamin D, our body can't absorb and use the mineral. So vitamin D is vital for building — and holding — strong bones and teeth. Researchers at the Bone Metabolism Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston say vitamin D may also reduce the risk of tooth loss by preventing the inflammatory response that leads to periodontal disease, a condition that destroys the thin tissue (ligaments) that connects the teeth to the surrounding jawbone. Vitamin D comes in three forms: calciferol, cholecalciferol, and ergocalciferol. Calciferol occurs naturally in fish oils and egg yolk. In the United States, it's added to margarines and milk. Cholecalciferzl is created when sunlight hits our skin and ultraviolet rays react with steroid chemicals in body fat just underneath. Ergocalciferol is synthesized in plants exposed to sunlight. Cholecalciferol and ergocalciferol justify vitamin D's nickname: the Sunshine Vitamin.

1.32 Vitamin D Deficiency

Vitamin D deficiency is characterized by inadequate mineralization or by demineralization of the skeleton. Among children, vitamin D deficiency is a common cause of bone deformities known as rickets. Vitamin D deficiency in adults leads to a mineralization defect in the skeleton, causing osteomalacia, and induces secondary hyperparathyroidism with consequent bone loss and osteoporosis. Potential roles for vitamin D beyond bone health, such as effects on muscle strength, the risk for cancer and for type 2 diabetes, are currently being studied. The Agency for Healthcare Research and Quality recently reviewed the effectiveness and safety of vitamin D on outcomes related to bone health (Cranney *et al.,* 2007).

Table 1.5: Vitamin D deficiency diseases

• Alzheimer's	• Depression	• Insomnia
• Anxiety	• Insomnia	• Irritability
• Autism	• Multiple Sclerosis	• Reduced IQ
• Brain birth-defects	• Fatigue and malaise	• Schizophrenia
• Dementia	• Parkinson's	• Psychosis
• Aneurysm	• Hypertension	• Muscle wasting
• Arthritis and pain	• Hip fractures	• Osteoarthritis
• Asthma	• Hypothyroid	• Osteoporosis
• Chronic pain	• Hemorrhoids	• Periodontal disease
• Diabetes	• Migraines	• Rickets
• Fibromyalgia	• Multiple sclerosis	• Seizure
• Heart disease	• Muscle weakness	• Stroke

(Cranney *et al.,* 2007)

1.32.1 Vitamin D deficiency diseases on Immune system

Once foods were fortified with vitamin d and rickets appeared to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved. However, rickets can be considered the tip of the vitamin D–deficiency

iceberg. In fact, vitamin D deficiency remains common in children and adults. In uteri and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture. The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease (Pearce and Cheetham, 2010).

1.32.2 Vitamin D deficiency diseases on Cancer

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

1.32.3 Vitamin D deficiency causes autoimmune diseases, Osteoarthritis, and Diabetes

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

1diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet auto antibodies in offspring.53 For 10,366 children in Finland who were given 2000 IU of vitamin D3 per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80%.75 Among children with vitamin D deficiency the risk was increased by approximately 200%. In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome.53 Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D (Holick, 2004).

1.32.4 Vitamin D deficiency causes Cardiovascular Disease

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

1.32.5 Vitamin D deficiency causes Schizophrenia and Depression

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

1.32.6 Vitamin D deficiency causes Lung Function and Wheezing Illnesses

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

1.32.7 Vitamin D deficiency causes Mal absorption and Medication of vitamin D

Patients with mild or moderate hepatic failure or intestinal fat-mal absorption syndromes, as well as patients who are taking anticonvulsant medications, glucocorticoids, or other drugs that activate steroid and xenobiotic receptor, require higher doses of vitamin D .Exposure to sunlight or ultraviolet B radiation from a tanning bed or other ultraviolet B–emitting device is also effective. Sunlight and Artificial Ultraviolet B Radiation Sensible sun exposure can provide an adequate amount of vitamin D3, which is stored in body fat and released during the winter.

1.33 Vitamin D Toxicity

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

1.33.1 Toxic doses

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

1.33.2 Serum levels

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

1.34 Symptoms of vitamin D toxicity and overdose

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

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

It is fairly difficult to become toxic using vitamin D3. If we think we may be toxic because were having an adverse reaction to vitamin D but we have not been using excessive amounts like those described above, or symptoms could be due to reasons other than toxicity.

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

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

In most cases, vitamin D toxicity can be corrected without lasting problems, provided the body has not remained in a hypercalcemia state for too long. Hypocalcaemia has the potential to cause

soft tissue calcification, resulting in deposits of calcium crystals in the heart, lungs, and/or kidneys. With prolonged hypercalcemia, permanent damage is possible if calcification is severe enough.

1.35 Adverse Effects of Vitamin D Therapy

The primary toxicity associated with calcitriol reflects its potent effect to increase intestinal calcium and phosphate absorption, along with the potential to mobilize osseous calcium and phosphate. Hypercalcemia, with or without hyperphosphatemia, commonly complicates calcitriol therapy and may limitits use at doses that effectively suppress PTH secretion. As described earlier, noncalcemic vitamin D analogs provide alternative interventions, although they do not obviate the need to monitor serum calcium and phosphorus concentrations. Hypervitaminosis D is treated by immediate withdrawal of the vitamin, a low-calcium diet, administration of glucocorticoids, and vigorous fluid support. As noted earlier under hypercalcemia, forced saline diuresis with loop diuretics is also useful. With this regimen, the plasma Ca2+concentration falls to normal, and Ca2+in soft tissue tends to be mobilized. Conspicuous improvement in renalfunction occurs unless renal damage has been severe (Goodman and Gillman, 2002).

1.36 Symptoms of vitamin D toxicity

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

- vomiting
- poor appetite
- constipation (possibly alternating with diarrhea)
- weakness
- weight loss
- tingling sensations in the mouth
- confusion
- heart rhythm abnormalities

- The immediate symptoms of vitamin D overdose are:
- abdominal cramps
- nausea and vomiting

It is fairly difficult to become toxic using vitamin D3. If we think we may be toxic because we are having an adverse reaction to vitamin D but we have not been using excessive amounts like those described above, or symptoms could be due to reasons other than toxicity. If the results show a serum 25(OH)D level of 200-250 ng/mol (500-750 mol/L) or more, it could be toxic. The following measures should be taken until vitamin D levels return to normal:

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- drinking 8 glasses of water daily

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

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

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

hydroxylase to25-hydroxyvitamin D. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status.

1.38 Analogs of Calcitriol

Several vitamin D analogs suppress PTH secretion by the parathyroid glands but have less or negligible hypercalcemic activity. They therefore offer a safer and more effective means of controlling secondary hyperparathyroidism. Calcipotriol (calcipotriene) is a synthetic derivative of calcitriol with a modified side chain that contains a 22-23 double bond, a 24(S)-hydroxy functional group, and carbons 25 to 27 incorporated into a cyclopropane ring. Calcipotriol has comparable affinity with calcitriol for the vitamin D receptor, but it is less than 1% as active as calcitriol in regulating calcium metabolism. This reduced calcemic activity largely reflects the pharmacokinetics of calcipotriol (Kissmeyer and Binderup, 1991).

Calcipotriol has been studied extensively as a treatment for psoriasis, although its mode of action is not known; a topical preparation is available for that purpose. In clinical trials, topical calcipotriol has been found to be slightly more effective than glucocorticoids with a good safety profile. Paricalcitol (1,25-dihydroxy-19-norvitamin D2) is a synthetic calcitriol derivative that lacks the exocyclic C19 and has a vitamin D2 rather than vitamin D3 side chain. It reduces serum PTH levels without producing hypercalcemia or altering serum phosphorus (Martin *et al.*, 1998). In an animal model, paricalcitol prevented or reversed PTH-induced high-turnover bone disease (Slatopolsky *et al.*, 2003). Paricalcitol administered intravenously is FDA approved for treating secondary hyperparathyroidism in patients with chronic renal failure. 22-Oxacalcitriol (1,25-dihydroxy-22-oxavitamin D3, OCT, maxicalcitol, OXAROL) differs from calcitriol only in the substitution of C-22 with an oxygen atom. Oxacalcitriol has a low affinity for vitamin D-binding protein; as a result, more of the drug circulates in the free (unbound) form, allowing it to be metabolized more rapidly than calcitriol with a consequent shorter half-life. Oxacalcitriol is a potent suppressor of PTH gene expression and shows very limited activity on intestine and bone. It is a useful compound in patients with overproduction of PTH in chronic renal failure or even with primary hyperparathyroidism (Cunningham, 2004).

1.39 Indications for Therapy with Vitamin D

The major therapeutic uses of vitamin D may be divided into four categories:

- prophylaxis and cure of nutritional rickets;
- treatment of metabolic rickets and osteomalacia, particularly in the setting of chronic renal failure
- treatment of hypoparathyroidism
- prevention and treatment of osteoporosis

1.40 Nutritional Rickets

Nutritional rickets results from inadequate exposure to sunlight or deficiency of dietary vitamin D. The condition, once extremely rare in the United States and other countries where food fortification with the vitamin is practiced, is now increasing. Infants and children receiving adequate amounts of vitamin D-fortified food do not require additional vitamin D; however, breast-fed infants or those fed unfortified formula should receive 400 units of vitamin D daily as a supplement. The usual practice is to administer vitamin A in combination with vitamin D. A number of balanced vitamin A and D preparations are available for this purpose. Since the fetus acquires more than 85% of its calcium stores during the third trimester, premature infants are especially susceptible to rickets and may require supplemental vitamin D. Treatment of fully developed rickets requires a larger dose of vitamin D than that used prophylactically. One thousand units daily will normalize plasma Ca^{2+} and phosphate concentrations in approximately 10 days, with radiographic evidence of healing within about 3 weeks. However, a larger dose of 3000 to 4000 units daily often is prescribed for more rapid healing, particularly when respiration is compromised by severe thoracic rickets. Vitamin D may be given prophylactically in conditions that impair its absorption (e.g., diarrhea, steatorrhea, and biliary obstruction). Parenteral administration also may be used in such cases.

1.41 Treatment of Osteomalacia and Renal Osteodystrophy

Osteomalacia, distinguished by undermineralization of bone matrix, occurs commonly during sustained phosphate depletion. Patients with chronic renal disease are at risk for developing osteomalacia but also may develop a complex bone disease called renal osteodystrophy. In this setting, bone metabolism is stimulated by an increase in PTH and by a delay in bone mineralization that is due to decreased renal synthesis of calcitriol. In renal osteodystrophy, low bone mineral density may be accompanied by high-turnover bone lesions typically seen in

patients with uncontrolled hyperparathyroidism or by low bone remodeling activity seen in patients with adynamic bone disease. The therapeutic approach to the patient with renal osteodystrophy depends on its specific type. In high-turnover (hyperparathyroid) or mixed highturnover disease with deficient mineralization, dietary phosphate restriction, generally in combination with a phosphate binder, is recommended because phosphate restriction is limited by the need to provide adequate protein intake to maintain nitrogen balance. Although highly effective, aluminum is no longer used as a phosphate binder because it promotes adynamic bone disease, anemia, myopathy, and occasionally dementia. Calcium-containing phosphate binders along with calcitriol administration may contribute to oversuppression of PTH secretion and likewise result in adynamic bone disease and an increased incidence of vascular calcification. Highly effective non-calcium-containing phosphate binders have been developed. Sevelamer hydrochloride, a nonabsorbable phosphate-binding polymer, effectively lowers serum phosphate concentration in hemodialysis patients, with a corresponding reduction in the phosphate product. Sevelamer hydrochloride consists of cross-linked poly [allylamine×calcium hydrochloride] that is resistant to digestive degradation. Partially protonated amines spaced one carbon from the polymer backbone chelate phosphate ions by ionic and hydrogen bonding. Side effects of sevelamer include vomiting, nausea, diarrhea, and dyspepsia. Sevelamer does not affect the bioavailability of digoxin, warfarin, enalapril, or metoprolol (Monier-Faugere *et al.,* 2001). Renal osteodystrophy associated with low bone turnover (adynamic bone disease) is increasingly common and may be due to oversuppression of PTH with aggressive use of either calcitriol or 100 pg/ml), a high PTH level<other vitamin D analogs. While PTH levels generally are low does not exclude the presence of adynamic bone disease, especially with PTH assays that do not distinguish between biologically active and inactive PTH fragments. Current guidelines suggest that treatment with an active vitamin D preparation is indicated if serum 25-OHD levels are less than 30 ng/ml and serum calcium is less than 9.5 mg/dl (2.37 mM). However, if 25-OHD and serum calcium levels are elevated, vitamin D supplementation should be discontinued. If the serum calcium level is less than 9.5 mg/dl, treatment with a vitamin D analog is warranted irrespective of the 25-OHD level (Eknoyan *et al.,* 2003).

1.41.1Hypoparathyroidism

Vitamin D and its analogs are a mainstay of the therapy of hypoparathyroidism. Dihydrotachysterol (DHT) has a faster onset, shorter duration of action, and a greater effect on

bone mobilization than does vitamin D and traditionally has been a preferred agent. Calcitriol also is effective in the management of hypoparathyroidism and certain forms of pseudohypoparathyroidism in which endogenous levels of calcitriol are abnormally low. However, most hypoparathyroid patients respond to any form of vitamin D. Calcitriol may be preferred for temporary treatment of hypocalcemia while awaiting effects of a slower-acting form of vitamin D.

1.42 Miscellaneous uses of Vitamin D

Vitamin D is used to treat hypophosphatemia associated with Fanconi syndrome. Large doses of vitamin D (over 10,000 units/day) are not useful in patients with osteoporosis and even can be dangerous. However, administration of 400 to 800 units/day of vitamin D to frail, elderly men and women has been shown to suppress bone remodeling, protect bone mass, and reduce fracture incidence (see later section on osteoporosis). Clinical trials suggest that calcitriol may become an important agent for the treatment of psoriasis. As such nontraditional uses of vitamin D are discovered, it will become important to develop noncalcemic analogs of calcitriol that achieve effects on cellular differentiation without the risk of hypercalcemia (Kowalzick, 2001).

CHAPTER 2
LITERATURE REVIEW

2.1:Knowledge of Calcium and Vitamin D Supplementation on Bone Density in Men and Women 65 Years of Age or older

During 1995-1997 Dawson-Hughes *et al* studied in Washington about the knowledge of Calcium and Vitamin D supplementation on bone density in men and women 65 years of age or older. They studied only healthy, ambulatory men and women 65 years of age or older who were recruited through direct mailings and presentations in the community. The criteria for exclusion included current cancer or hyperparathyroidism; a kidney stone in the past five years; renal disease; bilateral hip surgery; therapy with a bisphosphonate, calcitonin, estrogen, tamoxifen, or testosterone in the past six months or fluoride in the past two years; femoral-neck bone mineral density more than 2 SD below the mean for subjects of the same age and sex; dietary calcium intake exceeding 1500 mg per day; and laboratory evidence of kidney or liver disease. And they found rates of change in Bone Mineral Density in 318 Subjects who completed the study. They found that the difference between the calcium–vitamin D and placebo groups was significant at all skeletal sites after one year, but it was significant only for total-body bone mineral density in the second and third years. During this treatment there was significantly less bone loss at the hip, spine, and total body in the calcium–vitamin D group; during the second and third years, however, there was significantly less loss only in the total body (Dawson-Hughes *et al*., 1997).

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

In 2013 Uddin*et al* studied in Bangladesh about the awareness regarding the importance of calcium and vitamin D among the undergraduate pharmacy students in Bangladesh. They have taken 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. They 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%) (Uddin*et al.*, 2013).

2.3:Knowledge Regarding Vitamin D among Private University Students in Malaysia

In 2014 Sharmaine Audrey et alstudied in Malaysia about the knowledge regarding vitamin D among private university students in Malaysia. They have done the study among 360 private university students using self administered questionnaires regarding vitamin D knowledge. They found that most students are aware and having good knowledge regarding vitamin D with male having a higher knowledge compare 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 vitamin D which is 600 IU per day (Sharmaine Audrey *et al* ., 2014).

2.4: Awareness of Calcium and Vitamin D Intakes in an Adult Canadian Population

In 2009 Poliquin, Joseph and Gray-Donaldstudied in Canada about theawareness ofcalcium and vitamin D intakes in an adult canadian population. They have taken randomly 9423 participants. They found the daily intake for calcium was estimated to be 1038 (614)mg for women and 904 (583)mg for men; for vitamin D were 5.6 μg and 4.8 μg for women and men, respectively. They also found the intakes for calcium and vitamin D in men and women under age 51 were close to the adequate daily intake levels. Older adults, however, may be at risk of deficiency (Poliquin, Joseph and Gray-Donald, 2009)

2.5: Calcium intakes among Australian women: Geelong Osteoporosis Study

In 2000 Pasco *et al* studied in Australia about the calcium intakes among Australian women: Geelong Osteoporosis Study. They have done the study among randomly selected 1045 women. They found that most of the women in all ages they had intakes the calcium below the recommended dietary intake. And they also found that about 76% of women consume less than the recommended dietary intake even when the supplemental calcium is included. Therefore the women are at risk of bone loss (Pasco *et at.*, 2000).

AIM AND OBJECTIVE OF THIS STUDY:

The aim and objective of this study was to find out how much knowledge men have on Calcium and Vitamin D daily dietary requirements and deficiency diseases.

SIGNIFICANCE:

Calcium and Vitamin D are two very important minerals required for proper physiological function. As a result many types of diseases can occur due to calcium and vitamin D deficiency. Most of the studies carried out on calcium and vitamin D deficiency have been on women. Very few studies have been done on men. As calcium is very essential for our body function, there are some diseases that occur due to calcium deficiency. Osteoporosis and many other bone disorders may occur. Osteoporosis occur in women in huge amounts due to menopause and lack of knowledge on calcium and vitamin D. I felt it was essential to research how aware men are of the recommended daily intake requirements of these essential minerals and in which food they occur. This is the reason I have chosen to carry out my research on men.

CHAPTER 3
METHODOLOGY

3.1: Study design

In this study data was collected through a structured questionnaire. The study protocol was reviewed and approved by the supervisor.

3.2: Study area

The study was conducted in different areas of Bangladesh specifically in Dhaka city and Chadpur city.

3.3: Study population

A total of 200 men were included in the study and interviewed as per the questionnaire.

3.4: Data collection

From February 2016 to May 2016, was the study period during which the data was collected. To complete the study in time a work schedule was prepared depending on different tasks of the study.

3.5: Statistical analysis

Data will be organized, tabulated and aggregated using Microsoft excel. Mean a proportions of the epidemiological, social, behavioral and clinical parameters were compared amongst the study population.

3.6 QUESTIONNAIRE

Part 1: Personal data

1	Age:			
2	Do you have child?	□Yes	□No	
3	Are you suffering from any bone disorder?	□Yes	□No	
4	Were you ever been prescribed calcium supplement?	□Yes	□No	Reason
5	Were you ever been prescribed vitamin D?	□Yes	□No	Reason

Part 2: Awareness and knowledge regarding calcium and vitamin D:

6	Do you think calcium is an important mineral?	□Yes	□No
7	Write 3 sources of Calcium:		□do not know
8	Do you agree that Vitamin D is essential for normal physiological function?	□Yes	□No
9	Write 3 sources of Vitamin D:		□do not know
10	From where did you learn about	□ books	□ family

	calcium?	□ internet	□ teacher
		□ media	□ doctor
		□ others:	
11	Do you know what should be the daily intake of calcium?	□ For men:	☐ Do not know
12	Do you know what should be the daily intake of Vitamin D?	□ For men:	☐ Do not know
13	What is osteoporosis?		□ Do not know
14	What diseases do children suffer due to calcium deficiency?		□ Do not know
15	Do you think women are more affected by osteoporosis than men?	☐ Yes	☐ No
16	What is the daily sunlight exposure?	□ less than 1hr	□ greater than 1hr
		□ greater than 2 hr	□greater than 3 hr
		□greater than 4 hr	□ do not know
		□ others	

CHAPTER 4

RESULT

4.1: Number of respondents who had bone disorder

Table 4.1: Number of respondents who had bone disorder

Number of respondents who had bone disorder	Yes	No
Number	42	158
Percentage (%)	21%	79%

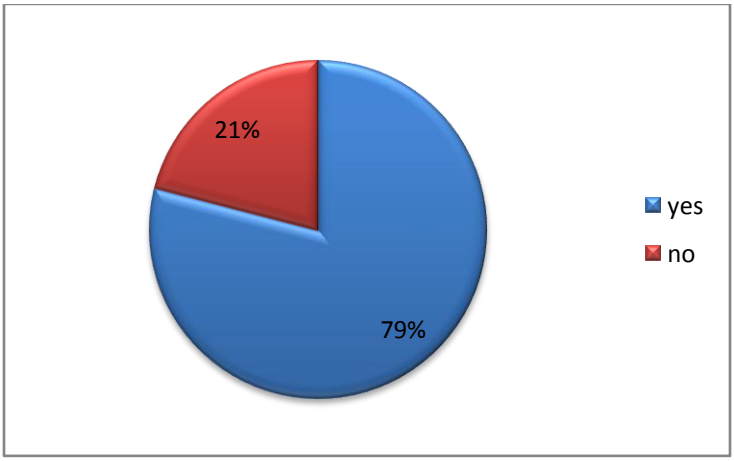

Figure 4.1: Number of respondents who had bone disorder

According to this data we can say that most of the male respondents do not suffer any type of bone disorder.

4.2: Number of respondents who have been prescribed Calcium supplement

Table 4.2: Number of respondents who have been prescribed Calcium supplement

Number of respondents with Calcium supplement	Yes	No
Number	46	154
Percentage (%)	23%	77%

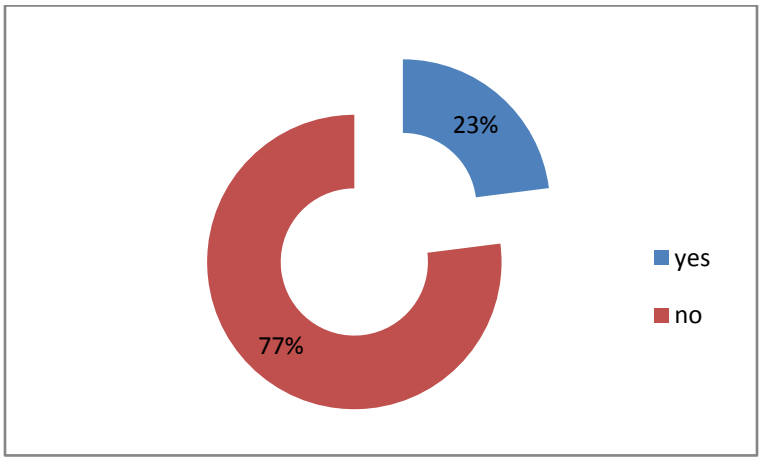

Figure 4.2: Number of respondents who have been prescribed Calcium supplement

From this data majority of the population were not prescribed any calcium supplement. Very few of the population were prescribed calcium.

4.3: Number of respondents who have been prescribed Vitamin D supplement

Table 4.3: Number of respondents who have been prescribed Vitamin D supplement

Number of respondents who have been prescribed Vitamin D supplement	Yes	No
Number	28	172
Percentage (%)	14%	86%

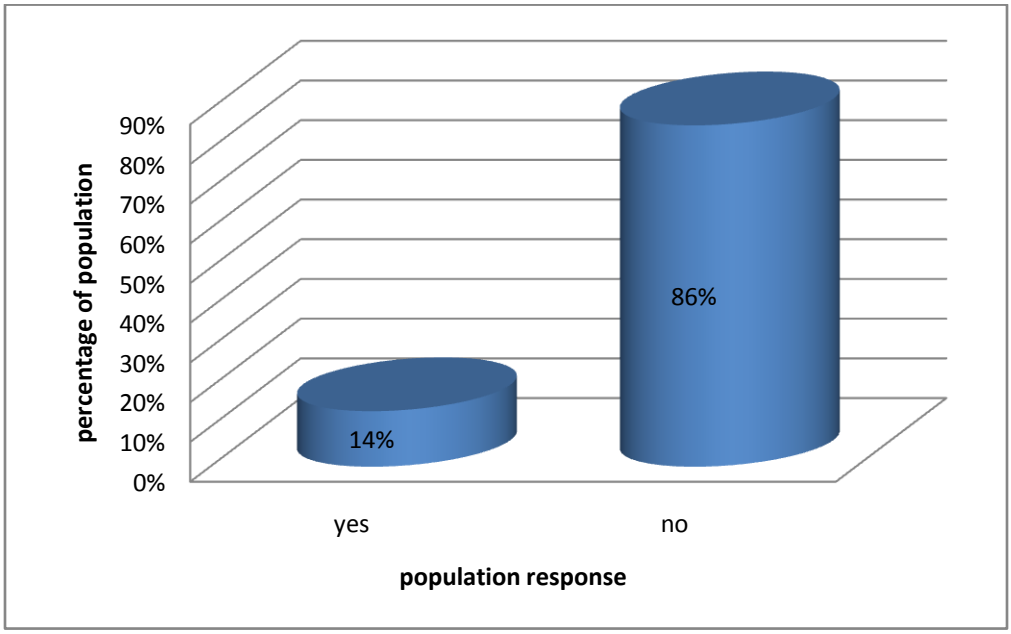

Figure 4.3: Number of respondents who have been prescribed Vitamin D supplement

Very few amount of male respondents take any prescribed Vitamin D supplement.

4.4: Number of respondents who had knowledge about importance of Calcium

Table 4.4: Number of respondents who had knowledge about importance of Calcium

Number of respondents who had knowledge about importance of Calcium	Yes	No
Number	190	10
Percentage (%)	95%	5%

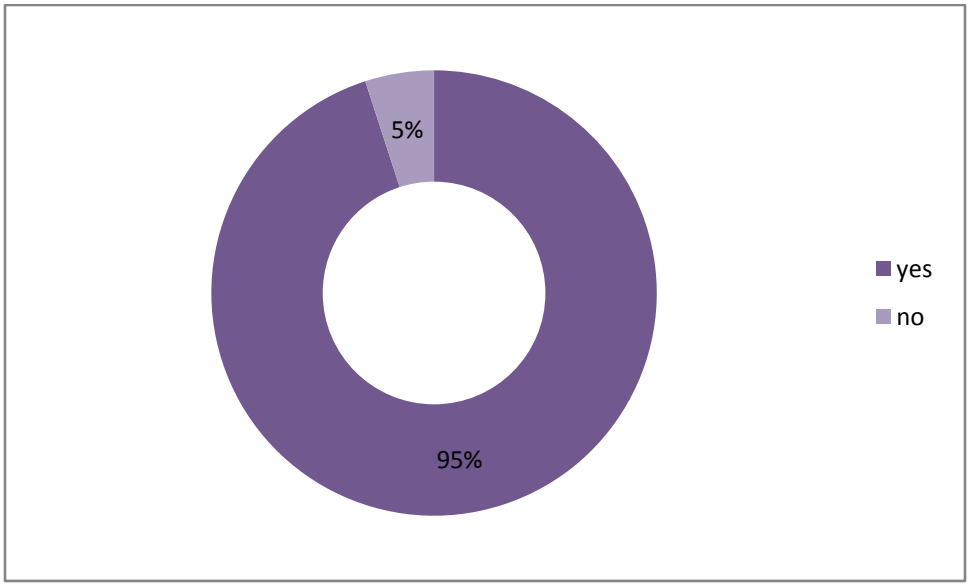

Figure 4.4: Number of respondents who had knowledge about importance of Calcium

Majority of the respondents know about the importance of Calcium minerals.

4.5: Number of respondents who had knowledge about sources of calcium

Table 4.5: Number of respondents who had knowledge about sources of calcium

Number of respondents who had knowledge about sources of calcium	Yes	No
Number	132	68
Percentage (%)	66%	34%

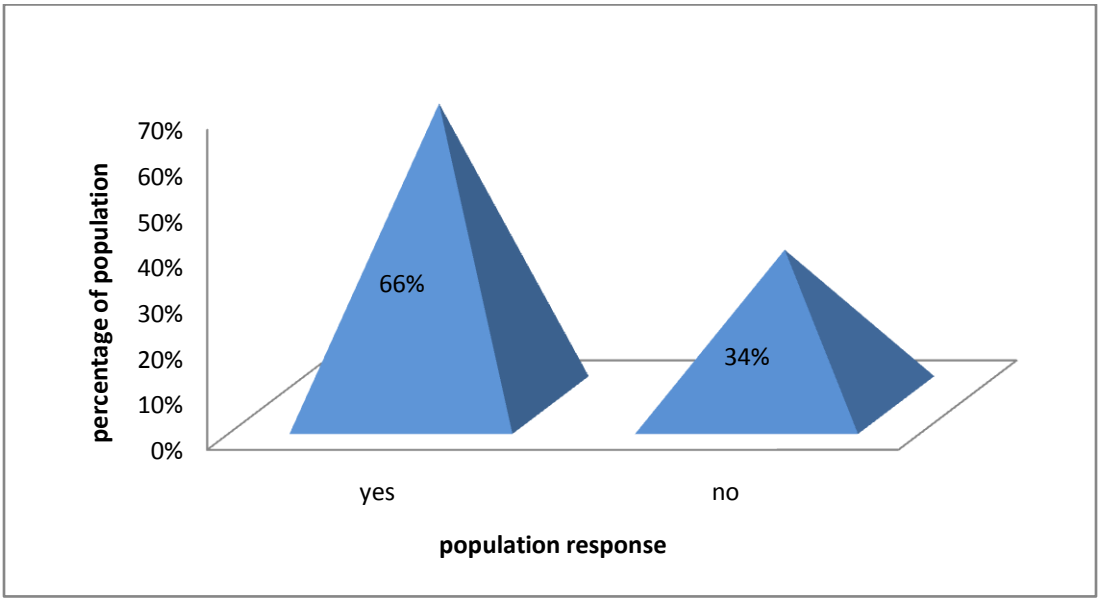

Figure 4.5: Number of respondents who had knowledge about sources of calcium

The sources of Calcium most of the respondents had knowledge about it.

4.6: Number of respondents who had knowledge about importance of vitamin D

Table 4.6: Number of respondents who had knowledge about importance of vitamin D

Number of respondents who had knowledge about importance of vitamin D	Yes	No
Number	190	10
Percentage (%)	95%	5%

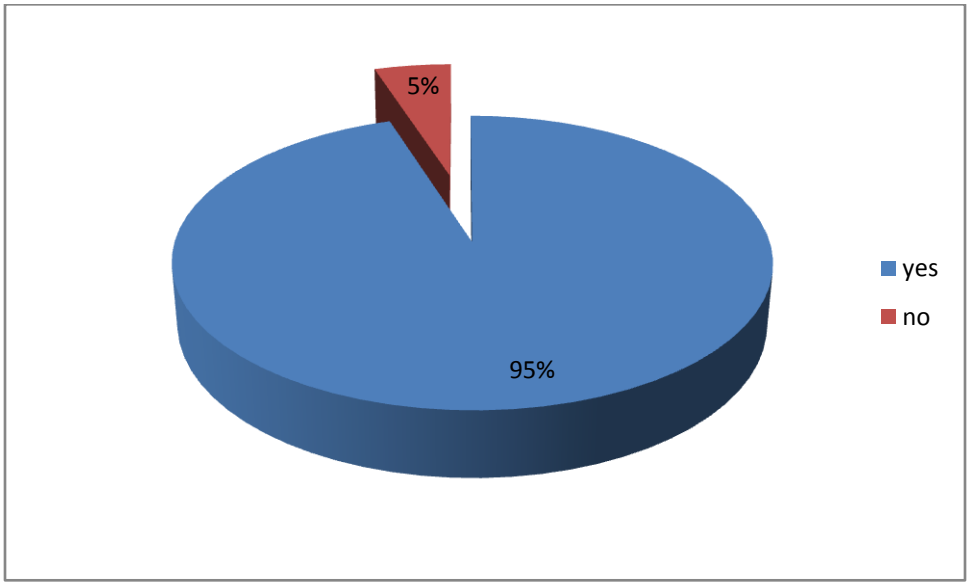

Figure 4.6: Number of respondents who had knowledge about importance of vitamin D

Most of the male respondents had knowledge that Vitamin D was an important mineral for normal physiological function.

4.7: Number of respondents who had knowledge about sources of calcium

Table 4.7: Number of respondents who had knowledge about sources of calcium

Number of respondents who had knowledge about sources of calcium	Yes	No
Number	98	102
Percentage (%)	49%	51%

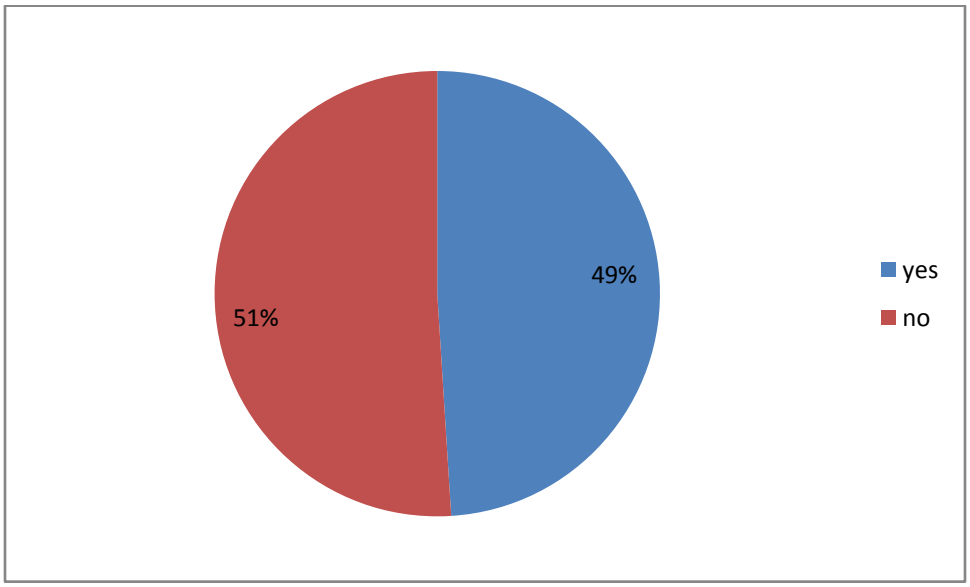

Figure 4.7: Number of respondents who had knowledge about sources of calcium

Slim majority of the male respondent do not know about the sources of Vitamin D.

4.8: Information sources of calcium and vitamin D

Table 4.8: Information sources of calcium and vitamin D

Information sources of calcium and vitamin D	Number	Percentage (%)
Books	111	56%
Family	77	39%
Internet	56	28%
Teacher	47	24%
Media	61	30%
Doctor	47	23%
Others	8	4%

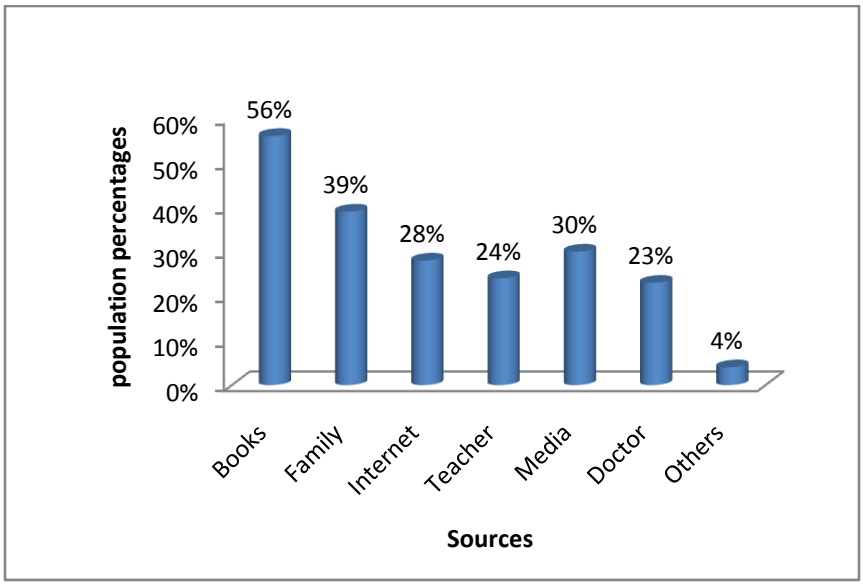

Figure 4.8: Information sources of calcium and vitamin D

Most of the male respondents had learned about calcium from books, family, media and doctors and minority of the respondents learned from others sources.

4.9: Number of respondents who had knowledge about daily intake of Calcium

Table 4.9: Number of respondents who had knowledge about daily intake of Calcium

Number of respondents who had knowledge about daily intake of Calcium	Yes	No
Number	6	194
Percentage (%)	3%	97%

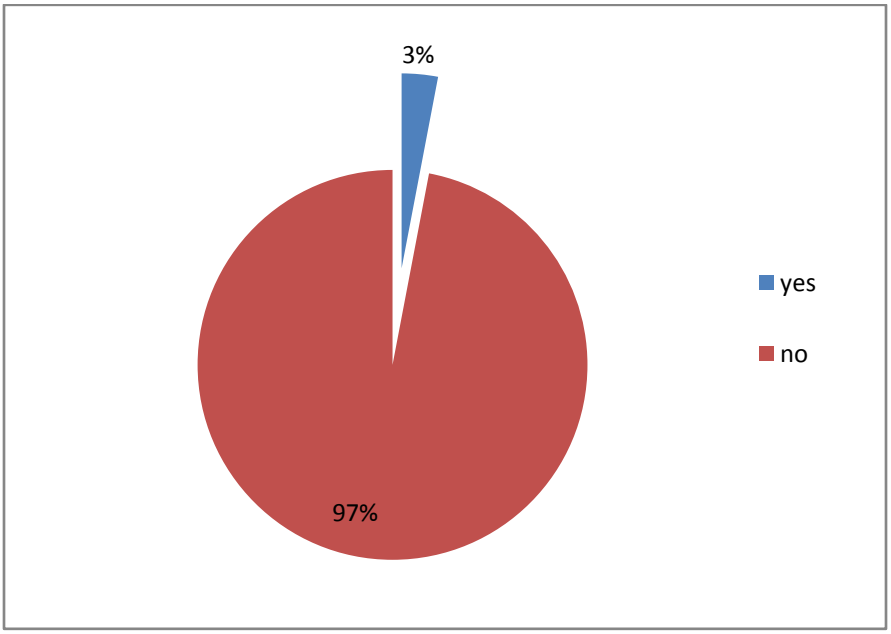

Figure 4.9: Number of respondents who had knowledge about daily intake of Calcium

Majority of the respondents had no knowledge about the daily intake of Calcium.

4.10: Number of respondents who had knowledge about osteoporosis

Table 4.10: Number of respondents who had knowledge about osteoporosis

Number of respondent who had knowledge about osteoporosis	Yes	No
Number	76	124
Percentage (%)	38%	62%

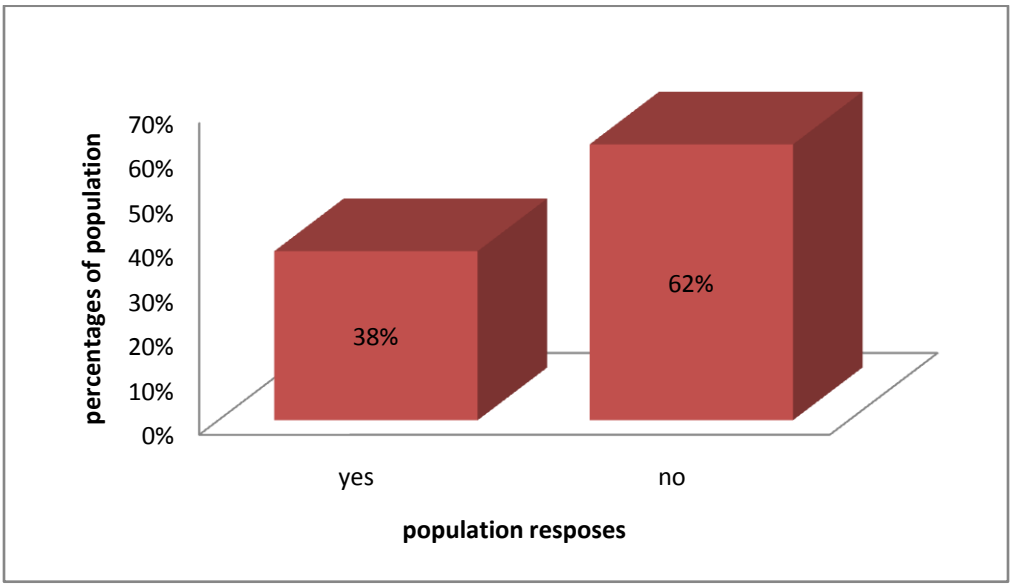

Figure 4.10: Number of respondents who had knowledge about osteoporosis

A large number of male respondents had no knowledge about osteoporosis.

4.11: Number of respondent knowledge about Calcium deficiency diseases in children

Table 4.11: Number of respondent knowledge about Calcium deficiency diseases in children

Number of respondents knowledge about Calcium deficiency diseases in children	Yes	No
Number	158	42
Percentage (%)	79%	21%

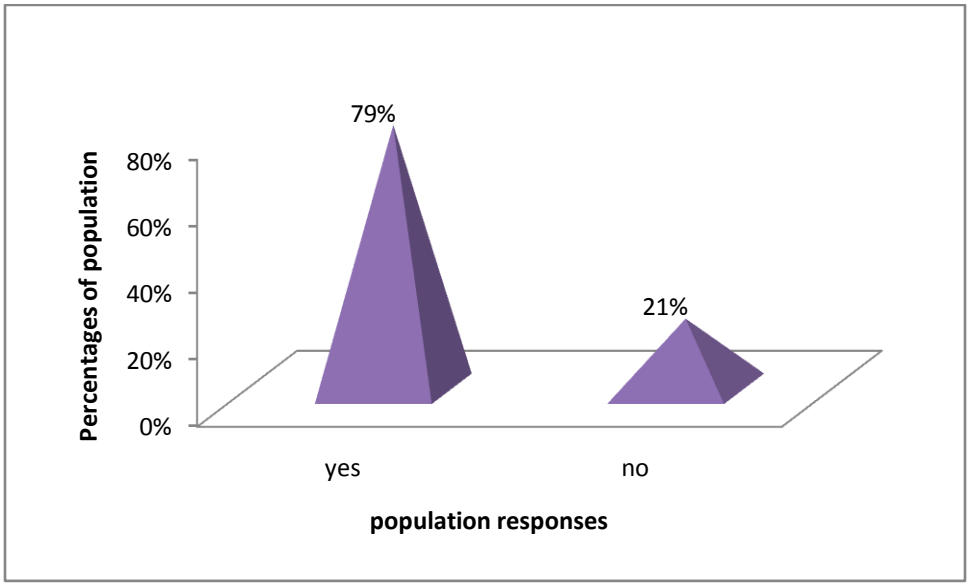

Figure 4.11: Number of respondent knowledge about Calcium deficiency diseases in children

Most of the respondent had knowledge about the calcium deficiency diseases in children.

4.12: Number of respondents who had knowledge that women are more affected than men by Osteoporosis

Table 4.12: Number of respondents who had knowledge that women are more affected than men by Osteoporosis

Number of respondents who had knowledge that women are more affected than men by Osteoporosis	Yes	No
Number	158	42
Percentage (%)	79%	21%

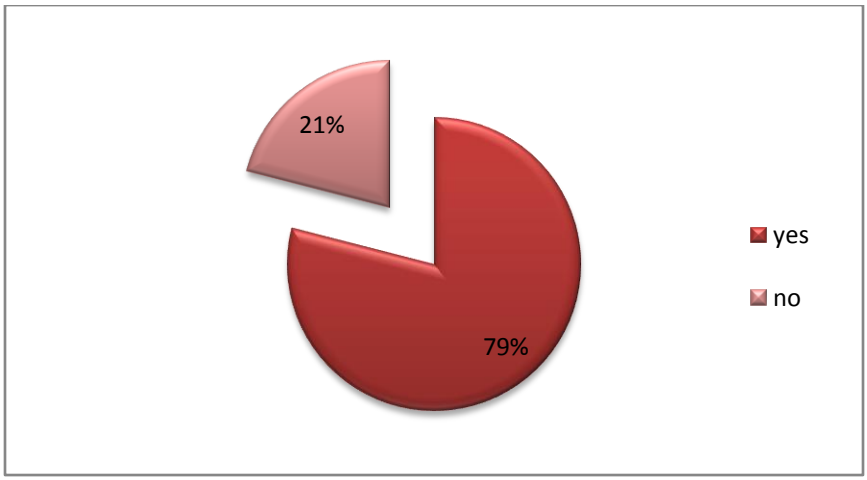

Figure 4.12: Number of respondents who had knowledge that women are more affected than men by Osteoporosis

Majority of the male respondents thought that women are more affected by osteoporosis than men.

4.13: Number of respondent who had knowledge about daily sun light exposure duration

Table 4.13: Number of respondent who had knowledge about daily sun light exposure duration

Number of respondent who had knowledge about daily sun light exposure duration	Number	Percentage (%)
Less than 1 hr	65	33%
Greater than 1 hr	32	11%
Greater than 2 hr	28	14%
Greater than 3 hr	14	7%
Greater than 4 hr	9	4%
Do not know	57	29%
others	5	3%

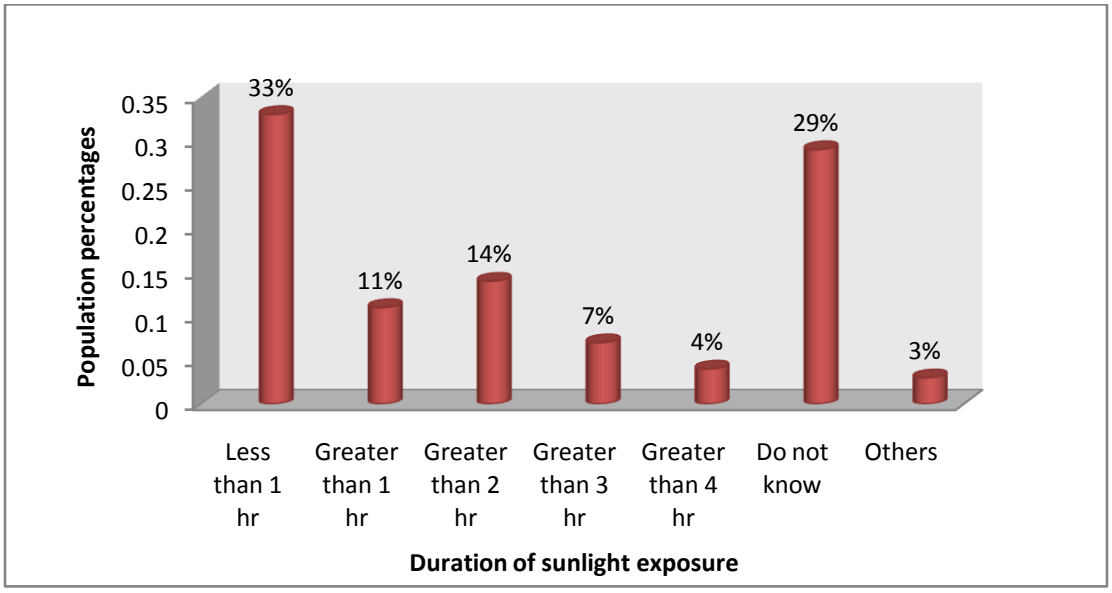

Figure 4.13: Number of respondent who had knowledge about daily sun light exposure duration

Majority of the respondents thought that less than 1 hr sun light exposure was needed and some of the respondents do not know about this.

CHAPTER 5

DISCUSSION AND CONCLUSION

The main objective in this study was awareness of deficiency diseases of calcium and vitamin D among the male respondents. We got sample from 200 men respondents.

The respondents were asked whether they were suffering any bone disorders. From the survey it was found that the majority had no bone disorders and very few respondents showed response that they have been suffering from bone disorders. Also about 77% of the respondents were not prescribed any calcium supplements and 23% of the respondents were prescribed calcium supplements. Now most of the population about 86% of the men do not take any prescribed vitamin D supplements and 14% men take prescribed vitamin D supplement.

The respondents of this survey also know that calcium and vitamin D are two important minerals for normal physiological function and very few of the respondents do not think about it. The men were asked to mention the three sources of calcium and vitamin D, we found that most of the respondents had knowledge about the sources. They know about milk, eggs, vegetables, cheese, yogurt, meat etc as calcium sources and as vitamin D sources they know liver, meat, eggs, fish oil, vegetables oil, sea fish etc.

The respondents were asked about the source of their knowledge and information they have about calcium. Majority of the respondents answered that they first knew about calcium from books and also from their family, internet, teachers, media, doctor and other sources.

The respondents do not have any knowledge about the daily intake of calcium and vitamin D. Majority of the respondents were familiar with the term osteoporosis. The male respondents also thought that female are more affected than men by osteoporosis.

Vitamin D and calcium deficiency diseases have re-emerged as a global public-health concern and is now linked to a range of infectious, inflammatory and neoplastic diseases throughout the course of life 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.

So according to the Bangladesh perspective majority of the population do not know about the importance of calcium and vitamin D. we need to take adequate step to teach more about the importance of calcium and vitamin D in their day to day life.

CHAPTER 6
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