"STUDY OF SERUM VITAMIN D LEVEL IN ISCHEMIC HEART DISEASE-A CROSS SECTIONAL STUDY"

By

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Dissertation submitted to the

In partial fulfillment of the requirements for the degree of

MD

In

GENERAL MEDICINE

Under the guidance of

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LIST OF ABBREVIATIONS USED

CVD	: Cardiovascular disease
CAD	: Coronary Artery Disease
ACS	: Acute Coronary Syndrome
CBC	: Complete blood count
FBS	: Fastng blood sugar
PPBS	: Post prandial blood sugar
LDL	: Low Density Lipoprotein
HDL	: High Density Lipoprotein
STEMI	: ST-segment Elevation Myocardial Infarction
NSTEMI	: Non–ST-segment Elevation Myocardial Infarction
UA	: Unstable Angina
PCI	: Percutaneous Coronary Intervention
CAC	: Coronary Artery Calcification
CFR	: Coronary Flow Reserve
IMT	: Intima-Media Thickness
AP	: Angina Pectoris
TC	: Total leucocyte Count
IHD	: Ischemic Heart Disease
ECG	: Electro Cardiographs

ABSTRACT

Background:

Vitamin D deficiency is highly prevalent worldwide, and is also notedto be high in India. Low levels of 25(OH) D, the principle circulating storage form of vitamin D, is present in as many as one third to one half of otherwise healthy middle aged to elderly population. Endothelial dysfunction plays an important role in pathogenesis of CAD and vitamin D deficiency is postulated to promote endothelial dysfunction. Because hypovitaminosis D is prevalent and easily correctable, establishing the relationship between vitamin D and risk of Acute coronary Syndrome is important.

Objective :

1) To estimate vitamin D levels in IHD patients.
2) To correlate vitamin D levels with complications of IHD.

Methodology:

A Cross Sectional study of 80 patients admitted to BLDEU'S Shri B.M Patil Medical college Hospital and Research Centre Vijayapur between December 2014 to March 2016 with diagnosis of IHD. Patients aged more than 18 years were included in studies. The Vitamin D levels were analyzed in all the patients and correlated with different parameters for statistical significance.

Results :

During our study period 80 patients were assessed as mentioned above. The mean age of our study group was 61±12.1 years. Of the study population there were 57 male patients and 23 were females accounting to 71.2 % and 28.8 % respectively.

Out of 80 patients 66 had Vitamin D deficiency in 45 were males and 21 were females. In that 34 patients had heart failure with hypotension and 1 had ventricular tachycardia, I had Left Ventricular Apical clot.

Conclusion:

There is a high prevalence of Vitamin D deficiency (82.5%) among acute coronary syndrome patients. The mean age group is 58.5±9.6 years. Vitamin D deficiency is associated with increased risk of complications(75.75%) in acute coronary syndromes. Vitamin D deficiency is one of the independent risk factor for acute coronary syndrome. Vitamin D deficiency is noticed more in STEMI. Vitamin D deficiency in females was more common than compared to males.

Key Words : Acute coronary syndromes, Vitamin D deficiency, IHD, Left Ventricular Apical clot, ventricular tachycardia.

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INTRODUCTION

Ischemic heart disease is the most common, serious, chronic life threatening illness in the world. It is a worldwide epidemic in terms of mortality[1]. IHD is now occurring in low income and middle income countries[1].

As it is well known that common risk factors are Age, sex, Family History, Genetic factors, which are non-modifiable and modifiable risk factors are Smoking, hypertension, dyslipidemia, Diabetes mellitus, Obesity, Sedentary life style, stress. Still our understanding of how to prevent and treat the traditional cardiovascular risk factors is largely unknown. There is need for further investigations to know the other nontraditional risk factors[1]. The common nontraditional risk factors are persons living in high altitudes, decreased sun exposure, dark skinned people.

Vitamin D deficiency is highly prevalent in the United States and worldwide[7]. Although the best characterized sequelae of vitamin D deficiency involve the musculoskeletal system, a growing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system[8]. Vitamin D receptors have a broad tissue distribution that includes vascular Smooth muscle [9 10],endothelium[11] and cardiomyocytes[6].

Vitamin D has been tagged as very important triggering factor for Cardiovascular disease (CVD)[12]. Vitamin D deficiency is a highly prevalent condition. The vitamin D axis affects vascular smooth muscle cell proliferation, inflammation, vascular calcification, Renin-Angiotensin System (RAS), and blood pressure all of which affect the risk of CVD and myocardial infarction (MI)[2]. Low

vitamin D level causes an increase in insulin resistance, hypertension, inflammation, and increased cardiovascular risk. Vitamin D deficiency is emerging as one more important risk factor for Ischemic Heart Disease so as the prevalance of Vitamin D as risk factor is not studied in this part of state hence study is undertaken.

OBJECTIVE OF THE STUDY

1) To estimate vitamin D levels in IHD patients.
2) To correlate vitamin D levels with complications of IHD.

REVIEW OF LITERATURE

History of Vitamin D

Man is reported to have been aware since early antiquity of the substance we now know as vitamin D. The first scientific description of a vitamin D-deficiency, namely rickets, was provided in the 17th century by both Dr. Daniel Whistler (1645) and Professor Francis Glisson (1650). The major breakthrough in understanding the causative factors of rickets was the development in the period 1910 - 1930 of nutrition as an experimental science and the appreciation of the existence of vitamins. Considering the fact that now we accept that the biologically active form of vitamin D, namely 1, 25(OH)2-vitamin D3, is a steroid hormone, it is somewhat ironic that vitamin D, through a historical accident, became classified as a vitamin. It was in 1919/20 that Sir Edward Mellanby, working with dogs rose exclusively indoors (in the absence of sunlight or ultraviolet light), devised a diet that allowed him to unequivocally establish that the bone disease, rickets was caused by a deficiency of a trace component present in the diet. In 1921 he wrote, "The action of fats in rickets is due to a vitamin or accessory food factor which they contain, probably identical with the fat-soluble vitamin." Furthermore, he established that cod liver oil was an excellent antirachitic agent.

Shortly thereafter E.V. McCollum and associates observed that by bubbling oxygen through a preparation of the "fat-soluble vitamin" they were able to distinguish between vitamin A (which was inactivated) and vitamin D (which retained activity). In 1923 Goldblatt and Soames clearly identified that when a precursor of vitamin D in the skin (7-dehydrocholesterol) was irradiated with sunlight or ultraviolet light, a substance equivalent to the fat-soluble vitamin was produced. Hess

and Weinstock confirmed the dictum that "light equals vitamin D". They excised a small portion of skin, irradiated it with ultraviolet light, and then fed it to groups of rachitic rats. The skin that had been irradiated provided an absolute protection against rickets, whereas the un radiated skin provided no protection whatsoever; clearly, these animals were able to produce by UV irradiation adequate quantities of "the fat-soluble vitamin", suggesting that it was not an essential dietary trace constituent. In parallel studies, Steenbock and Black at the Biochemistry Department of the University of Wisconsin found that rat food which was irradiated with ultra violet light also acquired the property of being antirachitic. However, because of the rapid rise of the science of nutrition –and the discovery of the families of water-soluble and fat-soluble vitamins – it rapidly became firmly established that the antirachitic factor was to be classified as a vitamin.

The chemical structures of the vitamins D were determined in the 1930s in the laboratory of Professor Adolf Otto Reinhold Windaus at the University of Göttingen in Germany. Professor Windaus had some 55 doctoral and postdoctoral chemists working on the 'vitamin D project'. Professor Windaus received a Nobel Prize in Chemistry in 1928 for his work on sterols and their relationship to vitamins. Vitamin D2 which could be produced by ultraviolet irradiation of ergosterol was chemically characterized in 1932. Vitamin D3 was not chemically characterized until 1936 when it was shown to result from the ultraviolet irradiation of 7-dehydrocholesterol. Virtually simultaneously, the elusive antirachitic component of cod liver oil was shown to be identical to the newly characterized vitamin D3. These results clearly established that the antirachitic substance vitamin D was chemically a steroid, more specifically a seco-steroid.

Nutritional Aspects of Vitamin D

The World Health Organization had responsibility for defining the "International Unit" of vitamin D3. Their most recent definition provided in 1950 states that "the International Unit of vitamin D recommended for adoption is the vitamin D activity of 0.025 micrograms (25 nanograms) of the international standard preparation of crystalline vitamin D3. Thus, 1.0 IU of vitamin D3 is 25 nanograms, which is equivalent to 65.0 pmoles. With the discovery of the metabolism of vitamin D3 to other active seco-steroids, particularly 1α, 25(OH)2 D3, it was recommended that 1.0 unit of 1α, 25(OH)2 D3 be set equivalent in molar terms to that of the parent vitamin D3. Thus, 1.0 unit of 1α, 25(OH)2 D3 has been operationally defined to be equivalent to 65 pmoles.

The vitamin D requirement for healthy adults has never been precisely defined. Since vitamin D3 is produced in the skin after exposure to sunlight, humans do not have a requirement for vitamin D when sufficient sunlight is available. However, vitamin D does become an important nutritional factor in the absence of sunlight. It is known that a substantial proportion of the U.S. population is exposed to quite suboptimal levels of sunlight especially during the winter months; it is likely that during these intervals that a regular dietary supply of vitamin D3 should be provided. In addition to geographical and seasonal factors, ultraviolet light from the sun may also be blocked by air pollution. The tendency to wear clothes, to live in cities where tall buildings block adequate sunlight from reaching the ground, to live indoors, to use synthetic sunscreens that block ultraviolet rays, and to live ingeographical regions of the world that do not receive adequate sunlight, all contribute to the inability of the skin to biosynthesize sufficient amounts of vitamin

D3. Under these conditions vitamin D becomes a true vitamin in that it must be supplied in the diet on a regular basis.

Since vitamin D3 can be endogenously produced by the body and since it is retained for long periods of time by vertebrate tissue, it is difficult to determine with precision the minimum daily requirements for this seco-steroid. The requirement for vitamin D is also known to be dependent on the concentration of calcium and phosphorus in the diet, the physiological stage of development, age, sex, degree of exposure to the sun, and the amount of pigmentation in the skin.

In the United States, adequate amounts of vitamin D can readily be obtained from the diet and from casual exposure to sunlight. However, in some parts of the world where food is not routinely fortified and sunlight is often limited during some periods of the year, obtaining adequate amounts of vitamin D becomes major problem. The 13th and 14th Vitamin D Workshops reported in white papers that two thirds of the world population has a vitamin D deficiency.

Vitamin D3 versus Vitamin D2

For decades since the determination of the chemical structures of vitamin D3 and vitamin D2 in the 1930's it has been assumed that both vitamins had equivalent biological activity in humans. This was based on biological determination in rats of their comparative antirachitic activity. However in 1997, the IOM vitamin D reference intake publication for vitamin D, serum 25-hydroxyvitamin D [25(OH) D], rather than antirachitic activity, was defined as the functional indicator of vitamin D status.

In a 2010 paper by R. Heaney and coworkers it was reported that vitamin D3 is approximately 87% more potent in raising and maintaining serum 25(OH) D levels than was vitamin D2. In addition, vitamin D3 produced a 2- to 3-fold greater storage

of vitamin D than does equimolar D2. For neither was there evidence of sequestration in fat, as had been postulated for doses in this range.

Thus the authors felt that given the greater potency and lower cost, vitamin D3 should be the preferred choice for correcting vitamin D deficiency in humans.

Food Sources

Animal products constitute the bulk source of vitamin D that occurs naturally in unfortified foods. Salt water fish such as herring, salmon, sardines, and fish liver oils are good sources of vitamin D3. Small quantities of vitamin D3 are also derived from eggs, veal, beef, butter, and vegetable oils while plants, fruits, and nuts are extremely poor sources of vitamin D. In the United States, artificial fortification of foods such as milk (both fresh and evaporated), margarine and butter, cereals, and chocolate mixes help in meeting the RDA recommendations.

Requirements for vitamin D:

Since vitamin D3 is produced in the skin after exposure of 7-dehydrocholesterol to sunlight, the human does not have a requirement for vitamin D when sufficient sunlight is available. Man's tendency to wear clothes, to live in cities where tall buildings block adequate sunlight from reaching the ground, to live indoors, to use synthetic sunscreens that block ultraviolet rays, and to live in geographical regions of the world that do not receive adequate sunlight, all contribute to the inability of the skin to biosynthesize sufficient amounts of vitamin D3. Thus vitamin D3 does become an important nutritional factor in the absence of sunlight. It is known that a substantial proportion of the U.S. population is exposed to suboptimal levels of sunlight. This is particularly true during winter months. Under these

conditions, vitamin D becomes a true vitamin which dictates that it must be supplied in the diet on a regular basis.

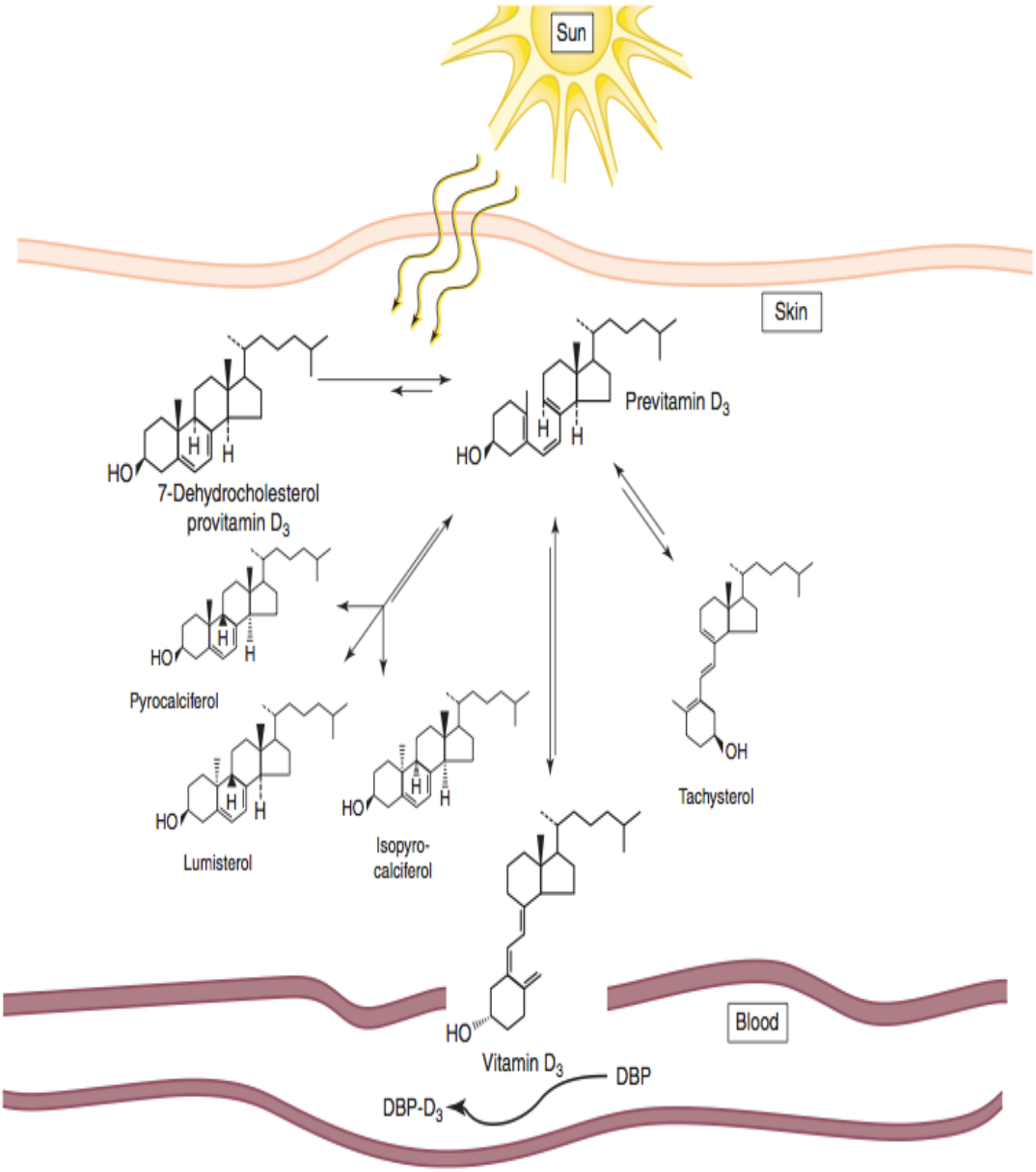
The current "adequate intake" allowance of vitamin D recommended in 2010 by the Food and Nutrition Board of the US Institute of Medicine is 600 IU/day (15 μgrams / day) for children and adult males and females up to age 70. For adults greater than 70 years, the recommended intake is 800 IU (20 μgrams/day). The adequate allowance for pregnancy and lactation is set at 600 IU/day (15 μg/day). These recommendations are all summarized in a 2010 publication from the Food and Nutrition Board of the Institute of Medicine.

Vitamin D Metabolism

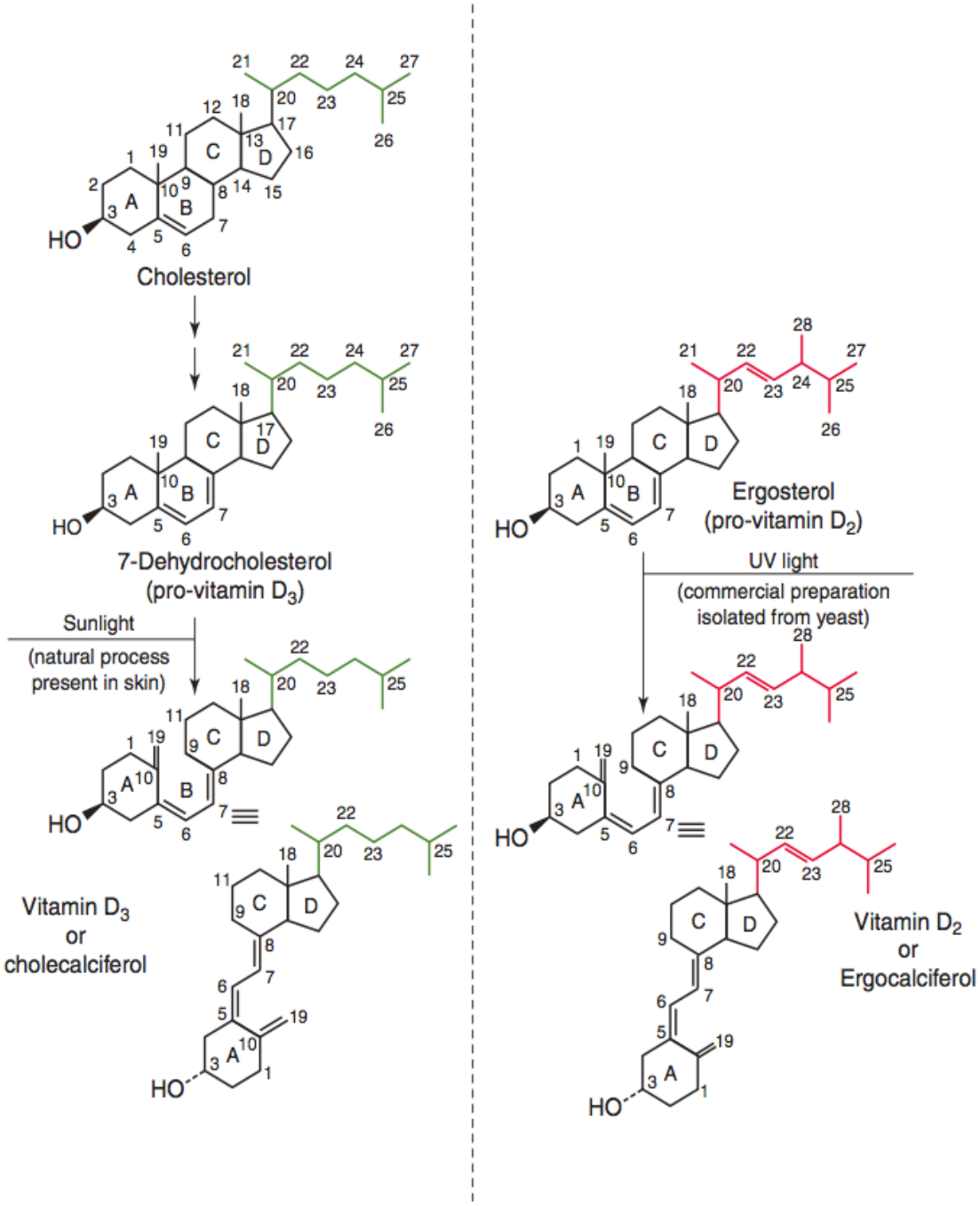
Vitamin D can be synthesized in sufficient amounts by most vertebrates on adequate exposure of the skin to sunlight (UVB rays). It is critical that most vertebrates obtain a sufficient amount of vitamin D either from their diet or from adequate exposure of the skin to sunlight. The term “vitamin D” refers to compounds vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol).

Vitamin D is produced in the skin on exposure to sunlight. Vitamin D is derived from 7-dehydrocholesterol by ultraviolet irradiation of the skin. Vitamin D3 is also found in animal food sources e.g., fatty fish (e.g., salmon, mackerel and tuna) cod liver oil, milk, etc. Vitamin Dis found in vegetal sources like sun-exposed yeast and mushrooms. Notably, most dietary sources are not sufficiently rich in their vitamin D content. Vitamin D (both forms D3 or D2) is a prohormone which requires two 11 hydroxylation’s to finally attain its biologically active form—[1,25(OH)]D. The first hydroxylation occurs in the liver, at position C25 to form 25-hydroxyvitamin D, also known as 25(OH)D or calcidiol. 25(OH)D is the major circulating form of vitamin D.

The second hydroxylation occurs at position C1a to form 1,25 (OH)2D, also known as calcitriol. [1,25(OH)]D is produced primarily but not exclusively in the kidneys. [1,25(OH)]D is released in blood, where it binds to vitamin D binding protein (DBP) and reaches its target tissues to exert its endocrine functions through the vitamin D receptor (VDR). [1,25(OH)]D also produced in several extra renal tissues for its paracrine and autocrine functions. Most cells in the body have VDR. Many cell types can also produce [1,25(OH)2]D. [1,25(OH)]D is capable of regulating a wide variety of genes that have important functions in regulating cell growth and differentiation.



Vitamin D synthesis



Vitamin D structure

Vitamin D and Skeletal Health

Rickets, osteomalacia and osteoporosis are widely prevalent all over the world. The most well recognized function of [1,25(OH)2]D involves regulation of calcium and phosphorus balance for bone mineralization and remodeling. Without adequate levels of [1,25(OH)2]D in the bloodstream, dietary calcium cannot be absorbed. Low calcium levels lead to an increase in serum PTH concentration, which leads to increased tubular reclamation of calcium in kidneys and resorption from the skeleton at the cost of lowering bone density. In the long term this leads to weakened and brittle bones that break easily. Approximately 40%–60% of total skeletal mass at maturity is accumulated during childhood and adolescence. Rickets results from inadequate mineralization of growing bone. Thus it is a childhood disease and it is manifested as bone deformities, bone pain and weakness. Biochemical abnormalities consistently include hypophosphatemia, elevated alkaline phophatase levels and serum 25(OH) D levels are usually below 5 ng/mL. Chronic vitamin D deficiency in adults results in osteomalacia, osteoporosis, muscle weakness and increased risk of falls[41-46]. Epidemiological support for skeletal benefits of vitamin D is well known[42,46-50].

Vitamin D: Extra skeletal Effects

Biochemical studies have implicated vitamin D deficiency in many chronic diseases including, but not limited to, infectious diseases, autoimmune diseases, cardiovascular diseases, diabetes and cancer. Numerous epidemiological publications support the extra skeletal benefits of vitamin D and they cannot be ignored even though majority of these are association studies or small randomized controlled trials. Nevertheless, stronger evidence is required with the aid of more robust and reliable statistical methods such as randomized controlled trials (RCTs). These RCTs should

be well-designed, well-executed and conducted worldwide to generate dependable and incontrovertible data, in order to assess the benefits of vitamin D supplementation not only as a preventive measure but also as adjuvant therapies[51,52].

Immunity

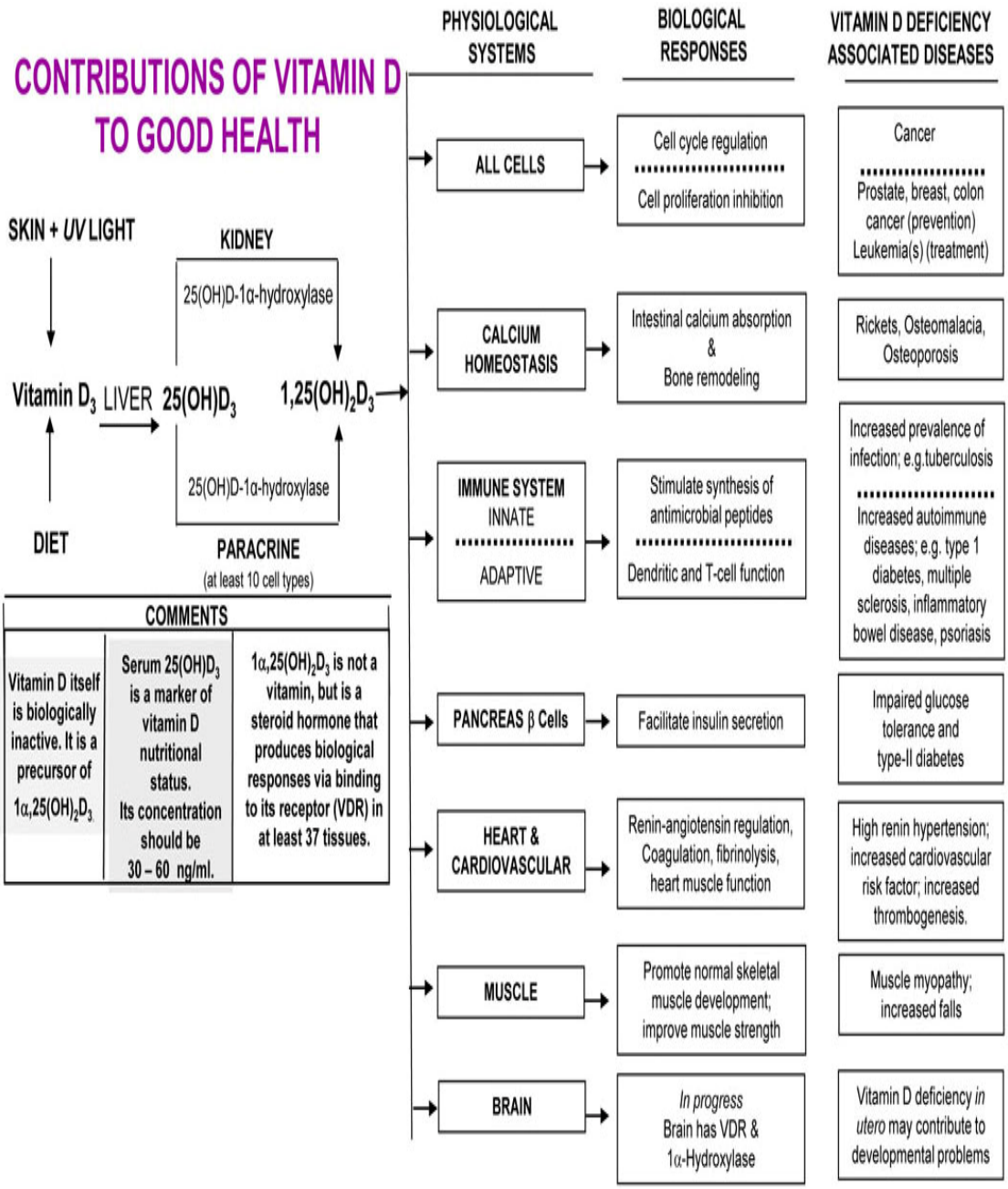
As early as in the 19th century, cod liver oil (a rich source of vitamin D) was used for treating tuberculosis (TB). Skin exposure to sunlight was an effective therapy for treating Mycobacterium infections of the skin. In 1903, Finsen received the Nobel Prize for demonstrating that Lupus vulgaris, the epidermal form of TB, could be cured using light from an electric arc lamp. In early 1900s, growing awareness of benefits of sun exposure pertaining treatment of infectious diseases led to the development of sanatoriums in "sun-rich areas". These sanatoriums enabled regimented sun exposure, diet and exercise. These sanatoriums primarily hosted TB patients[53]. Recent studies have linked vitamin D deficiency with increased risk of developing TB[54,55], otitis media[56], upper respiratory tract infections[57] and influenza[58].

Cardiovascular Health

Cardiovascular diseases (CVDs), including heart failure and coronary artery disease are a major cause of morbidity and mortality worldwide. There is accumulating epidemiological evidence from observational studies suggesting that CVDs are associated with vitamin D deficiency[23,59]. Increased risk of hypertension was associated with living at higher latitudes[60]. 25(OH)D level <21 ng/mL was associated with increased risk of hypertension, diabetes, obesity and high triglyceride levels—all associated with increased cardiovascular mortality[61]. There is a significant association between osteoporosis and vascular calcification and vitamin D levels are inversely related to vascular calcification which in turn may affect AMI risk[23]. Direct effects of vitamin D on the myocardium might partially explain the link between

vitamin D deficiency and adverse cardiovascular outcome. This notion is supported by observations that human cardiomyocytes express enzymes for the metabolism of vitamin D as well as a functional vitamin D receptor, which is up-regulated in myocardial hypertrophy[83,3]. In animal models of heart failure, active vitamin D treatment was shown to reduce cardiac hypertrophy and to attenuate myocardial dysfunction[4]. Several genes that are up-regulated in the course of cardiac hypertrophy, involving those of natriuretic peptides and renin, are down-regulated by vitamin D [4]. Importantly, there exists increasing molecular and clinical evidence that a sufficient vitamin D status is required for maintenance of diastolic function of the heart [3,4]. Furthermore, there are several case reports of vitamin D–deficient children with dilated cardiomyopathy that could be successfully treated with vitamin D and calcium [5]. In line with this are data from a cohort of over 3,000 patients referred for coronary angiography that showed a significant association of vitamin D deficiency with reduced left ventricular function [91]. In the same study cohort, vitamin D deficiency was prospectively associated with deaths caused by heart failure and with sudden cardiac deaths [91]. These results fit well with observations that active vitamin D treatment in hemodialysis patients was shown to regress cardiac hypertrophy and to reduce QT interval and dispersion [4,7]. In conclusion, there exists compelling evidence that vitamin D supplementation might be useful for the prevention and treatment of myocardial diseases. 25(OH)D levels are largely affected by sun exposure, it is plausible that some other consequence of sun exposure other than vitamin D production is responsible for the observed association with MI. Nevertheless, much evidence supports mechanisms whereby vitamin D could affect CVD risk. Of the potentially relevant mechanisms, vitamin D affects vascular smooth muscle cell proliferation, inflammation, vascular calcification, and blood pressure through the

RAS[1]. It is now increasingly recognized that adequate vitamin D status is not only important for bone health and the prevention of osteoporosis but also for optimal function of many other organs and tissues throughout the body, including the cardiovascular (CV) system.3 Cardiac myocytes have cytosolic vitamin D receptors 2 (VDR)4 that bind active vitamin D (1,25 dihydroxy vitamin D), but unlike vascular smooth muscle cells, cardiac myocytes lack 1α-hydroxylase activity, an enzyme that converts inactive vitamin D(25 hydroxy vitamin D) to active vitamin D. Hence cardiac muscle is strongly dependent upon circulating active vitamin D or calcitriol levels. In the past, several in vitro studies have shown that calcitriol regulates intracellular calcium metabolism and thus myocardial contractility. Consequently, 25(OH)D deficiency has been associated with aberrant cardiac contractility, cardiomegaly, and increased ventricular mass due to myocardial collagen deposition, independent of its known effects on blood pressure[31].Various studies have reported reduced 25(OH)D concentrations in patients with previous and prevalent cardiovascular or cerebrovascular diseases[62].



Role of Vitamin D in different systems

Genetic Determinants of Vitamin D

Recently, genetic markers of various exposures have become popular instruments for evaluating causal effects. The most frequently used genetic markers, single-nucleotide polymorphisms (SNPs), are DNA sequence variations with a single nucleotide in the genome differing between members of a biological species or paired chromosomes in a human. A number of known SNPs, including common variants at the DHCR7/NADSYN1 and CYP2R1 loci, have been shown to be associated with circulating 25-hydroxyvitamin D. Also, loss-of-function mutations in the Filaggrin gene have been found to result in up to 10% higher serum vitamin D concentrations, supposedly due to a decreased UV-protection of the keratinocytes. Mutations affect almost 10% of Northern Europeans, of which 2282del4 and R501X account for about 80% of the known mutations. Filaggrin deficiency is known to cause ichtyosis vulgaris, which is characterized by xerosis, keratosis pilaris and palmar hyperlinearity, but also increases the risk of atopic dermatitis, allergic rhinitis, asthma, and food allergies.

Vitamin D and Mortality

Vitamin D affects a large number of genes, including those responsible for the regulation of cellular differentiation, proliferation, apoptosis, and angiogenesis, giving it the potential to affect much more than the musculoskeletal system .Low vitamin D status has been associated with mortality in several studies. A meta-analysis of vitamin D supplementation reported a decrease in mortality, whereas a recent one found reduced mortality with vitamin D and calcium supplementation in the elderly, but no effect of vitamin D supplementation alone. A Cochrane review found that vitamin D3 seemed to decrease mortality in elderly people, whereas vitamin D2 had no statistically significant effect; the study concluded that more RCTs are needed.

The specific causes of death underlying the association with mortality are uncertain, but there is no shortage of possibilities: in observational studies, in addition to cardiovascular disease (CVD), low vitamin D status is associated with an increased risk of endocrine and metabolic diseases such as diabetes mellitus, obesity, and metabolic syndrome, cancers such as colorectal cancer, lung cancer, and breast cancer, respiratory disease such as chronic obstructive pulmonary disease (COPD) and respiratory infections, diseases of the digestive system such as liver disease, inflammatory bowel disease, and coeliac disease, and mental disorders such as dementia, and depression, and kidney disease such as albuminuria.

Definition and Prevalence of Vitamin D Deficiency

Although a consensus regarding the optimal level of serum 25(OH)D has not yet been established, most experts define vitamin D deficiency as a 25(OH)D level of <20 ng/ml (50 nmol/l) and vitamin D insufficiency as 21 to 29 ng/ml. For all studied end points to date, the optimal concentration of 25(OH)D is at least 30 ng/ml.

Vitamin D levels

Serum 25-Hydroxyvitamin D (ng/ml)	Vitamin D Status
≤10	Severe deficiency
10–20	Deficiency
21–29	Insufficiency
≥30	Sufficiency
>150	Toxicity

Acute coronary syndromes

The clinical presentations of CAD are highly variable. Chest discomfort is usually the predominant symptom in chronic stable angina, unstable angina, micro vascular angina and acute myocardial infarction. However syndromes of CAD also occur in which ischemic chest comfort is absent or not prominent such as asymptomatic myocardial ischemia, congestive heart failure, cardiac arrhythmias and sudden death. The contemporary approach to patients presenting with ischemic discomfort is to consider that they are experiencing an acute coronary syndrome. The twelve lead ECG is pivotal for segregating patients into those presenting with ST segment elevation and those presenting without ST segment elevation[81].

Hypertension:

High blood pressure often confers silent cardiovascular risk and its prevalence is steadily increasing. Of the estimated 50 million people with high blood pressure, almost one third evade diagnosis and only one fourth receive effective treatment. Hypertension prevalence increased with age(reaching more than 65 percent after the age of 60 years) and tended to be more prevalent in women than men. According to JNC 8 blood pressure >150/90mmHg in >60yrs and 140/90 mmHg in<60yrs pharmacologic treatment should be started. In diabetes>140/90mmHg pharmacologic treatment should be started regardless of age.

Hyperlipidemia and elevated low density lipoprotein cholesterol:

The emergence of data from prospective cohort studies such as Framingham heart study, The multiple risk factor intervention trial (MRFIT), Atherosclerosis risk in communities (ARIC) study established the concept of cholesterol as a culprit in coronary heart disease.

High density lipoprotein cholesterol, apo lipoproteins and other lipid subclasses:

Abundant prospective cohort studies have demonstrated a strong inverse relationship between HDL cholesterol and vascular risk. Despite evidence favoring apo lipoprotein AI and B 100 as replacements for HDL and LDL cholesterol, there remains little clinical data that uses of these measures improve overall risk prediction.

Triglyceride rich lipoprotein:

The role of triglyceride in atherogenesis remains controversial. A cautious approach to triglyceride reduction would seem prudent, because randomized trial data using fenofibrate among diabetic patients with elevated triglyceride have failed to find significant reduction in risk using this approach.

Metabolic syndrome, insulin resistance and diabetes:

Insulin resistance and diabetes rank among the major cardiovascular risk factors. Insulin resistance itself promotes atherosclerosis even before it produces frank diabetes. The definition adopted by National cholesterol education program adult treatment panel regains at least three of the following five criteria:

1. Waist circumference >102 cm in men and >88 cm in women.
2. Serum triglycerides of at least 150 mg/dl.
3. HDL cholesterol <40 mg/dl in men and <50 mg/dl in women.
4. Blood pressure of at least 130/85 mm Hg.
5. Serum glucose concentration of at least 110 mg/dl.

Novel atherosclerotic risk factors:

1. High sensitivity C- reactive protein

2. Hyper homocystinemia

3. Fibrinogen fibrin D dimer

4. Lipoprotein (a)

Pathophysiology:

Ischemic heart disease is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium. It typically occurs when there is an imbalance between myocardial oxygen supply and demand. Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. The major determinants of myocardial oxygen demand are heart rate, myocardial contractility and myocardial wall tension. About 70% of the total resistance to flow occurs across three sets of arteries.

1. Large epi cardial arteries R1
2. Pre arteriolar vessels R2
3. Arteriolar and intra myocardial capillary vessels R3

Effects of ischemia:

Regional disturbances of ventricular contractility cause segment akinesia or in severe cases bulging (dyskinesia) which can greatly reduce myocardial pump function. Angina pectoris when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction. The severity and duration of the imbalance between myocardial oxygen supply and demand determine whether the damage is reversible or whether it is permanent, with subsequent myocardial necrosis.

Ischemia also causes characteristic changes in the electrocardiogram as evidenced by inversion of T waves, when more severe by displacement of ST segment. Transient T wave inversion likely reflects non transmural, intramyocardial ischemia. Transient ST segment depression often reflects subendocardial ischemia and ST segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to isolated ventricular premature beats or even ventricular tachycardia or ventricular fibrillation. Most patients who die suddenly from IHD do as a result of ischemia induced tachyarrhythmia.

Clinical features:

Patients with IHD fall into two large groups

1. Patients with chronic coronary artery disease who most commonly present with stable angina.
2. Patients with acute coronary syndrome composed of patients with acute MI with ST segment elevation on their presenting ECG (STEMI) and those with unstable angina and Non ST segment elevation (UA/NSTEMI). Almost one half of patients with UA/NSTEMI are women, while more than three fourths of patients with STEMI are men.

Stable angina pectoris

The typical patient with angina is a man older than 50 years or a woman older than 60 years of age who complain of chest discomfort usually described as heaviness, pressure, squeezing, smothering or choking and only rarely as frank pain. When the patient is asked to localize the sensation, he or she will typically place their hand over the sternum, sometimes with a clenched fist (Levine's sign). Angina is

usually crescendo decrescendo in nature typically lasts 2-5 minutes and radiate to either shoulder and to both arms.

However, especially in women and diabetics, angina pectoris maybe a typical in location. The typical textbook symptoms of substernal chest pain or pressure radiating to the arms may not be the primary symptoms in women presenting with CAD. Angina equivalents are symptoms of myocardial ischemia other than angina. These include dyspnea, nausea, fatigue and faintness and are more common in the elderly, women and in diabetic patients. The new onset of symptoms and their relationship to activity has more clinical relevance than their physical location. Women report symptoms more often during daily activities and mental stress than during exercise.

Unstable angina:

Unstable angina is defined as angina pectoris or equivalent ischemic discomfort with at least one of the three features:

1. It occurs at rest (or with minimal exertion) usually lasting>10 minutes
2. It is severe and of new onset (i.e. within the prior 4-6weeks)
3. It occurs with a crescendo pattern (i.e. clinically more severe, prolonged or frequent than previously)

The diagnosis of NSTEMI is established if a patient with clinical features of unstable angina develops evidence of myocardial necrosis, as reflected in elevated cardiac biomarkers.

Clinical presentation of STEMI:

Pain is the most common presenting complaint in patients with STEMI. It is similar in character to angina pectoris, but commonly occurs at rest, is usually more severe and lasts longer. The pain of STEMI may radiate is high as the occipital area but not below the umbilicus. However STEMI presents without pain in elderly, women and diabetics in whom it can present as pulmonary edema, loss of consciousness, appearance of arrhythmia or merely an unexplained drop in arterial pressure.

Physical findings:

Although many patients have a normal pulse rate and blood pressure within the first hour of STEMI, about one fourth of patients' with anterior infarction havemanifestations of sympathetic nervous system hyperactivity such as tachycardia and/or hypertension. Up to one half of patients with inferior infarction show evidence of parasympathetic hyper activity such as bradycardia and/or hypotension.

1. The precordium is usually quiet and the apical impulse maybe difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infracted myocardium may develop in periapical area within the first days of illness and then may resolve.
2. S3, S4 may be heard.
3. Paradoxical splitting of S2
4. Transient mid systolic apical systolic murmur due to dysfunction of the mitral valve apparatus.
5. Pericardial friction rub and decrease in volume of pulse.

Laboratory findings:

The laboratory tests of value in confirming the diagnosis may be divided into four groups

1. ECG
2. Serum cardiac biomarkers
3. Cardiac imaging
4. Nonspecific indices of tissue necrosis and inflammation.

ECG:

The ECG is a cornerstone in the diagnosis of acute and chronic ischemic heart disease. The findings depend on several key factors: the nature of the process [reversible (i.e., ischemia) versus irreversible (i.e., infarction)], the duration (acute versus chronic), extent (trans mural versus subendocardial), and localization (anterior versus infer posterior), as well as the presence of other underlying abnormalities (ventricular hypertrophy, conduction defects). When the acute ischemia is transmural, the ST vector is usually shifted in the direction of the outer (epicardial) layers, producing ST elevations and sometimes, in the earliest stages of ischemia, tall, positive so-called hyper acute T waves over the ischemic zone. With ischemia confined primarily to the sub endocardium, the ST vector typically shifts toward thesub endocardium and ventricular cavity, so that overlying (e.g., anterior pre cordial) leads show ST-segment depression (with ST elevation in lead aVR). Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. From a clinical viewpoint, the division of acute myocardial infarction into ST segment elevation and non-ST elevation types is useful since the efficacy of acute reperfusion therapy is limited to the former group. The ECG leads are more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example,

acute transmural anterior (including apical and lateral) wall ischemia is reflected by ST elevations or increased T-wave positivity in one or more of the precordial leads (V1 to V6) and leads I and aVL. Inferior wall ischemia produces changes in leads II, III, and aVF. Posterior wall ischemia may be indirectly recognized by reciprocal ST depressions in leads V1 to V3. Prominent reciprocal ST depressions in these leads also occur with certain inferior wall infarcts, particularly those with posterior or lateral wall extension.

Right ventricular ischemia usually produces ST elevations in right-sided chest leads. When ischemic ST elevations occur as the earliest sign of acute infarction, they are typically followed within a period ranging from hours to days by evolving T-wave inversions and often by Q waves occurring in the same lead distribution. With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial tissue may lead to decreased R-wave amplitude or abnormal Q waves in the anterior or inferior leads. Loss of depolarization forces due to posterior or lateral infarction may cause reciprocal increases in R-wave amplitude in leads V1 and V2 without diagnostic Q waves in any of the conventional leads. Atrial infarction may be associated with PR-segment deviations due to and atrial current of injury, changes in P-wave morphology, or atrial arrhythmias. In the weeks and months following infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG following Q wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder (akinetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm. The ECG has important limitations in both sensitivity and specificity in the diagnosis of ischemic heart

disease. Although a single normal ECG does not exclude ischemia or even acute infarction, a normal ECG throughout the course of an acute infarct is distinctly uncommon.

Serum cardiac biomarkers:

Certain proteins called serum cardiac biomarkers are released from necrotic heart muscle after STEMI. The temporal pattern of protein release is of diagnostic importance, but contemporary urgent reperfusion strategies necessitate making a decision based largely on a combination of clinical and ECG findings. Biomarkers such as cardiac specific Troponin T (CTnT) and cardiac specific Troponin I (CTnI) may increase after STEMI to levels>20 times higher than the upper reference limit. They are particularly valuable in differentiating skeletal muscle injury from small MI that may be below the detection limit for CK and CKMB measurements and they are therefore of particular value in distinguishing UA from NSTEMI. Levels of CTnT and CtnI rise as early as 3 hours after STEMI and elevated for 7 to 10 days after STEMI. Creatine phosphokinase rises within 4 to 8 hours and generally return to normal by 48 to 72 hours. A ratio of CKMB: CK activity =2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CKMB elevation.

Cardiac imaging:

Abnormalities of wall motion on two-dimensional echocardiography are almost universally present. Although acute STEMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool. In the emergency department setting, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether

the patient should receive reperfusion therapy. Echo cardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for therapy with an angiotensin-converting enzyme inhibitors. Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of STEMI. Several radio nuclide imaging techniques are available for evaluating patients with suspected STEMI. However, these imaging modalities are used less often than echocardiography because they are more cumbersome and lack sensitivity and specificity in many clinical circumstances. Myocardial perfusion imaging with 201Tl or 99mTc-sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium, reveal a defect ("cold spot") in most patients during the first few hours after development of a transmural infarct. However, although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and thus is not specific for the diagnosis of acute MI. Radionuclide ventriculography, carried out with 99mTc-labeled red blood cells, frequently demonstrates wall motion disorders and reduction in the ventricular ejection fraction in patients with STEMI. While of value in assessing the hemodynamic consequences of infarction and in aiding in the diagnosis of RV infarction when the RV ejection fraction is depressed, this technique is nonspecific, as many cardiac abnormalities other than MI alter the radionuclide ventriculogram.

Few studies that correlate Vitamin D levels in ACS are:

A study by Giovannucci E et al in 2008 published that "Low levels of 25(OH)D are associated with higher risk of myocardial infarction in a graded manner, even after controlling for factors known to be associated with coronary artery disease"[8].

Lee JH et al published a study stating that Vitamin D levels are low in patients with acute coronary syndromes[7].

A study by Scragg and colleagues was conducted in the Central Auckland area of New Zealand between March 1986 and 1988. Cases were patients between 35-64 years of age, who were diagnosed with AMI per the WHO-MONICA project criteria. Age and sex matched controls were obtained by random sampling of the general population. About 179 case-control pairs were analyzed. The results indicated that the mean plasma 25(OH)D level in the cases was lower compared to the controls (32 nmol/lit vs. 35 nmol/lit, p value=0.017). He also suggested that exposure to sunlight may be thus beneficial in protecting against MI[22].

A study by Khalili H et al stated that lower Vitamin D levels are associated with increased mortality in patients with acute coronary syndromes[29].

Sathyamurthy et al published a study where they assessed 25 Hydroxy vitamin D3 levels in patients with ACS. Levels of 25 Hydroxy vitamin D3, serum calcium and high sensitive C-reactive protein (Hs CRP) on day 1 and day 5 were measured in 50 consecutive patients (Male: Female 46:4) admitted with ACS and compared them with 35 controls (Male: Female 25:10) .72% of their patient population had vitamin D insufficiency and there was statistically significant difference in 1st day sample and 5th day samples of vitamin D, Hs CRP and calcium levels and the P value is <0.05.

Evidence is beginning to accumulate implicating vitamin D and its receptors in the pathogenesis of both coronary artery disease and ACS[30].

James B Wetmore et al stated a study where the Vitamin D deficiency in acute MI was mediated through the NT-proBNP pathways and stated that the mechanism of vascular inflammation needs investigation[31].

Marijana Kneevie, Praveek et al from Croatia reported a high prevalence of hypovitaminosis D in Croatian patients with ACS[32].

Luis C.L Correa et al established severe vitamin D deficiency is independently associated with in-hospital cardiovascular mortality in patients with acute coronary syndromes[33].

Tami L.Blair et al studied the association between Vitamin D and ACS and stated that Vitamin D deficiency is prevalent among patients diagnosed with CAD regardless of their mode of presentation. However, it appears that severe 25[OH] Vitamin D deficiency in those with chronic (stable) coronary artery disease is most prevalent and best predicts risk of future cardiovascular events[34].

Dror Y et al in his study Vitamin D Levels for Preventing Acute Coronary Syndrome and Mortality: Evidence of a Non-Linear Association has proven that a safe range exists for Vitamin D levels and both hypovitaminosis and hypervitaminosis are contributory factors to increased mortality in ACS[35].

Wang TJ et al in their study "Vitamin D deficiency and risk of cardiovascular disease" stated that Vitamin D deficiency is associated with incident cardiovascular disease[23].

Suzanne Judd et al in their study titled “Vitamin D Deficiency and Risk for Cardiovascular Disease” has stated that the potential for vitamin D to have a role in the prevention and/or treatment of cardiovascular disease has some biologic plausibility and it may be prudent to screen individuals who are at highest risk for vitamin D insufficiency[24].

Lee JH et al reported very high prevalence up to 75% as 25(OH) D deficient and 21% as insufficient, making a total of 96% of patients with abnormally low 25(OH)D levels who presented with coronary artery disease[26].

Mahdavi K et al reported 72% of patients with acute coronary syndrome to had serum 25- hydroxyvitamin D level of 20 ng/ml or less[27].

In another study 92% of the subjects had suboptimal levels of 25(OH) D, with 22.2% being severely deficient and reported that optimal 25(OH)D levels substantially lowered all-cause and cardiovascular disease mortality in subjects with the metabolic syndrome[28].

Karur .S et al[1]: In this study 314 enrolled patients of Ischemic heart disease,212(67.5%) were 25(OH)D deficient and 50(16%) were insufficient, for a total of 83.5% of patients with abnormality low 25(OH)D levels. No significant heterogeneity was observed among age or gender sub groups but 25(OH)D deficiency was more commonly seen in those with lower socioeconomic status, lower activity levels, hypercholesterolemia(LDL), hypertriglyceridemia and concluded that Vitamin D deficiency is present in most of the patients with acute myocardial infarction and it is associated with many of its risk factors.

Giovannucci E et al[2] : Vitamin D deficiency may be involved in the development of atherosclerosis and coronary heart disease in humans. Assessed prospectively whether plasma 25- hydroxyl vitamin D (25[OH]D) concentrations are associated with risk of coronary heart disease. A nested case control study was conducted in 18225 men in the health Professionals Follow up study; the men were aged 40 to 75 years and were free of diagnosed cardiovascular disease at blood collection.. During 10 years of follow-up, 454 men developed nonfatal myocardial infarction or fatal coronary heart disease. Concluded that low level of 25(OH)D are associated with higher risk of myocardial infarction in a graded manner , even after controlling factors known to be associated with coronary artery disease.

Kevin Fiscella et al[3] In this study 25- hydroxyl vitamin D(25[OH]D)levels measured in 128 patients admitted to the hospital with ischemic heart disease (75 with angina pectoris and 53 with acute MI)and 409 control subjects and found that 25(OH)D levels were significantly lower in those with angina (23.5 ng/mL [to convert to nan moles per liter, multiply by 2.496] or MI (24.0 ng/mL) than in controls(28.8ng/mL)and concluded that low serums levels of 25(OH)D are associated with increased cardiovascular mortality , interventional trials among persons with low vitamin D are needed to determine whether oral supplementation improves cardiovascular outcome.

John H. Lee et al[4] concluded that Vitamin D deficiency is present in a majority of AMI patients in a multi-center US cohort. Screening and treatment should be considered to correct this common vitamin deficiency and investigated as a potential means of further improving AMI patients' cardiovascular risk factors and outcomes.

Lu Wang, Joann E. Manson, Yiqing song, Howard D. Sesso[5],- —Vitamin D status has been linked to the risk of cardiovascular disease (CVD). Methods and Results—A 6,123 CVD cases in 65,994 participants were included for a meta-analysis. Comparing the lowest to the highest 25(OH)-vitamin D categories, the pooled relative risks (RR) was 1.52 (95% CI: 1.30-1.77) for total CVD, 1.42 (95% CI: 1.19-1.71) for CVD mortality, 1.38 (95% CI: 1.21-1.57) for coronary heart disease, and 1.64 (95% CI: 1.27-2.10) for stroke. These associations remained strong and significant when analyses were limited to studies that excluded participants with baseline CVD and had better controlled for season and confounding. They used a fractional polynomial spline regression analysis to assess the linearity of dose-response association between continuous 25(OH)-vitamin D and CVD risk. The CVD risk increased monotonically across decreasing 25(OH)-vitamin D below approximately 60 nmol/L, with a RR of 1.03 (95% CI: 1.00-1.06) per 25 nmol/L decrement in 25(OH)-vitamin D. Conclusions—This meta-analysis demonstrated a generally linear, inverse association between circulating 25(OH)-vitamin D in the range of 20-60 nmol/L and risk of CVD.

MATERIALS AND METHODS

1. SOURCE OF DATA:

The information for the study will be collected from ISCHEMIC HEART DISEASE patients admitted to BLDEU'S Shri B.M Patil Medical college Hospital and Research Centre Vijayapur between December 2014 to March 2016.

2. METHOD OF COLLECTION OF DATA:

Information will be collected through prepared proforma from each patient. All patients will be interviewed as per the prepared proforma and then complete clinical examination will be done.

Inclusion Criteria: Patients with Acute coronary syndrome [STABLE ANGINA, UNSTABLE ANGINA, ST ELEVATION MI, NON ST ELEVATION MI].

Exclusion criteria : All patients with modifiable risk factors of IHD are excluded like HYPERTENSION, TYPE 2 DIABETES MELLITUS, ALCOHOL, SMOKING.

3. TYPE OF STUDY

CROSS SECTIONAL STUDY.

4. SAMPLE SIZE

With 95% level of confidence and expected prevalence of Ischaemic heart disease as 28.5% and ± 10% margin of error the minimum sample size is 80 patients[13].

So the formula- N=Z2.P(1-P)/D2

Where Z=1.96 at 95% level of confidence.

P=Prevalence.

D=margin of error.

METHOD : 5ml of blood is drawn from patients with IHD and serum samples sent to a centralized laboratory for analysis using the ELECYS assay. Normal 25(OH)D levels are ≥ 30ng/ml, and patients with levels <30 and >20ng/ml were classified as in sufficient and those levels with ≤ 20ng/ml as deficient[1].

5. STATISTICAL METHOD:-

1) Mean ± SD.
2) Graphical presentation
3) Chi-square test.
4) Student t-test.

Investigations required in this study are routine standardized procedures.

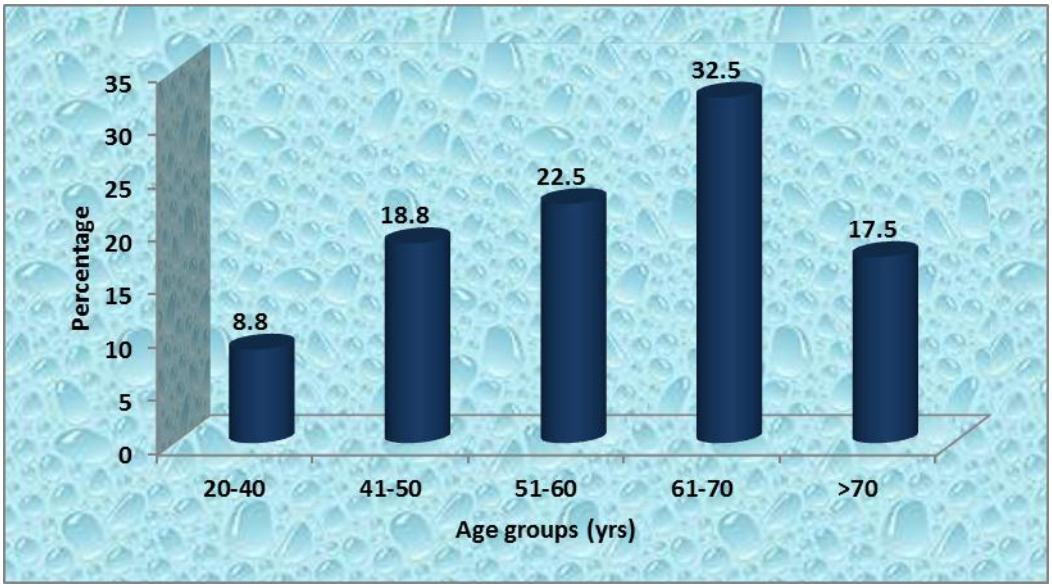
INVESTIGATIONS

- CBC
- URINE ROUTINE
- FBS AND PPBS
- LIPID PROFILE
- ECG
- CHEST X-RAY
- ECHO
- STRESS TEST AS AND WHEN REQUIRED
- CARDIAC ENZYMES.
- SERUM VITAMIN D LEVELS.

RESULTS

During our study period 80 patients were studied as mentioned above. The mean age of our study group was 61 ± 12.1 years. Of the study population there were 57 male patients and 23 were females accounting to 71.2 % and 28.8 % respectively.

Graph 1: Distribution of cases according to Age:



Graph 2: Distribution of cases according to Sex:

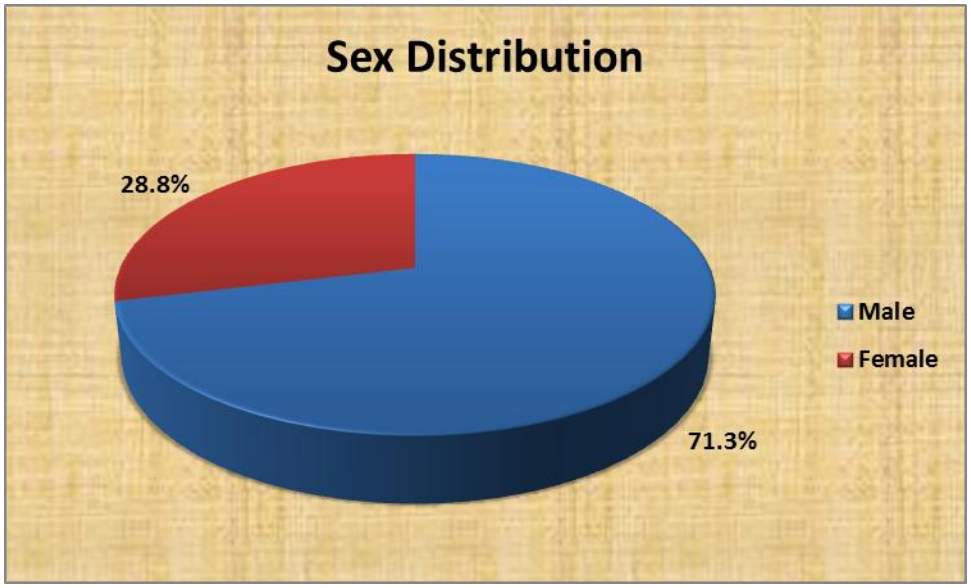


Table 1: Total number of patients with Vitamin D deficiency.

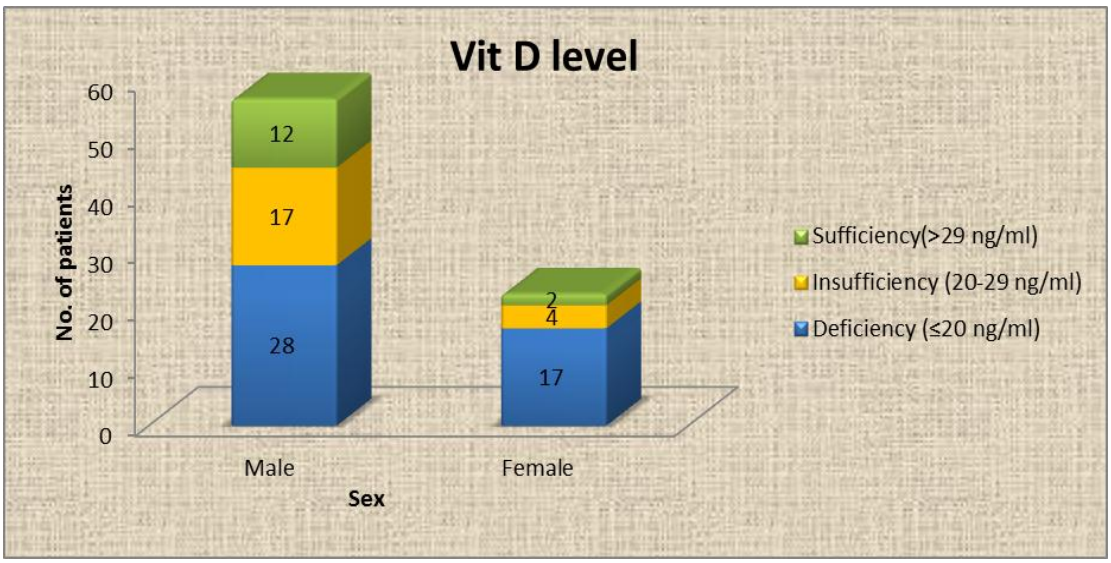
Vitamin D levels	Deficiency	%
Male	45	68.18
Female	21	31.82
Total	66	100

P value=0.188 is not significant.

Table 2: Distribution of cases according to vit D level.

Sex	**Deficiency (≤ 20 ng/ml)**		**Insufficiency (20-29 ng/ml)**		**Sufficiency(>29 ng/ml)**		**p value**
	N	**%**	**N**	**%**	**N**	**%**	
Male	28	62.2	17	81.0	12	85.7	0.123
Female	17	37.8	4	19.0	2	14.3	
Total	45	100.0	21	100.0	14	100.0	

Graph 3: Distribution of cases according to vit D level.

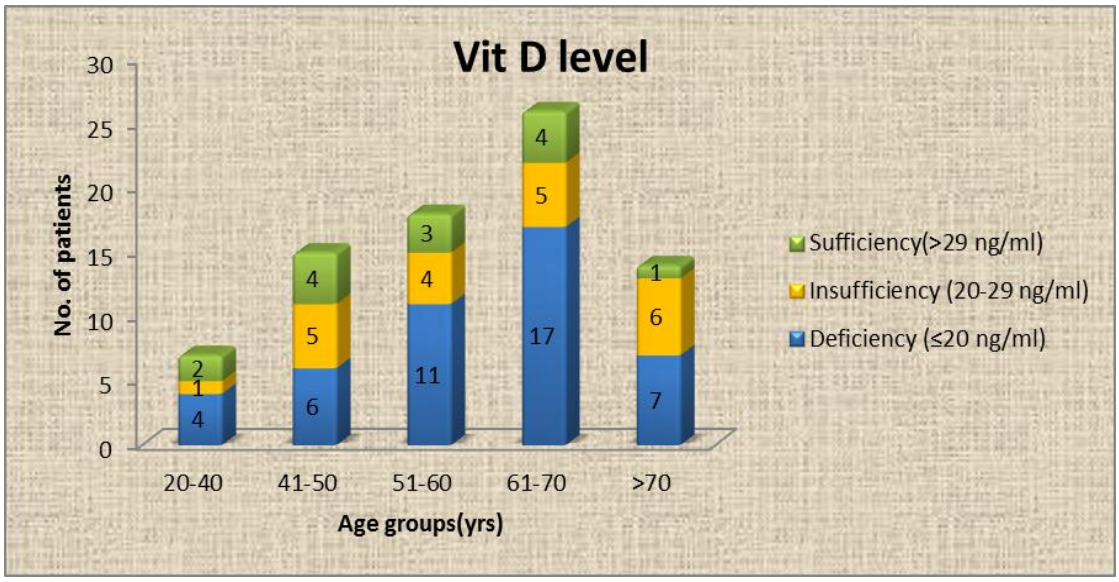


In deficiency group 28(62.2%) male had vitamin D deficiency and 17(37.8%) of female had same. In insufficiency 17(81%) of male and 4(19%)of female had vitamin D insufficiency. In sufficiency only 12(85.7%)male and 2(14.3%) had vitamin D sufficiency. 73.91% of female patients had vitamin D deficiency it is significant amount.

Table 3: Distribution of cases according to age group.

Age groups (yrs)	Deficiency (≤ 20 ng/ml)		Insufficiency (20-29 ng/ml)		Sufficiency (>29 ng/ml)		p value
	N	%	N	%	N	%	
20-40	4	8.9	1	4.8	2	14.3	0.631
41-50	6	13.3	5	23.8	4	28.6	
51-60	11	24.4	4	19.0	3	21.4	
61-70	17	37.8	5	23.8	4	28.6	
>70	7	15.6	6	28.6	1	7.1	
Total	45	100.0	21	100.0	14	100.0	

Graph 4: Distribution of cases according to age group.

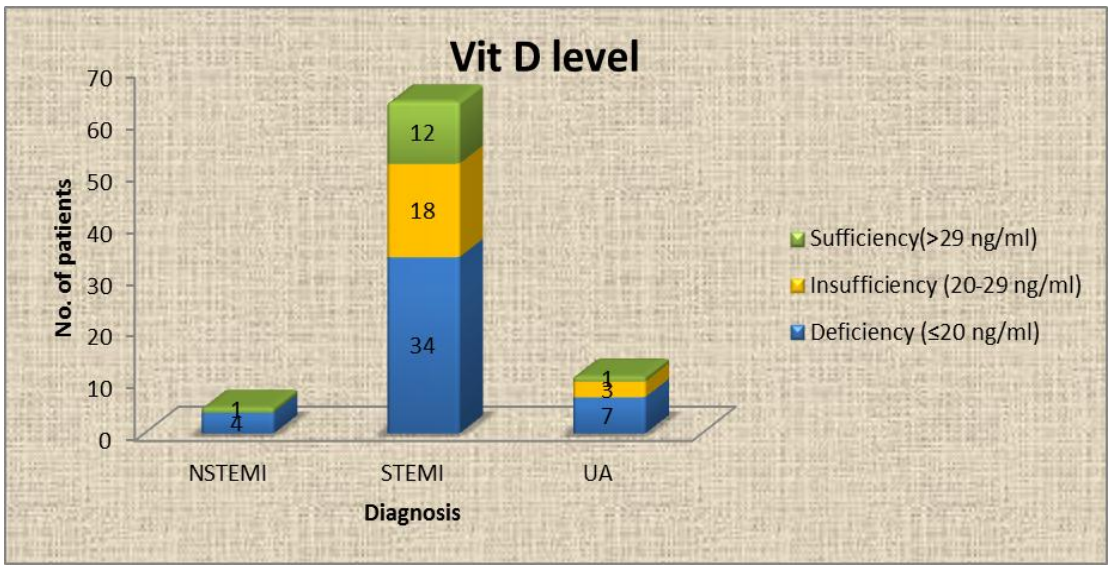


Most of the patients in our study group were in age from 50 to 70 years, 37.8% in age between 61 to 70 years and 24.4% in between 51 to 60 years.

Table 4: Distribution of cases according to ACS associated with vit D level.

Diagnosis	Deficiency (≤ 20 ng/ml)		Insufficiency (20-29 ng/ml)		Sufficiency (>29 ng/ml)		p value
	N	%	N	%	N	%	
NSTEMI	4	8.9	0	0.0	1	7.1	0.856
STEMI	34	75.6	18	85.7	12	85.7	
UA	7	15.6	3	14.3	1	7.1	
Total	45	100.0	21	100.0	14	100.0	

Graph 5: Distribution of cases according to ACS associated with vit D level.

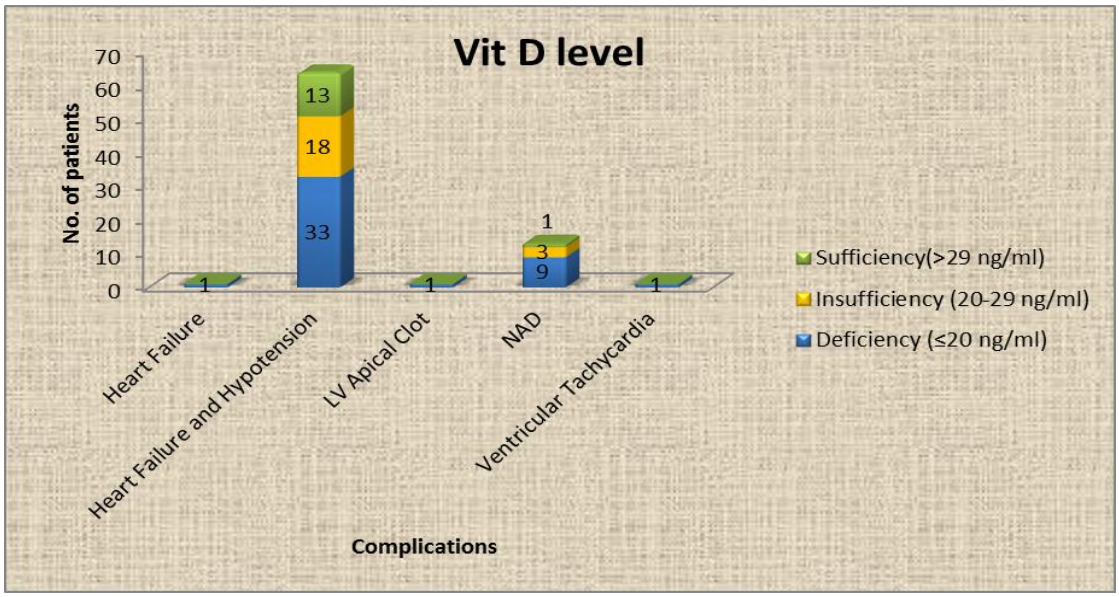


In our study 53.12% of patients with STEMI had vitamin D deficiency, 28.12% had insufficiency and 18.75% had sufficiency. Among NSTEMI 80% had deficiency and 20% had sufficiency. Among UNSTABLE ANGINA 63.63% had deficiency and 27.27% had insufficiency and 9.09% had sufficiency.

Table 5: Distribution of cases according to complications associated with vit D level.

Complications	Deficiency (≤ 20 ng/ml)		Insufficiency (20-29 ng/ml)		Sufficiency (>29 ng/ml)		p value
	N	%	N	%	N	%	
Heart Failure	1	2.2	0	0.0	0	0.0	0.946
Heart Failure and Hypotension	33	73.3	18	85.7	13	92.9	
LV Apical Clot	1	2.2	0	0.0	0	0.0	
NAD	9	20.0	3	14.3	1	7.1	
Ventricular Tachycardia	1	2.2	0	0.0	0	0.0	
Total	45	100.0	21	100.0	14	100.0	

Graph 6: Distribution of cases according to complications associated with vit D level.

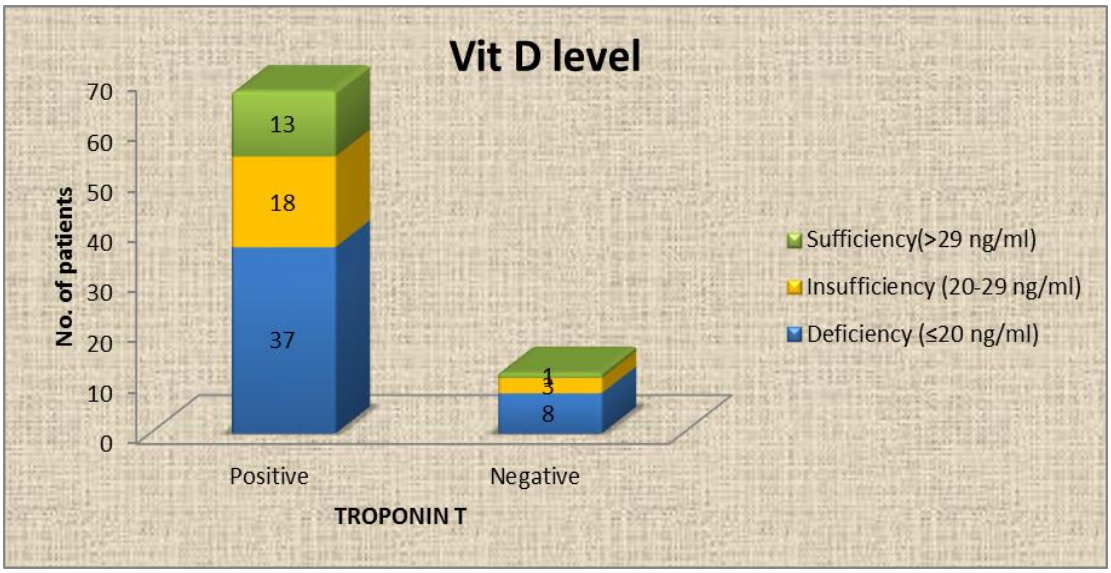


In our study 73.3% of deficient group had heart failure with hypotension, 2.2% had ventricular tachycardia and 2.2% had LV apical clot. There is no significant correlation with sufficient group.

Table 6: Distribution of cases according to Troponin T.

TROPONIN T	Deficiency (≤ 20 ng/ml)		Insufficiency (20-29 ng/ml)		Sufficiency (>29 ng/ml)		p value
	N	%	N	%	N	%	
Negative	8	17.8	3	14.3	1	7.1	0.619
Positive	37	82.2	18	85.7	13	92.9	
Total	45	100.0	21	100.0	14	100.0	

Graph 7: Distribution of cases according to Troponin T

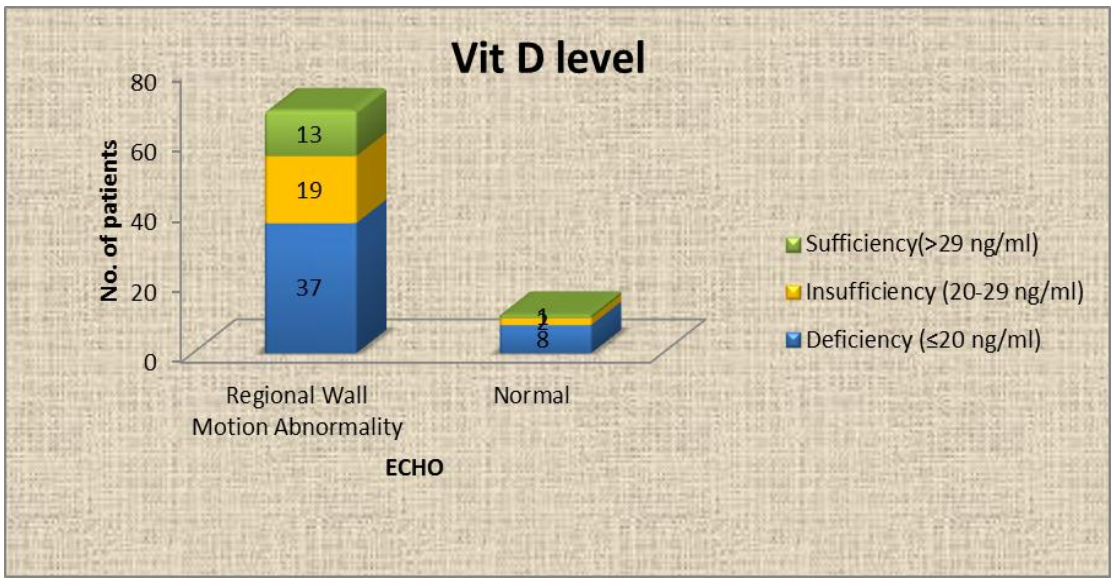


Out of 68 patients of Troponin T positive 55(80.88%) had Vitamin D deficiency.

Table 7: Distribution of cases according to ECHO findings.

ECHO	Deficiency (≤ 20 ng/ml)		Insufficiency (20-29 ng/ml)		Sufficiency (>29 ng/ml)		p value
	N	%	N	%	N	%	
Normal	8	17.8	2	9.5	1	7.1	0.485
Regional Wall Motion Abnormality	37	82.2	19	90.5	13	92.9	
Total	45	100.0	21	100.0	14	100.0	

Graph 8: Distribution of cases according to ECHO findings.

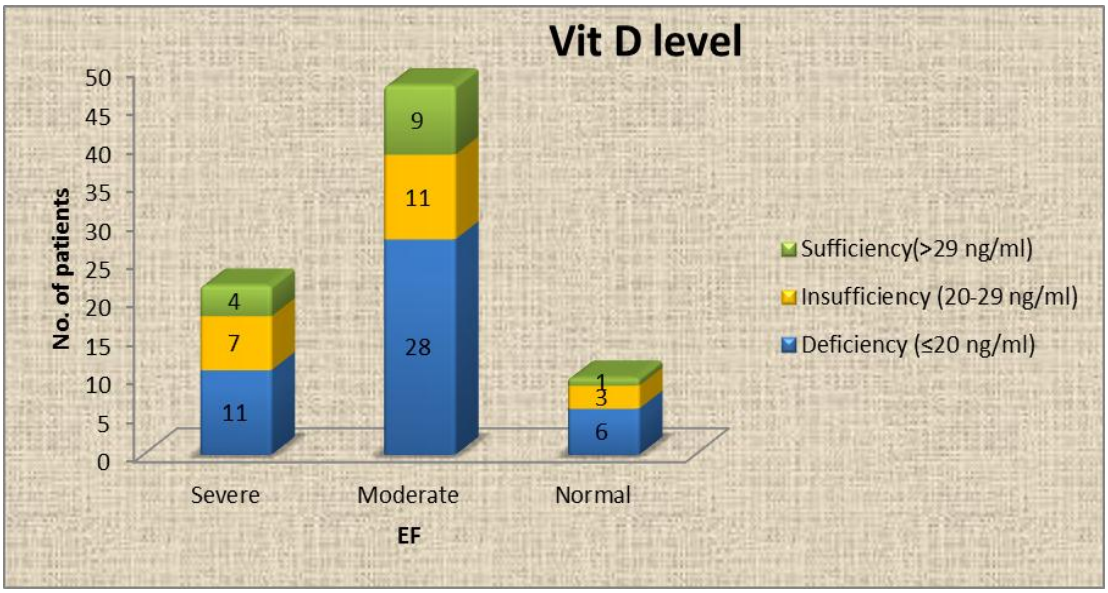


In our study 53.62% of deficient group had regional wall motional abnormality compared to insufficiency (27.53%) and sufficiency (18.84%) sufficiency. There was the significant correlation.

Table 9 : Distribution of cases according to EF findings.

EF	Deficiency (≤ 20 ng/ml)		Insufficiency (20-29 ng/ml)		Sufficiency (>29 ng/ml)		p value
	N	%	N	%	N	%	
Severe	11	24.4	7	33.3	4	28.6	0.721
Moderate	28	62.2	11	52.4	9	64.3	
Normal	6	13.3	3	14.3	1	7.1	

Figure 8: distribution of cases according to EF findings.



In our study 50% of deficient group had ejection fraction of heart of less than 30%, 31.8% in insufficiencyand 18.8% in sufficiency. 58.35% had ejection fraction of 30-60% in deficiency group, 22.91% in insufficiency and 18.75% in sufficiency group.

DISCUSSION

With acute coronary syndromes being one of the leading causes of mortality and morbidity all over the world, science has spread its arms in every possible direction to unsheathe the hidden reversible risk factors for ACS. Vitamin D levels have been the point of interest for many authors for a very long time.

In our study the mean age was 58.5 years with the mean age in Vitamin D deficient patients being slightly higher 61 years. In a study from Iran by Siadat et al[82], the mean age was 58.7 years and in a study from Bangalore by Karur S et al the mean age was 54.09 years which goes in agreement with our study[83].

The male female ratio there were more males compared to females of double the ratio male: female ratio being 2.4:1. We found a significant Vitamin D deficiency in female patients compared to male patients. In our study 73.91% of females had Vitamin D deficient. The study by Karur S et al did not find any difference with respect to sex in their study[83].

Our data suggested that there is high prevalence of vitamin D deficiency or insufficiency (82.5%) in acute coronary syndrome patients. This data is consistent with a study by Satyamurthy et al[30] who reported a 72% Vitamin D deficiency in AMI patients. The study by Karur S et al reported 83.5% deficient or indeficient subjects in their study[83]. A study by Scragg R et al also notes the inverse relationship between the vitamin D levels and the incidence of cardiovascular disease[23].

Our study also correlated with Martins, D et al[62] Serum 25(OH)D levels are associated with important cardiovascular disease risk factors in US adults. Prospective studies to assess a direct benefit of cholecalciferol (vitamin D) supplementation on

cardiovascular disease risk factors are warranted[62]. Vitamin D deficiency has important cardiovascular risk factor in our study.

Our study also correlated with Pilz, S et al[51]. Vitamin D deficiency is common, and the cardiovascular system is a target tissue for vitamin D. Experimental studies showed beneficial vitamin D effects on cardiovascular risk factors, the heart and the blood vessels. Clinical studies have largely, but not consistently, indicated that cardiovascular disease and mortality are associated with vitamin D deficiency.

In our study there is 82.5% vitamin D deficiency in acute coronary syndrome which correlated with study done by Marijana Kneæevi Ê PraveËek et al [32] of 60 patients with ACS, mean 25(OH)D level was 34.9 nmol/L; vitamin D deficiency was present in 76% and only 8% had optimal 25(OH)D levels. Nearly one third were severely deficient (36%), with 25(OH)D levels <30 nmol/L. Those with severe vitamin D deficiency had significantly higher prevalence of NSTEMI as compared to those with higher 25(OH)D levels.

Our study also correlated with Seong Jae Hur et al[25] that Lower 25D levels appear to be associated with cTnT elevation, predicting worse CV outcome, mand are possible to involve cardiac hypertrophy or coronary artery disease.

Our study could not correlate with Mahdavi K et al[27] in which they concluded that Significant ($p<0.01$) correlation between the vitamin D deficiency and ACS in comparison to healthy controls was recorded. As in our study the p=0.188. 000Study recorded a very high vitamin D deficiency in patients of ACS and suggests significant correlation between the two. Vitamin D deficiency is a worldwide health problem. A very high prevalence (96%) of vitamin D deficiency has been reported in patients of coronary artery disease.

Our study also correlated with Lavie CJ et al[24] Vitamin D insufficiency is very common in the United States and world-wide. Several recent epidemiologic studies have demonstrated a strong association between vitamin D insufficiency and risk of cardiovascular disease.

Our study also correlated with Giovannucci E et al[8] that low levels of 25(OH)D are associated with higher risk of myocardial infarction in a graded manner, even after controlling for factors known to be associated with coronary artery disease.

Our study also correlated with Suzanne Judd et al[23] that Vitamin D insufficiency is very common in the United States and world-wide. Several recent epidemiologic studies have demonstrated a strong association between vitamin D insufficiency and risk of cardiovascular disease.

Our study also correlated with Mohammed Ahmed Abdel Rahman et al[98]. Vitamin D exerts biphasic effect on cardiac function according to its serum levels. Reduced vitamin D (<20ng/ml) appears to be associated with worse systolic functions in terms of end systolic volume and end systolic dimension.

Based on this above studies correlation it could be advised to get Vitamin D levels in all patients admitted with Ischemic heart diseases so that to initiate treatment for Vitamin D deficiency in order to improve the outcome.

CONCLUSION

1. There is a high prevalence of Vitamin D deficiency (82.5%) among acute coronary syndrome patients.
2. The mean age group is 58.5±9.6 years.
3. Vitamin D deficiency in females was more common than compared to males.
4. Vitamin D deficiency is noticed more in STEMI.
5. Lower the Vitamin D levels more the regional wall motion abnormality.
6. Vitamin D deficiency is associated with increased risk of complications (75.75%) in acute coronary syndromes.
7. Significant decrease in ejection fraction with deficient Vitamin D levels.
8. Vitamin D deficiency is one of the independent risk factor for acute coronary syndrome.

SUMMARY

With our study that included 80 ACS patients admitted in B.L.D.E hospital Vijayapur we attempted to study the levels of Vitamin D in ACS patients. The study was conducted from Dec 2014 to March 2016. A detailed history was taken, patients were thoroughly examined and relevant investigations were carried out. After the statistical evaluations, the following observations were made:

1. The mean age of the study group was 58.5 ±9.6 years
2. Of the 80 patients, 57 were males with a male: female ratio of 2.4:1.
3. STEMI was the most common presentation that was observed in 64/80 patients, NSTEMI was seen least in 5/80 patients and 11/80 had UNSTABLE ANGINA.
4. Vitamin D deficiency was seen in 82.5% of patients with acute coronary syndrome. 45 patients had Vitamin D deficiency levels (<20 ng/ml) while 21 patients had insufficiency (vitamin D levels 21-30 ng/ml) and 14 patients had sufficiency.
5. 73.91% of females had Vitamin D deficiency. This was significant when compared to the male population.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

Institutional Ethical Committee
BIJAPUR-586 103.
OUTWARD
No. 514
Date 24/11/14
BLDE U's Shri B.M. Patil Medical College

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 at 3.30pm. to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title "Study of Serum Vitamin D Level in Ischemic Heart Disease-A Cross Sectional Study"

—X—X—X—

Name of P.G. student DR. Darshan. Manohar. B-Patil.
Dept of General ~~Surgery~~ Medicine
Name of Guide/Co-investigator Dr Rajesh. M. Honnutagi Professor.
Dept of General ~~Surgery~~ Medicine

for

DR.TEJASWINI VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/ RESEARCH

I the undersigned……..……S/O.D/O.W/O…… aged……..years ordinarily resident of……..do here by state/declare that **Dr Darshan. Manohar. B. Patil of Shri B.M. Patil Medical College and Hospital** has examined me thoroughly on ……..at ……(place) and has explained to me in my own language……. that I am suffering from…… disease (condition) and this disease/condition mimic following diseases…… further **Dr. Darshan. Manohar. B. Patil** informed me that he is conducting dissertation/research titled "**STUDY OF SERUM VITAMIN D LEVEL IN ISCHEMIC HEART DISEASE-A CROSS SECTIONAL STUDY**" of **Shri B. M. Patil Medical College, Vijayapur**. Under the guidance of **Dr. RAJESH. M. HONNUTAGI** requesting my participation in the study.

Apart from routine treatment procedure of doing the video assisted laproscopic thoracoscopy treatment, the pre-operative, post operative and follow up observations will be utilized for the study as the reference data.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of results of the study which is useful reference for treatment of other similar cases in near fucture, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/photographs/videographs taken upon me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary based on information given to me, I can ask any clarification during the course of treatment/study related to Diagnosis, Proedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow up unless I request to discharge.

In view of anticipated or unexpected complications during the course of study, that I will be treated free of cost, as explained by the investigator.

After understanding the nature of dissertation or research, Diagnosis made, mode of treatment I the under signed Shri/Smt……..

Under my full conscious state of mind I agree to participate in the said research/Dissertation.

Signature of patient:

Signature of Doctor:

Witness 1:

Witness 2:

Date:

Place:

PROFORMA

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Occupation:

Residence:

Presenting complaints with duration:

History of present complaints:

Past History:

History of hypertension

History of diabetes mellitus

Personal History:

Diet/appetite:-

Sleep:-

Bladder and bowel habits :

Smoking/Tobacco chewing/Snuff Inhalation

Duration:-

Number of cigarettes/beedis pack year smoked:-

Amount of tobacco chewed/snuff inhaled:-

Alcohol

Duration
Quantity/Frequency
Type

Sexual History

History of multiple sexual partners

Family History:

History of suggestive of Ischemic Heart Disease/hypertension diabetis mellitus

Treatment History :

General Physical Examination

Height :

Weight :

Body Mass Index :

Vitals

PR:

BP:

RR:

Temp:

Hair :
Eyes :
Nose :
Ears :
Oral Cavity :
Neck :
Upper Limbs :
Chest :
Abdomen :
Genetilia :
Lower Limbs :
Skin :

SYSTEMIC EXAMINATION.

- Respiratory System
- Cardiovascular System
- Central Nervous System
- Per abdomen

INVESTIGATIONS

HAEMATOLOGY –

Haemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour

BIOCHEMISTRY–

Random blood sugar	
Fasting blood sugar	
Postprandial blood sugar	

URINE EXAMINATION -

Albumin	
Sugar	
Microscopy	

CHEST X RAY findings:-

SERUM VITAMIN D LEVEL:-

ECG:-

2D ECHO:-

LIPID PROFILE

TOTAL CHOLESTEROL	
TRIGLYCERIDES	
HDL-CHOLESTEROL	
LDL-CHOLESTEROL	
VLDL-CHOLESTEROL	

STRESS TEST

CARDIAC ENZYMES-CPK-MB AND TROPONIN-T

CPK-MB	
TROPONIN –T	

FINAL DIAGONOSIS

KEY TO MASTER CHART

TROP T	- TROPONIN T
RWMA	- REGIONAL WALL MOTION ABNORMALITY
PE	- PULMONARY EDEMA
TMT	- THREAD MILL TEST
VIT D	- VITAMIN D
COMP	- COMPLICATION
PPBS	- POST PRANDIAL BLOOD SUGAR
FBS	- FASTING BLOOD SUGAR
HDL	- HIGH DENSITY LIPID
LDL	- LOW DENSITY LIPID
NAD	- NOTHING SIGNIFICANT
P	- POSITIVE
N	- NEGATIVE
HF	- HEART FAILURE
HYPO	- HYPOTENSION
AWMI	- ANTERIOR WALL MYOCARDIAL INFARCTION
IWMI	- INFERIOR WALL MYOCRDIAL INFARCTION
ND	- NOT DONE
COMP	- COMPLICATIONS
IPNO	- IN PATIENT sNUMBER