DISSERTATION ON

A STUDY ON SERUM VITAMIN D LEVELS IN ACUTE CORONARY SYNDROME

Submitted to

The Tamil Nadu Dr. M.G.R. Medical University

In partial fulfillment of regulations for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH – I

DEPARTMENT OF GENERAL MEDICINE

KILPAUK MEDICAL COLLEGE

CHENNAI – 10

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON SERUM VITAMIN D LEVELS IN ACUTE CORONARY SYNDROME"** is a bonafide work done by Dr.SANDHYA SUNDARARAJAN, Post Graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under our guidance and supervision in partial fulfillment of the Rules and Regulations of **The Tamilnadu Dr.M.G.R. Medical University** for the award of **M.D. Degree Branch I, (General Medicine)** during the Academic period from May 2010 to April 2013.

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DECLARATION

I solemnly declare that the dissertation entitled " **A STUDY ON SERUM VITAMIN D LEVELS IN ACUTE CORONARY SYNDROME"** was done by me at Kilpauk Medical College, Chennai under the able guidance and supervision of **Prof. Dr. R.SABARATNAVEL, M.D.,** Professor, Department of General Medicine, Government Royapettah Hospital, Chennai.

This dissertation is to submitted to **The Tamilnadu Dr. M.G.R. Medical University, Chennai** towards the partial fulfillment of requirements for the award of the degree of **M.D. General Medicine Branch-I**.

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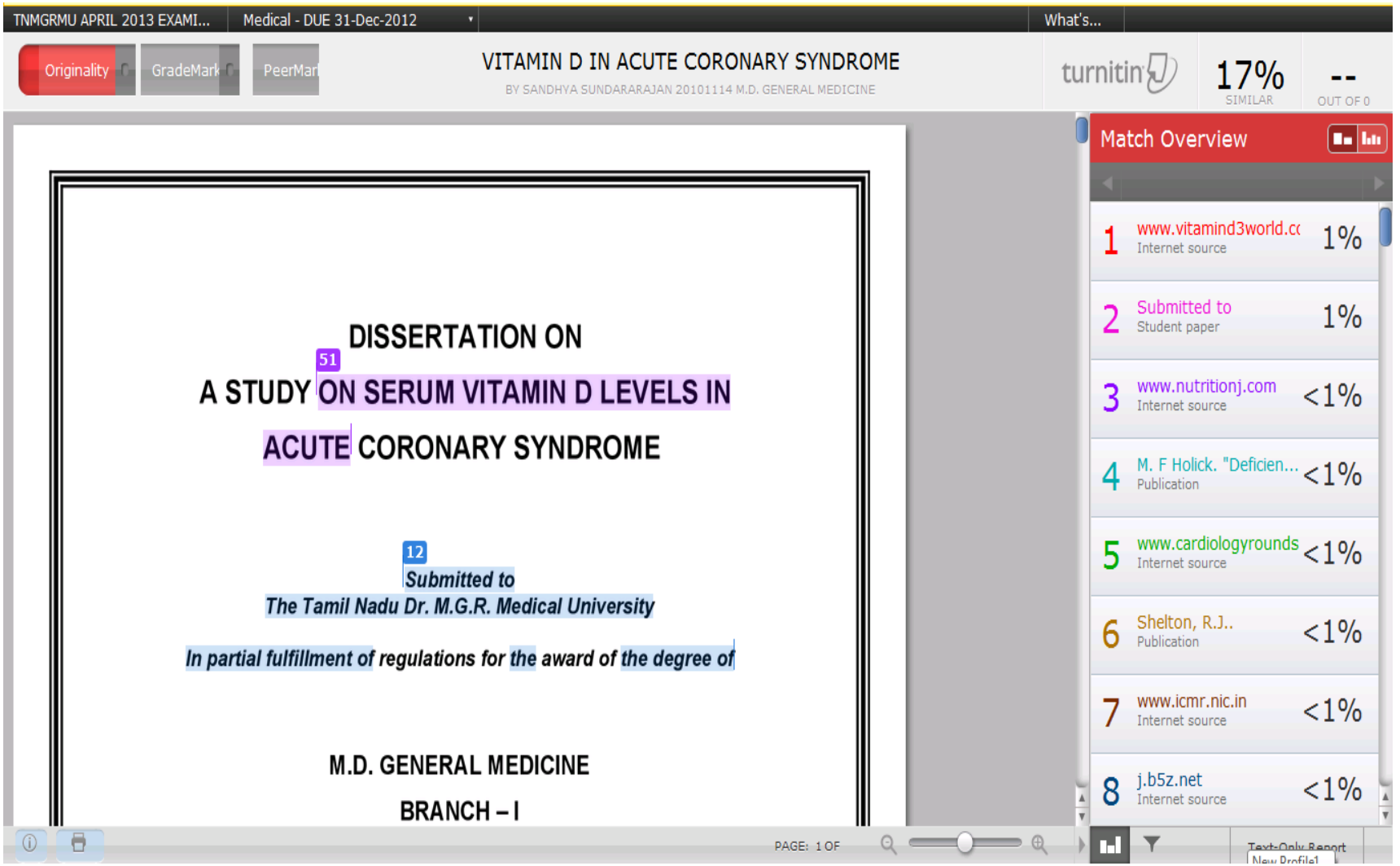
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ABSTRACT

INTRODUCTION

Coronary artery disease is now the most common cause of death and disability. Vitamin D deficiency is recently being associated with endothelial dysfunction, acute coronary syndromes and other cardiovascular risk factors such as diabetes and hypertension. Considering the growing burden of cardiovascular morbidity and mortality, there is an urgent need to study this association as Vitamin D deficiency is an easily detectable and correctable risk factor.

AIM OF THE STUDY

To study the correlation of low serum 25(OH) vitamin D levels as a risk factor for Myocardial Infarction.

MATERIALS AND METHODS

A total of 100 patients were included in our study which was an observational case control study. Based on the inclusion and exclusion criteria, we selected 50 cases of acute myocardial infarction who were admitted in the Intensive Coronary Care Unit at our hospital. We excluded the patients who had diabetes, hypertension and prior cardiac disease. The control group included 50 healthy age and sex matched individuals. The serum levels of 25(OH) Vitamin D

was assessed in each of these patients and analyzed for the presence of statistical significance.

OBSERVATION AND RESULTS

We found a positive correlation between low Vitamin D levels < 15ng/ml and the occurrence of first cardiovascular event in the patients admitted with acute myocardial infarction ($p = 0.001$). We also found a strong association between low Vitamin D levels and body mass index > 25 kg/m^2 ($p = 0.006$). The mean Vitamin D level in young patients < 40yrs of age with myocardial infarction was very low (mean = 9.58 ng/ml) when compared to the controls and those > 40yrs of age. There was no significant association between the Vitamin D status and other variables such as age, gender, lipid profile or serum calcium levels.

CONCLUSION

In this study, there was significant correlation between Vitamin D deficiency and coronary artery disease. BMI > 25 kg/m^2 was found to be associated with low Vitamin D levels thereby aggravating the occurrence of cardiovascular events in obese individuals. Hence, the early detection and management of Vitamin D deficiency is essential to prevent adverse cardiovascular events.

CONTENTS

INTRODUCTION

INTRODUCTION

Cardiovascular diseases are the commonest cause of mortality and morbidity worldwide.[1] The prevalence of cardiovascular disease has rapidly increased in the past few years. Though there are many well established risk factors for cardiovascular disease, emerging novel risk factors are being assessed by various epidemiological studies and continue to be an important aspect of debate regarding their nature of association and the role they play in reducing death and disability due to cardiovascular disease.

Over the recent years, there has been much emphasis and research over one such risk factor i.e. Vitamin D Deficiency which is now attracting importance from many medical and nutritional communities as knowledge emerges of its biological function and its association with decreased risk of many chronic diseases.

Hypovitaminosis D is a worldwide health problem. In addition to its well defined role as a major regulator of bone and calcium metabolism, several studies have found associations of poor Vitamin D status with coronary artery calcification and heart failure, as well as positive correlation with hypertension, diabetes mellitus, metabolic syndrome, atherosclerosis, peripheral arterial disease, cancer and many autoimmune disorders.

Vitamin D deficiency has been linked to an increased risk of Coronary Artery Disease (CAD) and cardiovascular (CV) death. Endothelial dysfunction

plays a vital role in the pathogenesis of Coronary Artery Disease and Vitamin D deficiency is postulated to promote endothelial dysfunction. Following the discovery of the expression of Vitamin D receptors and 1α hydroxylase in the myocardium and endothelium, several biological mechanisms that link Vitamin D with CAD and its risk factors have been identified. Vitamin D mainly acts through its role in maintaining calcium homeostasis and gene transcription to prevent cardiovascular diseases and its risk factors.

Many data have shown that cardiovascular morbidity and mortality are 30-50% more in the regions of less sun exposure due to season or latitude and that mortality from CAD is highest in winter. All these studies point to a causal association of Vitamin D, as its serum levels reduces in people who live away from the equator because of reduced exposure to ultraviolet rays. The prevalence of Vitamin D deficiency is even higher in dark skinned people and elderly persons.

Many studies worldwide have confirmed that myocardial infarction patients have lower Vitamin D levels than control subjects. It was postulated that those with low Vitamin D levels had almost 60% higher risk of myocardial infarction than those with the highest levels.

In spite of the rising proportions of CAD in Asians, only limited data are available on the relationship between Vitamin D, CAD and endothelial

dysfunction. Though numerous epidemiological studies have found significant association of Vitamin D deficiency with several cardiovascular risk factors like Diabetes, Hypertension and Dyslipidemia, the occurrence of Vitamin D deficiency itself as an independent risk factor for cardiovascular mortality is still disputed. Since Vitamin D deficiency can be easily measured and treated, trials to study the effect of hypovitaminosis D and its supplementation to prevent and treat cardiovascular diseases are currently considered important areas of research.

The increasing rate of coronary artery disease and the associated morbidity and mortality make it necessary to develop further research in this study population. Many studies have been done and many are going on to assess the Vitamin D status in these patients. A practical time to check for 25(OH) Vitamin D deficiency and to start treatment is at the time of an acute myocardial infarction. Hence this study was designed to determine whether the presence of Hypovitaminosis D has significant correlation with Coronary Artery Disease.

AIMS AND OBJECTIVES

AIM OF THE STUDY

1. The primary aim of our study was to assess the serum levels of 25(OH) Vitamin D in patients with Acute ST Elevation Myocardial Infarction and to compare their levels with that of age and sex matched controls.

2. To study if there is a causal association of Vitamin D deficiency as an independent risk factor for Coronary Artery Disease.

3. The secondary objectives were :

    i) To study the prevalence of Vitamin D deficiency in our study population and to assess the severity.

    ii) To identify whether any association exists between age, gender, body mass index, total cholesterol, triglyceride and calcium with serum levels of Vitamin D.

    iii) To study the lipid profile, body mass index and serum calcium in the cases and compare them with the controls.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORICAL PERSPECTIVE

The first documented description of a patient with an acute coronary syndrome is in the Ebers papyrus from 2600 BC, which states, "If you find a man with heart discomfort, with pain in his arms, at the side of his heart, death is near." The description is still apt, but the prognosis has changed over the centuries.

The origin of the current epidemic of cardiovascular disease can be traced back to the time of industrialization in the 1700s. The three factors largely responsible for this were an increase in the use of tobacco products, reduced physical activity and the adoption of a diet high in fat, calories and cholesterol. Although the clinical syndrome of angina was described in the 1770s, it was not until 1912 that James B. Herrick described Acute Myocardial Infarction (MI).

DEFINITIONS[4]

The term '*Acute Coronary Syndromes'* describes a spectrum of clinical syndromes that are divided into those with ST elevation or new left bundle branch block and those with unstable angina and non ST elevation MI.

Acute MI is defined as a rise and/or fall in cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit, along with evidence of ischemia. Established MI is defined by any one of the following i.e.

development of new pathologic Q waves on serial ECGs, imaging evidence of MI or pathologic findings of healed or healing MI.

Ischemia is defined as any symptoms of ischemia, ECG changes suggestive of new ischemia, development of pathologic Q waves or imaging evidence of infarction.

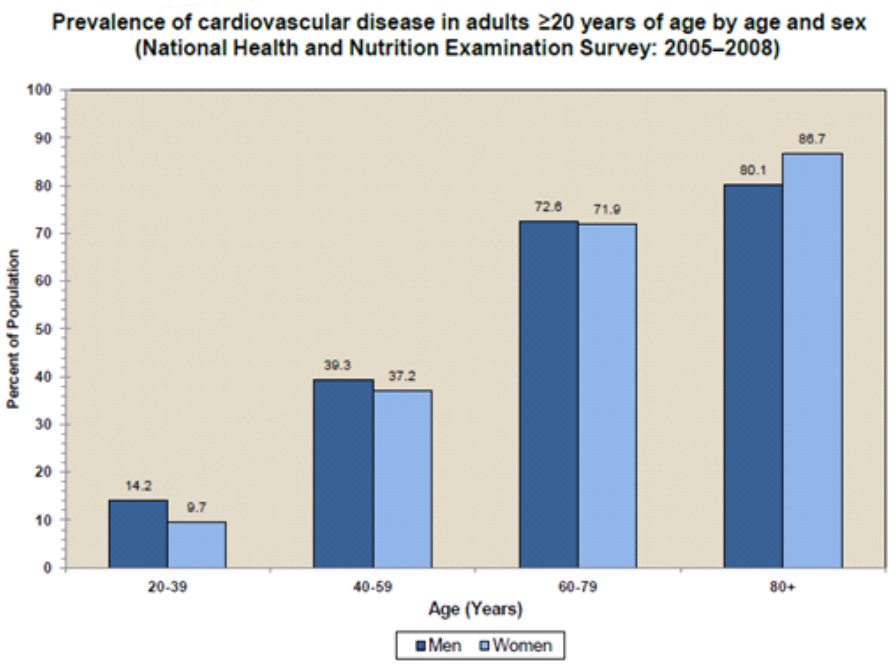
The term *unstable angina* describes a syndrome that is intermediate between chronic stable angina and MI. It is a clinical diagnosis based on a history of chest pain and exclusion of the diagnosis of MI by electrocardiography (ECG) or cardiac enzyme testing.

An occlusive thrombus can lead to an acute ST-segment elevation MI which denotes a full thickness (subendocardial to subepicardial) myocardial ischemia unless the subtended myocardium is richly collateralized. On the other hand, the thrombus formed may not be occlusive, but rather mural, and the patient may develop unstable angina or non ST segment elevation changes on the ECG such as ST depression or T wave changes.

INCIDENCE & SIGNIFICANCE

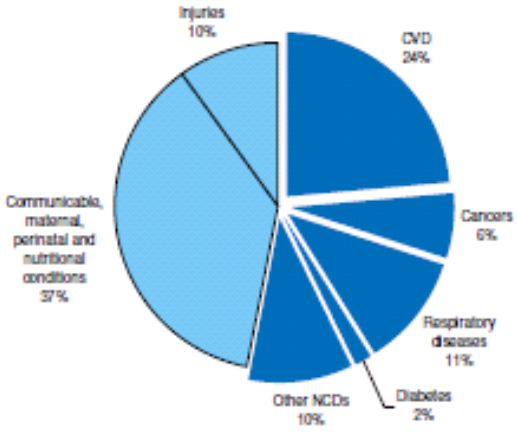
As per the World Health Report,[1] by the year 2020, cardiovascular diseases (CVD) will be the leading cause of mortality and morbidity in India.

With demographic shifts, epidemiological transition and increasing urbanization are associated with an increase in CVD risk factors such as smoking, sedentary lifestyle, obesity, hypertension and hypercholesterolemia. Mortality data from CVD in India were also reported by the World Health Organization. The Global Status on Non-Communicable Diseases Report (2011) has reported that there were more than 2.5 million deaths from CVD in India in 2008, two-thirds due to Coronary Heart Disease (CHD) and one-third due to stroke. Sub-analysis of the mortality trends shows that CHD mortality is higher in the south Indian states while stroke mortality is higher in the eastern Indian states.[2]



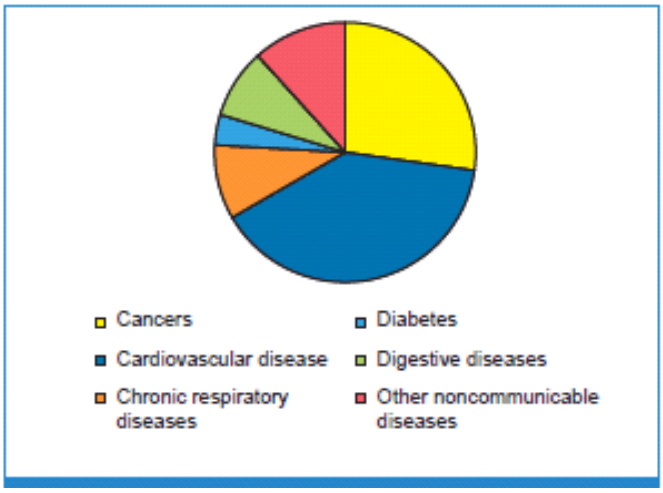
Morbidity - Disability adjusted life years (DALYs) lost from Coronary Heart Diseases in India are expected to double from the year 2000 to 2020 in both men and women to 7.7 million and 5.5 million, respectively.[2] In the last 50 years there have been multiple cardiovascular epidemiological studies in India that have defined prevalence of CHD and stroke and identified the burden of disease.

Proportional Mortality Rates for all ages in India



NCDs are estimated to account for 53% of all deaths.

Proportion of Non Communicable Disease (NCD) deaths < 70yrs age



Cardiovascular diseases - 39%

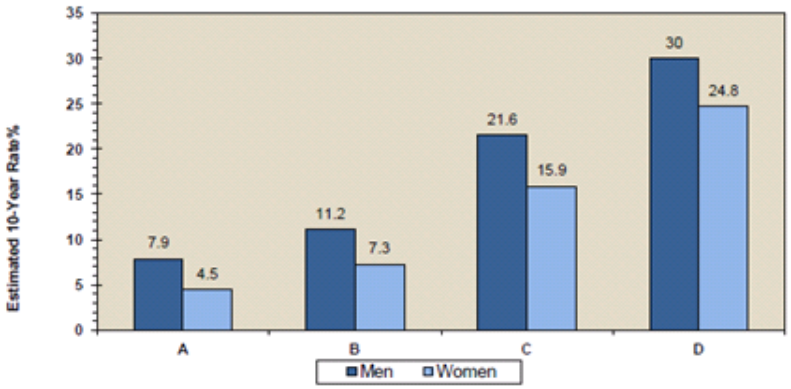
Cancer - 27%

Diabetes - 4%

Others - 30%

Annual Non Communicable Disease deaths are predicted to increase immensely to 52 million in 2030. Annual cardiovascular disease mortality is expected to increase by 6 million.[2]

Estimated average 10-year CVD risk in adults 50 to 54 years of age according to levels of various risk factors (Framingham Heart Study)



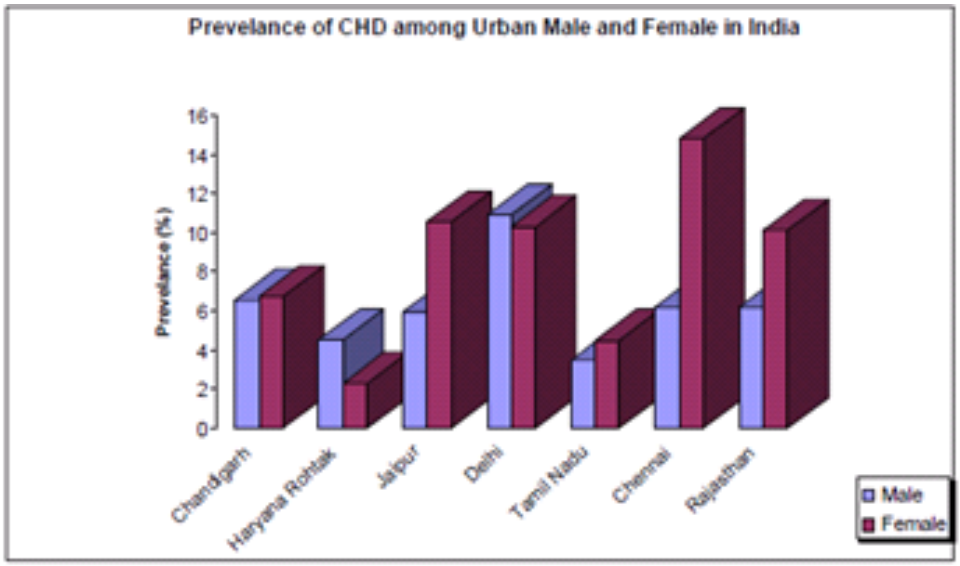
	A	B	C	D
Age	50-54	50-54	50-54	50-54
HDL Cholesterol, mg/dL	45-49	45-49	35-44	35-44
Total Cholesterol, mg/dL	160-199	200-239	200-239	200-239
Systolic BP mm/Hg, no treatment	120-129	130-139	130-139	130-139
Smoker	No	No	No	Yes
Diabetes	No	No	Yes	Yes

Studies in the middle of the last century reported a low prevalence of 1%-2% in urban locations and 0.5%-1% in rural locations with very little urban-rural

difference. In the intervening years the CHD prevalence in urban areas increased to 10%-12% while it increased to 4%-5% in rural areas.[2]

Urban India has high prevalence of coronary heart disease (8%-10%). It has been estimated that around 30 million people (14.1 million in urban areas and 15.7 million in rural areas) are suffering from CAD in India. Moreover, CAD occurs a decade sooner in India when compared to the west.[51]

Cardiovascular mortality data from India has reported large regional variations with annual mortality rates greater than 250/100,000 in southern and eastern regions of the country and less than 100/100,000 in central India.[2] There are large urban-rural differences in cardiovascular mortality also, with rates of less than 200/100,000 in rural areas and 450-500/100,000 in metropolitan urban locations.



The higher prevalence of cardiovascular risk factors in urban areas in India is in contrast to high income countries where the CVD risk factors are equal in urban and rural areas.

PATHOPHYSIOLOGY

The syndromes of unstable angina, non ST elevation MI and ST elevation MI are a continuum and the path physiology is heterogeneous and dynamic. The clinical presentation depends on the severity of the arterial injury, the size and type of thrombus formed, the extent and duration of ischemia and the amount of previous myocardial necrosis. The extent of ischemia depends on the myocardial distribution of the ischemia producing artery, the severity of the ischemia producing stenosis, the absence or presence of collateral circulation, factors that affect the supply of oxygenated blood and increased myocardial demands, including the heart rate, blood pressure and contractility.

The five major causes of acute coronary syndromes are thrombus, mechanical obstruction, dynamic obstruction, inflammation and increased organ demand.[4]

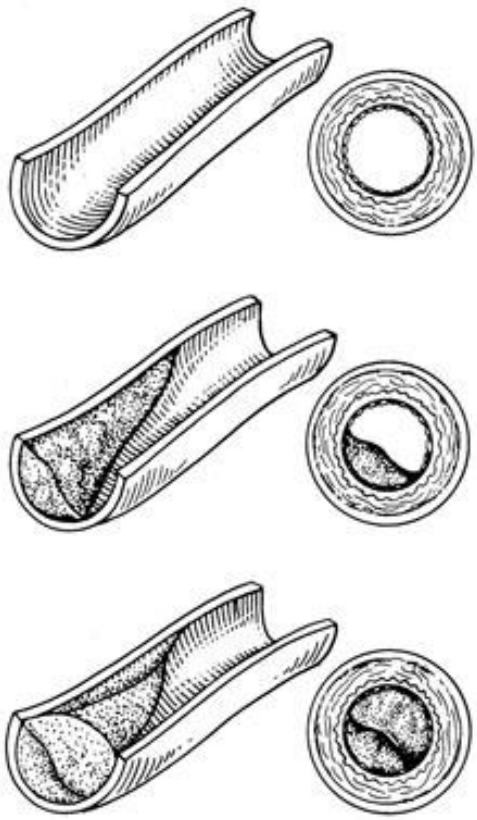
The major pathophysiologic mechanism is rupture or fissuring of an atheromatous plaque with superimposed thrombus. Superficial fissuring of a plaque usually results in platelet deposition, but there is less superimposed

thrombus formation in patients with unstable angina than in those with Q wave MI, which is usually associated with deep arterial injury and occlusive thrombus.

The atheromatous plaque develops in the following way:

- Damage occurs in the endothelium due to hypertension, diabetes, smoking or dyslipidemia.
- Monocytes approach these affected areas and transform into macrophages that cause local inflammation by releasing cytokines.
- Macrophages accumulate oxidized fat to form a fatty streak.
- The fatty deposits and white blood cells grow and send signals to smooth muscle cells in the media to divide and multiply. As a result, the lesion begins to stick out into the lumen.

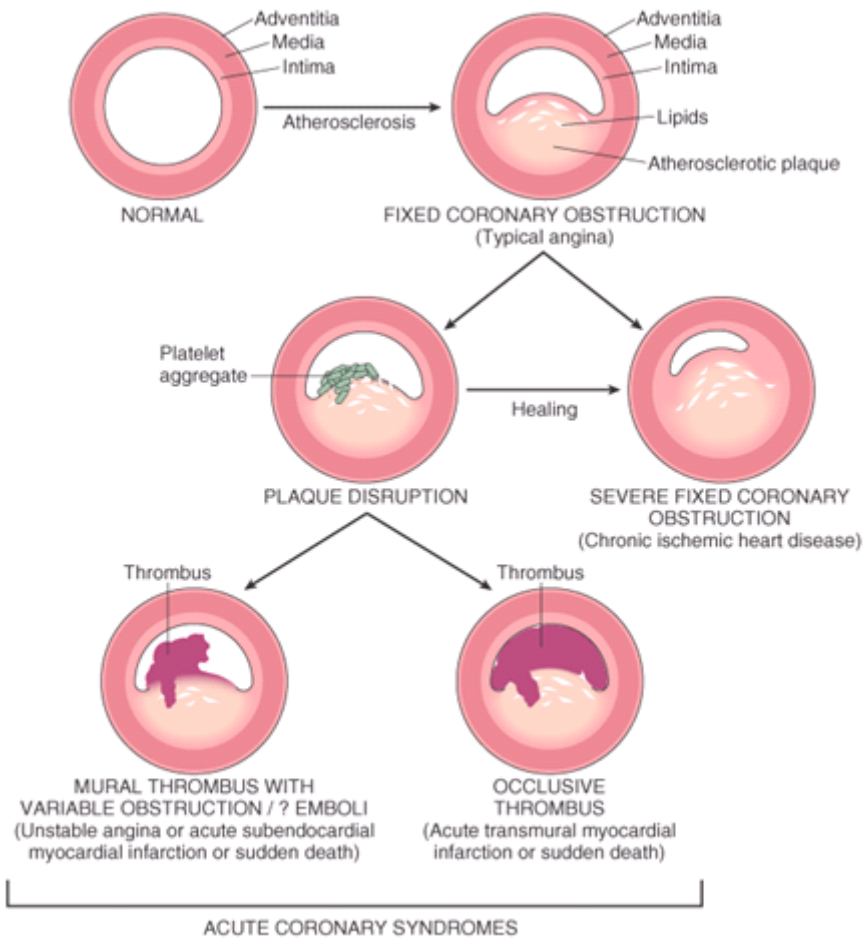
Atheromatous plaque formation



- Blood platelets can accumulate and form clots on the irregular surface of the plaque. The clot can remain there and clog the artery, or break off and lodge in a smaller artery, completely closing off blood flow beyond it resulting in tissue necrosis.
- As the atheroma progresses, calcification of the plaque occurs.

Angioscopic findings show that the thrombus associated with unstable angina is white or gray and consists mostly of platelets whereas the thrombus in patients with acute MI consists mostly of red blood cells.

Vascular pathology and Coronary syndromes



Loss of integrity of the arterial wall and platelet thrombus, with cessation of coronary blood flow through the infarct related artery, thus drives myocardial ischemia and injury. As described by Reimer and Jennings, the *wavefront* of necrosis extends from the subendocardium to the subepicardium.[4]

The extent of necrosis varies as a function of collateral flow, the length of time that coronary blood flow has halted and the extent of diminution of coronary blood flow.

RISK FACTORS

The four major risk factors of CHD are **hypertension, dyslipidemia, diabetes and smoking.** These risk factors can act independently or in a synergistic way to promote atherosclerosis.

The INTERHEART study was conducted among South Asians to study the cardiovascular risk factors.[3]

Risk of MI in relation to conventional risk factors among South Asians (INTERHEART STUDY)

Risk factor	Odds Ratio for presence of MI
Smoking	2.5
Dyslipidemia	4
High BP	3
Diabetes	2.5
Abdominal obesity	2.5
Psychosocial factors	2
Fruits/vegetables	0.7
Exercise	0.7
Alcohol	0.9

The INTERHEART study showed that apoA/apoB ratio and smoking constituted for 67% of the total Population Attributable Risk (PAR).

9 simple risk factors accounted for 90% of PAR in men and women. These risk factors are smoking, Diabetes, Hypertension, Waist Hip Ratio, Diet, Physical activity, Alcohol intake, apolipoprotein and psychosocial factors.

The CUPS (Chennai Urban Population Study) showed that in urban areas, the prevalence of cardiovascular risk factors were significantly higher in the low income groups when compared with the middle income groups.[2]

Prevalence of CVD risk factors in Chennai Urban Population Study (CUPS 4)

Risk Factor	Low income	Middle income
Diabetes %	12	6
Impaired fasting Glucose %	7	3
Hypertension %	15	8
Hypercholesterolemia %	24	14
Hyperinsulinemia %	17	7

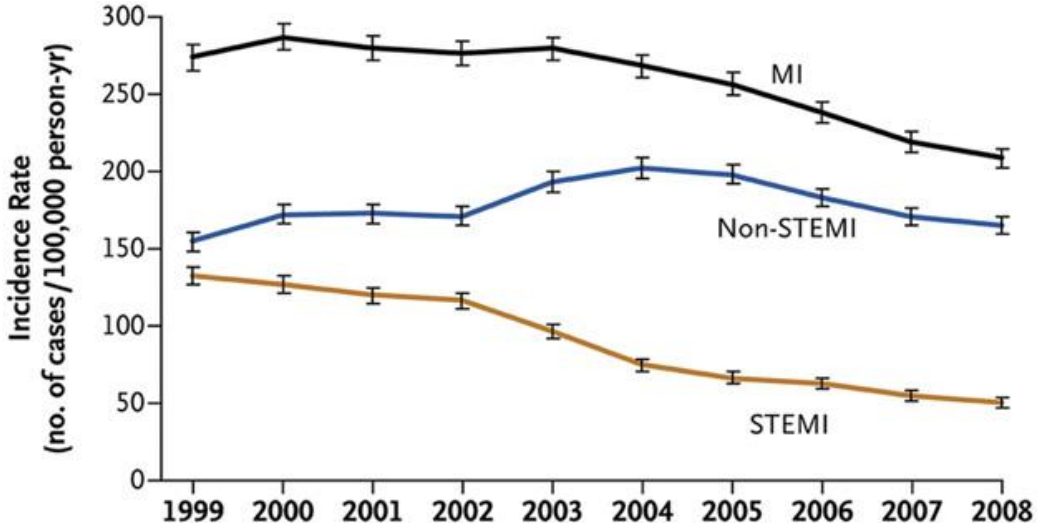
Major cardiovascular risk factors indicated in JNC-7 report are:

- Hypertension
- Smoking
- Obesity
- Physical inactivity
- Diabetes mellitus
- Dyslipidemia
- Microalbuminuria or estimated GFR< 60 ml/min
    - > 55 yrs for men,
    - > 65 yrs for women
- Family history of premature cardiovascular disease

- < 55 yrs for men
- < 65 yrs for women.

ACUTE MYOCARDIAL INFARCTION

Based on the ECG, acute MI may be broadly classified as ST Elevation MI (STEMI) or Non ST Elevation MI (NSTEMI). Since the pathophysiology in both the types is similar there is considerable overlap in acute coronary syndromes with respect to the ultimate outcome. However, the recognition of STEMI is important because it mandates the need for urgent reperfusion therapy.



Age and Sex adjusted incidence rates of acute MI from 1999 to 2008.[89]

Community incidence rates for STEMI have declined over the past decade, whereas those for non ST elevation MI have increased. [4]

Global Registry of Acute Coronary Events (GRACE) data from 2007 showed that 38% of patients had STEMI, 29% had NSTEMI and 29% had

Unstable Angina (UA). Among women, UA and NSTEMI were more common than STEMI. However, among men, STEMI was more common. NSTEMI was more common in older men than in younger men.

A clinical classification was developed further dividing MI into 5 types[4]

CLINICAL CLASSIFICATION OF DIFFERENT TYPES OF MI :

Type 1	Spontaneous MI related to ischemia from coronary plaque rupture or dissection
Type 2	MI due to ischemia resulting from increased oxygen demand or decreased blood supply
Type 3	Sudden cardiac death with symptoms of ischemia, new ST elevation or LBBB or coronary thrombus
Type 4a	MI associated with PCI
Type 4b	MI associated with stent thrombosis
Type 5	MI associated with CABG

Included in this classification was sudden cardiac death when there is evidence of myocardial ischemia (new ST elevation, left bundle branch block or coronary thrombus), biomarker elevation > 3 times the upper reference limit for

post percutaneous coronary intervention (PCI) patients or > 5 times the upper reference limit for post coronary artery bypass grafting (post CABG) patients. Documented stent thrombosis was also added in this new classification.

ACS	Prevalence in Asians [4]
Unstable angina	51.4%
NSTEMI	20.9%
STEMI	16.5%

STEMI

STEMI is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis.

An occlusive thrombus in the absence of significant collateral vessels results in acute ST elevation MI.

ECG DIAGNOSIS OF STEMI

European Society of Cardiology/ACCF/AHA/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction as

- New ST elevation at the J point in at least 2 contiguous leads of
  - ≥ 2 mm (0.2 mV) in men or
  - ≥ 1.5 mm (0.15 mV) in women in leads V2–V3 and/or

- ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads

- New or presumably new LBBB has been considered a STEMI equivalent.

In the presence of pre-existing LBBB, MI is diagnosed using the Sgarbossa criteria. Total score of 3 or more has a 90% specificity and 88% positive predictive value.

Sgarbossa criteria :[4]

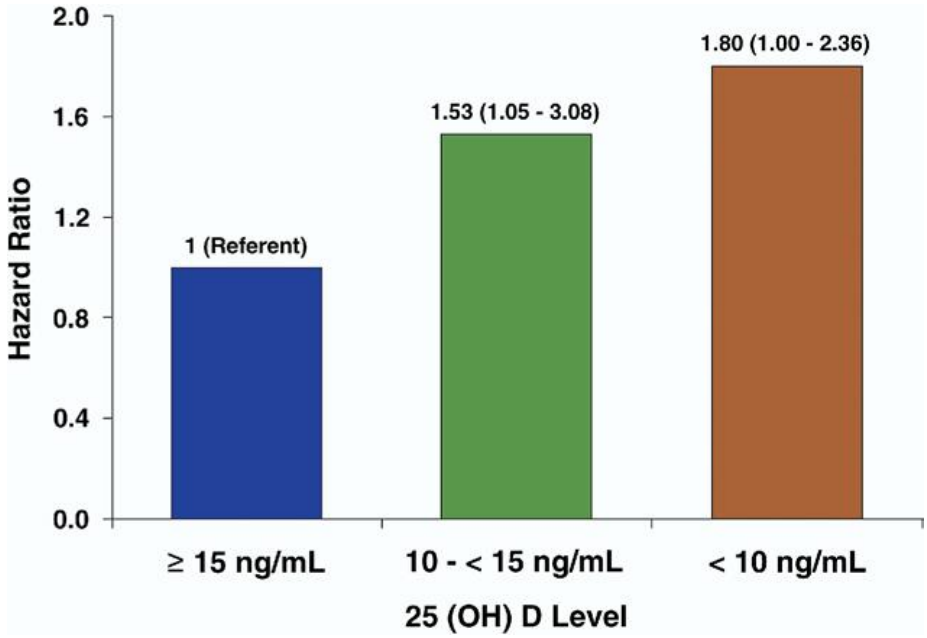
- ST segment elevation ≥ 1mm concordant with QRS – 5 points
- ST segment depression ≥ 1mm in lead V_1, V_2 or V_3 – 3 points
- ST segment elevation ≥ 5mm discordant with QRS – 2 points

NSTEMI

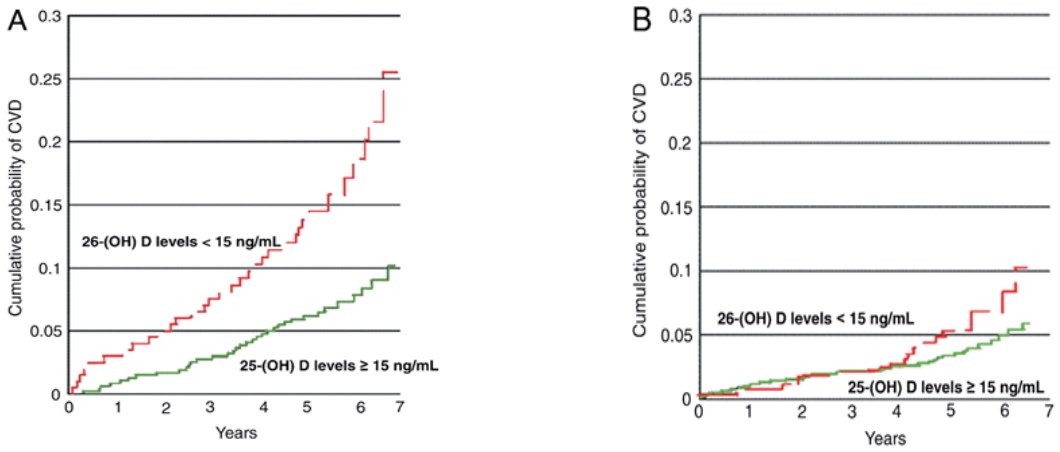
With both stable angina and UA, ischemia is fully reversible, with no evidence of myocardial necrosis. UA may or may not be associated with signs of ischemic changes on electrocardiography (ECG), such as ST segment depression or new T wave inversion. UA is closely related to NSTEMI, and the two entities are often indistinguishable from each other, especially during the initial evaluation of a patient. However, NSTEMI is associated with myocardial necrosis and resultant release of cardiac biomarkers.

VITAMIN D DEFICIENCY AND ITS ASSOCIATION WITH CARDIOVASCULAR DISEASES

It has been estimated that 1 billion people worldwide suffer from Vitamin D deficiency or insufficiency.[60] It is only in the last 15 years that emphasis has emerged regarding the extra skeletal manifestations of Vitamin D deficiency. An epidemiological link between low 25(OH) Vitamin D levels and an increased cardiovascular risk has been now recognized in many observational studies. In a large randomized trial by Wang et al [91], the relative risk of MI for those with sufficient Vitamin D levels was 0.43 and individuals with Vitamin D deficiency showed a hazard ratio of 1.62 for incident cardiovascular events.



Hazard ratio for Cardiovascular Diseases based on Vitamin D levels



They also demonstrated that there was increased cardiovascular risk in patients with hypertension (A) than in patients without (B) hypertension if their serum Vitamin D was < 15 ng/ml, in the Kaplan meier curves shown above.[91]

Vitamin D mainly acts through its role in maintaining calcium homeostasis and gene transcription to prevent cardiovascular diseases and its risk factors. The high prevalence of cardiovascular disease in renal failure has also been linked with low Vitamin D. Up to 40% increase in cardiovascular mortality in winter season has also been linked to poor Vitamin D status.[52]

MECHANISMS FOR PROTECTIVE ACTION OF VITAMIN D IN CARDIOVASCULAR DISEASES

PROTECTIVE ACTION ON THE ENDOTHELIUM

Vitamin D exerts its protective effects on the endothelium directly by regulating calcium ion entry or indirectly by protecting against oxidant stress.

Vitamin D deficiency leads to endothelial dysfunction by causing a proinflammatory and prothrombotic environment. This promotes atheroma formation and progression. Vitamin D deficiency is associated with high levels of Matrix Metalloproteinase 9 which causes vascular remodeling and increases arterial tone.[88]

INHIBITION OF RENIN

Yan Chun Li et al [90]demonstrated that Vitamin D Receptor (VDR) knockout mice developed hypertension, cardiac muscle hypertrophy and increased activation of the renin angiotensin aldosterone axis. They also demonstrated suppression of renin mRNA expression in the wild type mice that were given supplements of Vitamin D3.

Inhibition of renin gene expression occurs by sequestration of cAMP response element binding thereby inhibiting transcription of renin mRNA.

REGULATION OF PARATHORMONE

Vitamin D inhibits vascular smooth muscle proliferation and calcification by regulating Parathormone (PTH) levels. Parathormone promotes calcium deposition in vascular smooth muscle. Optimum Vitamin D levels inhibit PTH which, in high levels, is responsible for pathogenesis of many factors that increase the risk for heart disease and its adverse effects on the blood vessels.[28]

Vitamin D improves calcium uptake, inhibits platelet aggregation, increases nitric oxide synthase, inhibits thrombotic activity and also regulates the vasomotor reactivity to neural input.

IMMUNOMODULATORY EFFECTS – ANTI INFLAMMATORY ACTION

It reduces the proliferation of lymphocytes and the production of cytokines that promote atherogenesis. Its deficiency is associated with higher

C-reactive protein and IL-6 levels and lower IL-10 levels.

It inhibits prostaglandin and cyclo-oxygenase 2 activity, reduces matrix metalloproteinase 9 and many other pro-inflammatory cytokines which result in suppressed inflammation.[88]

PLAQUE STABILITY

Vitamin D inhibits the production of several pro-inflammatory cytokines while stimulating the effects of TH2 lymphocytes causing a reduction in matrix metalloproteinase. This reduces plaque production and instability.

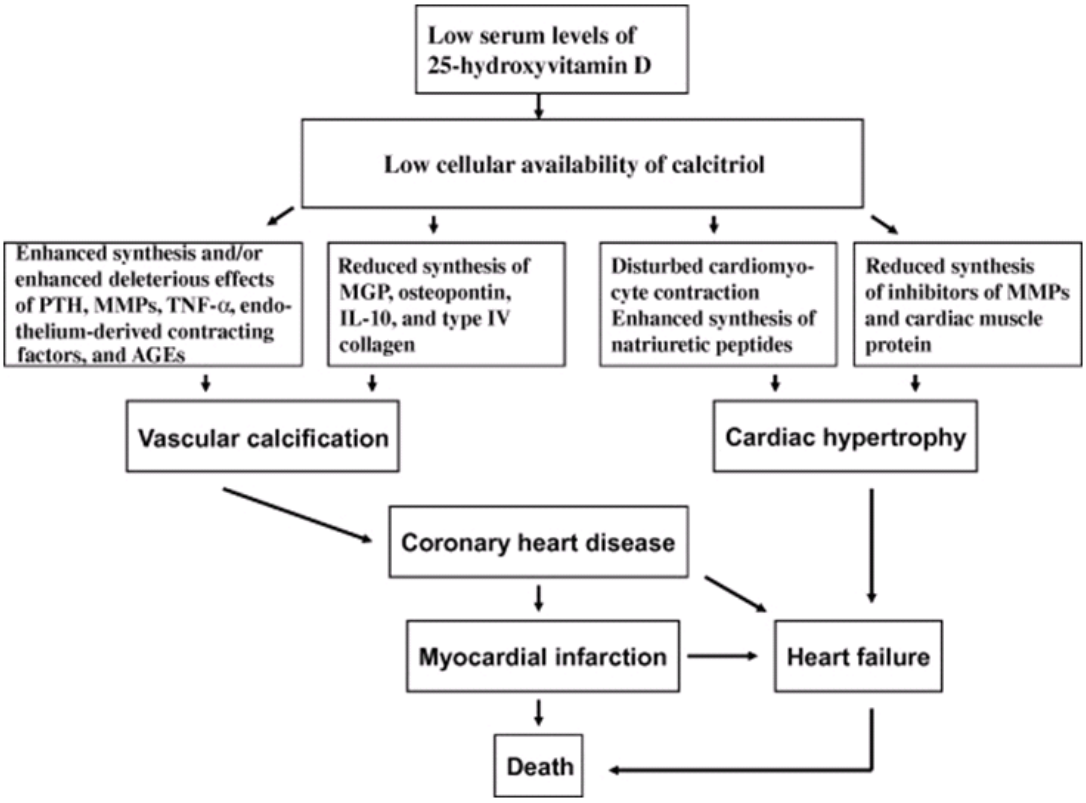
Laboratory studies of Vitamin D deficiency in mice have demonstrated increased thrombogenicity.

VITAMIN D AND EFFECT ON CARDIAC HYPERTROPHY

The Vitamin D receptor is present in virtually all tissues, including cardiomyocytes and endothelial cells. Vitamin D reduces the risk of cardiac hypertrophy through direct and indirect actions. Vitamin D directly acts to reduce cell size and inhibit the maturation of these myocytes and acts indirectly through

protein kinase C which is activated by norepinephrine, angiotensin II or PTH. Thus, by inhibiting PTH activity and by suppression of renin gene**,** Vitamin D can prevent cardiac muscle hypertrophy.

Hypovitaminosis D and cardiovascular complications



EFFECT ON CARDIAC CONTRACTILITY

Low Vitamin D levels result in reduced myosin isozyme in the ventricular muscle cells and hence reduced cardiac contractility. Inhibition of PTH induced calcium resorption from bone reduces the risk of cardiac valvular and vascular calcification.

VITAMIN D AND THE RISK OF ARRHYTHMIAS

Vitamin D deficiency can lead to arrhythmias due to disruption of calcium homeostasis because intracellular calcium plays an important role in regulating the activity of sodium channels to control the heart rate.

VITAMIN D AND ATHEROSCLEROSIS

PTH increases the risk of atherosclerosis by promoting the formation of intra-arterial plaque. Hence suppression of PTH activity reduces calcification and stenosis in the blood vessels.[28]

Vitamin D maintains normal vascular tone by promoting nitric oxide synthase production which suppresses platelet aggregation and thrombogenic activity. Many bone proteins governed by Vitamin D like matrix Gla protein and osteoprotegerin are present in the vessel wall and responsible for calcification of vessels in case of Vitamin D deficiency.

Vitamin D, through its anti inflammatory actions, affects dendritic cells and macrophages in such a manner that it reduces foamy macrophages and suppresses cholesterol uptake.

Moreover, the activity of Vitamin D is found to be enhanced by certain cardiac drugs such as beta blockers, thiazide diuretics, aspirin, etc. which suggests it may allow a reduction in drug dosages and hence its adverse effects. Statins increase Vitamin D levels by 70% after one year of treatment.

REGULATION OF OTHER CARDIOVASCULAR RISK FACTORS

Vitamin D, by inhibiting the renin angiotensin axis plays a vital role in controlling hypertension and preventing its adverse effects on the heart.

Vitamin D improves Insulin Sensitivity thereby reducing the incidence of diabetes mellitus and the associated risk of accelerated atherosclerosis.

VITAMIN D DEFICIENCY AND TYPE 2 DIABETES MELLITUS

The current prevalence of Type 2 DM is high in urban and rural India[50] and it is estimated that by the year 2030 India would harbor the maximum number of diabetics in the world.[26]

Several studies by Pittas et al have showed significantly increased risk of type 2 diabetes when Vitamin D levels fall less than 30 ng/ml[25]. It has also been noticed that glycemic status worsens during winter and this is associated with reduced 25(OH)D.[27]

The pancreas has VDR and 1α hydroxylase activity and hence it can convert 25(OH)D to 1,25(OH)2D to act in a paracrine or autocrine manner. Vitamin D deficiency can result in insulin resistance or reduced insulin secretion.

Mechanisms of Vitamin D in Type 2 DM :

i. improves β cell function directly or by increasing the intracellular ionized calcium which enhances insulin release

ii. increases insulin sensitivity by increasing the expression of insulin receptors and calcium dependent pathways in target cells that enhance glucose utilization

iii. inhibits β cell apoptosis [25]

VITAMIN D DEFICIENCY AND HYPERTENSION

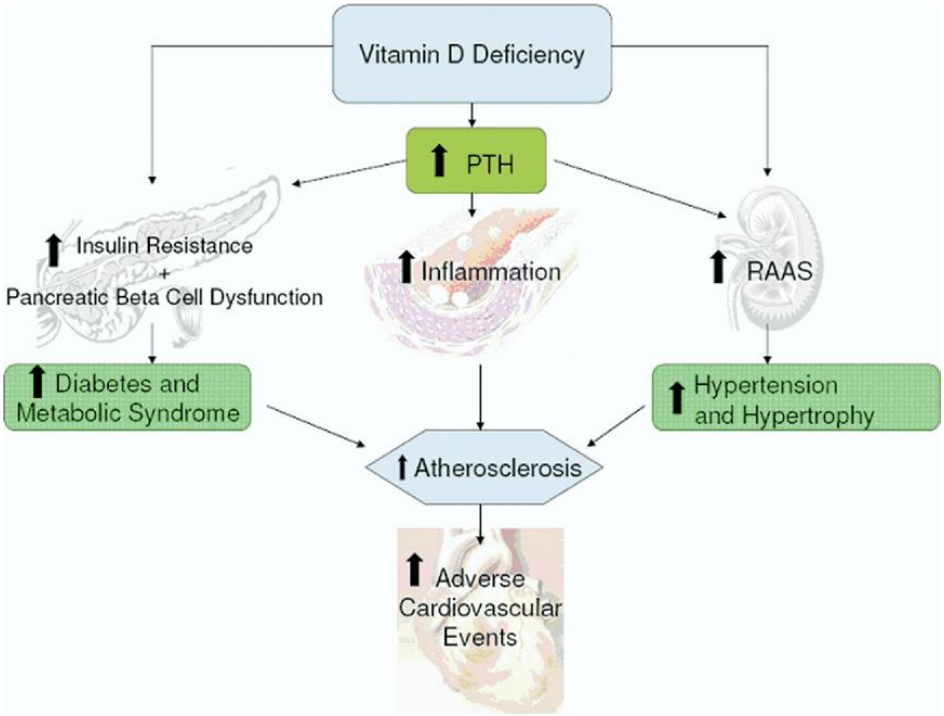
Pfeifer et al demonstrated a 9% fall in systolic BP after supplementing vitamin D (800 IU).[28] In another study, patients exposed to UVB radiation thrice a week for 3 months showed that 25(OH)D raised by 180% and both systolic and diastolic BP decreased by 6 mm Hg. As opposed to this, a large prospective study by Forman et al found no correlation between vitamin D supplementation and hypertension.[29]

Several mechanisms are implicated:

- Suppression of the Renin Angiotensin Aldosterone axis
- Direct effect on endothelial cells
- Regulation of Calcium metabolism[30]
- Nor Epinephrine and Angiotensin II play a vital role in the pathophysiology of hypertension. Impaired regulation can result in arrhythmias and myocardial infarction.

Patients with chronic kidney disease treated with Vitamin D show 20% fall in death rates and have also demonstrated the antiproteinuric effect of Vitamin D.[49]

Shown below is an illustration that briefly summarizes the various mechanisms by which Vitamin D deficiency can lead to adverse cardiovascular events.



VITAMIN D

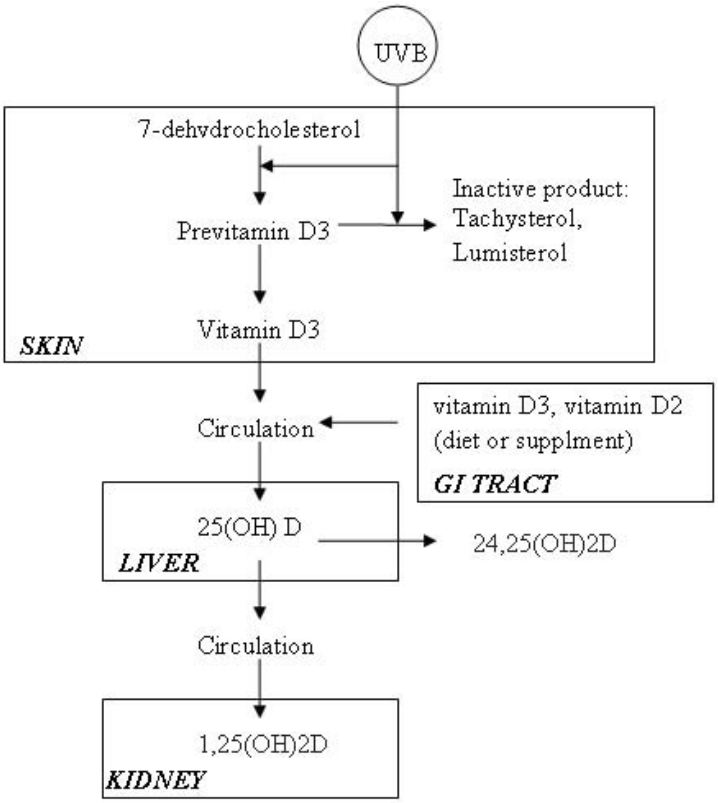
SYNTHESIS AND METABOLISM OF VITAMIN D

Vitamin D is a secosteroid. It refers to a group of fat soluble vitamins. The main precursors are Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol).[20]

7-dehydrocholesterol in the skin is converted to previtamin D3 on exposure to Ultraviolet B (UVB) rays of wavelength 290-320 nm. It is immediately

converted to Vitamin D. About 40 to 50% of circulating 25(OH)D is derived from skin. Vitamin D2 is formed in plants and obtained from diet.

Vitamin D2 and D3 are converted to 25-hydroxyvitamin D (calcidiol) in the liver by 25 hydroxylase activity. Biologically active 1,25-dihydroxyvitamin D (calcitriol) is formed by 1α hydroxylation in the kidneys.



MECHANISM OF ACTION

Circulating 25(OH)D is converted to the active hormone $1,25(OH)_2D$. Calcitriol is transported in the blood by Vitamin D Binding Protein (VDBP) and is carried to many target organs. This acts through the Vitamin D receptor (VDR) which belongs to the nuclear receptor superfamily. After activation, this receptor

dimerizes with the Retinoid X Receptor (RXR) and binds to Vitamin D responsive elements that regulate the transcription of various genes in the target cells.

More than 500 genes have been identified and around 37 different cell types are found to express VDR.[11] The Vitamin D receptor is present in almost all cells in the body and the 1α hydroxylase enzyme is found in many tissues. Around 10% of the human genome is regulated by Vitamin D. This ubiquitous nature of Vitamin D receptor is responsible for its pleiotropic actions.

SOURCES OF VITAMIN D

SUNLIGHT

The main natural source is ultraviolet B rays in sunlight. Twenty to thirty minutes of sunlight exposure between 10am and 3pm two or three times a week is considered sufficient. UVB exposure does not cause Vitamin D intoxication because excess UVB rays convert Vitamin D3 into inactive metabolites, tachysterol and lumisterol. UVB (0.5 MED) provides 3000 IU of Vitamin D3.

Shade and severe pollution reduces UVB rays by 60%.[2] These rays don't penetrate glass, so indoor exposure of sunlight is of no use.[3] Sunlight provides more quantity and more active Vitamin D than any other source.

FOOD[12]

Cod liver oil and oily fish are very good sources of Vitamin D3. Vegetables are generally a poor source and hence food fortification programmes play an important role.

Salmon fish (100gm) → 600 -1000 IU of Vitamin D3

Mackerel fish (100gm) → 250 IU of Vitamin D3

Tuna fish (100gm) → 230 IU of Vitamin D3

Cod liver oil (1 tsp) → 400 -1000 IU of Vitamin D3

Egg yolk → 20 IU of Vitamin D3

SUPPLEMENTS

Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol) are available as supplements but Vitamin D3 is most effective.

HYPOVITAMINOSIS D

There are many guidelines and experts that define different cut off values to assess hypovitaminosis D. But recent consensus suggests to take Serum 25(OH)D > 30 ng/ml as the "cut off" value because this is the threshold at which parathormone secretion is induced and optimum calcium absorption occurs.[7]

25(OH) VITAMIN D – REFERENCE RANGES [21]

- < 15 ng/ml - Vitamin D Deficiency
- 15.1-29.9 ng/ml - Vitamin D Insufficiency
- > 30 ng/ml - Vitamin D Sufficiency
- > 75 ng/ml - Vitamin D Intoxication

Vitamin D Deficiency is further classified as:

- <5 ng/ml - severe Hypovitaminosis D
- 5-10 ng/ml - moderate Hypovitaminosis D
- 10-15 ng/ml - mild Hypovitaminosis D

PREVALENCE OF HYPOVITAMINOSIS D

One billion people worldwide are estimated to be Vitamin D deficient. According to the World Health Organization, it is estimated that Vitamin D insufficiency is present in 50 to 80% of the population.[21]

It was only in the year 2000 that systematic studies of Vitamin D status were initiated in India and one such study showed that up to 90% of people in Delhi had low Vitamin D levels.[86] Subsequent studies have shown widespread Vitamin D Deficiency (VDD) in Indians irrespective of age or sex in both rural and urban areas.[9]

GLOBAL BURDEN : An estimated loss of 3.3 billion DALYs from bone disease due to Vitamin D deficiency, and Vitamin D insufficiency leading to other diseases that constitute 9.4% of the global disease burden has been reported.[12]

CAUSES FOR VITAMIN D DEFICIENCY

REDUCED SKIN SYNTHESIS

- Sunscreen use, skin pigmentation, aging and obesity reduce UVB related skin synthesis of Vitamin D. Season, latitude and time of day also determine skin production of Vitamin D.
- Elderly persons have reduced 7 dehydrocholesterol and spend less time outdoors.
- Dark skinned individuals have more melanin which competes with 7 dehydrocholesterol for absorption of UVB rays.

  Sunscreens with a sun protection factor (SPF) of 8 or more block UV rays.

INADEQUATE DIETARY INTAKE

- Infants, children and elderly are especially susceptible.
- Poor vitamin D content in human breast milk is another important factor.[4]

REDUCED BIOAVAILABILITY

- Malabsorption disorders[5]
- Obesity –Vitamin D is sequestered in body fat
- Drug interactions – Antiepileptics, Glucocorticoids, Rifampicin

- Liver failure - Impaired synthesis of 25(OH)D
- Renal failure – Impaired 1α hydroxylase activity

INCREASED LOSS OF 25(OH)D

- Nephrotic syndrome - urinary loss of 25(OH)D bound to Vitamin D binding protein

REDUCED SYNTHESIS OF ACTIVE VITAMIN D

- Chronic kidney disease
- Hyperphosphatemia increases fibroblast growth factor (FGF-23) which reduces 1α hydroxylase activity[6]

INHERITED DISORDERS

- Vitamin D dependent rickets
- Vitamin D resistant rickets
- Hypophosphatemic rickets - Autosomal dominant and X-linked

ACQUIRED DISORDERS

- Tumor induced osteomalacia - tumor secretion of FGF 23
- Primary hyperparathyroidism
- Granulomatous diseases like sarcoidosis, tuberculosis and some lymphomas
- Hyperthyroidism - increase metabolism of 25(OH)D

VITAMIN D DEFICIENCY – INDIAN SCENARIO[9]

It was previously a general misbelief that Vitamin D deficiency was not prevalent in India because our country is situated near the equator and receives ample sunshine. But recent data has proved that Vitamin D deficiency is very common in India (approximately 50- 90%).[62]

Several factors contribute to Vitamin D deficiency in India :

1. Diets low in calcium and Vitamin D especially in vegetarians.
2. High fibre content, phosphates and phytates in diet.
3. With urbanization, less time spent outdoors has led to inadequate sun exposure.
4. Humid and sultry climate reduces outdoor exposure to sunlight
5. Increased pollution hampers the ultraviolet rays.
6. Customs like Burqa/Pardah in Muslims.
7. Repeated and unspaced pregnancies can aggravate Vitamin D deficiency in the mother and the fetus.
8. Darker skin pigmentation
9. Lack of Vitamin D food fortification programmes
10. Liver, kidney, skin disorders, alcoholics, genetic factors, malabsorption disorders and inflammatory rheumatological conditions can lead to Vitamin D deficiency

VITAMIN D DEFICIENCY & CLINICAL DISEASE STATES

SYMPTOMS OF VITAMIN D DEFICIENCY

Many people remain asymptomatic or present with multiple non specific complaints such as[9]

- Fatigue, general muscle pain and weakness, muscle cramps
- Joint pain, weight gain, restless sleep
- Poor concentration
- Headache

DISEASES ASSOCIATED WITH VITAMIN D DEFICIENCY

- Rickets and Osteomalacia
- Osteoporosis and Osteopenia
- Malignancy
- Cardiovascular diseases, Hypertension
- Obesity, Metabolic Syndrome and Diabetes
- Autoimmune diseases, Multiple sclerosis
- Rheumatoid arthritis, Osteoarthritis
- Parkinson’s Disease, Alzheimer’s Disease
- Depression and Seasonal Affective Disorder
- Chronic fatigue syndrome, Fibromyalgia

VITAMIN D DEFICIENCY AND BONE HEALTH IN INDIANS

Vitamin D plays a vital role in maintaining serum calcium and phosphorus. In the absence of Vitamin D, only 10 to 15% of dietary calcium and 60% of phosphorus is absorbed.[12-14] Thus, Vitamin D is critical for skeletal mineralization.

Vitamin D deficiency causes secondary hyperparathyroidism and increases bone resorption leading to osteopenia and osteoporosis. Raised parathormone induces phosphaturia and hypophosphataemia causing defective mineralization of the osteoid.

Rickets and Osteomalacia are widely prevalent in India.[21] The associated pseudofractures are due to low peak bone mass. There is also wide prevalence of biochemical osteomalacia and osteoporosis in our population detected on routine screening. The beneficial effects of 25(OH) D on skeletal health starts from fetal life and infancy and continues up to adulthood.[12]

Numerous observational studies by Hollick et al , Dawson Hughes et al and many others have linked low levels of 25(OH)D to fractures.[20] But evidence is not consistent as some studies contradict these findings. Vitamin D deficiency has also been associated with osteoarthritis of the knee and hip joint.[24]

MUSCLE WEAKNESS

Skeletal muscle contains Vitamin D receptors and Vitamin D supplementation improves muscle metabolism. Many patients with nonspecific muscle weakness and muscle pains have inadequate Vitamin D levels.

NEWBORNS AND VITAMIN D DEFICIENCY

Vitamin D induces more than 3000 genes that affect fetal development[41] and thus plays a critical role in brain development and function.[42] It is essential to maintain Vitamin D sufficiency in utero and during early life to ensure normal receptor transcriptional activity in the brain.

Up to 84% of pregnant women in India have Vitamin D Deficiency which correlated well with reduced serum 25(OH) D in their newborns. Their off springs had reduced intrauterine development and postnatal skeletal growth.[43] Human breast milk contains very little Vitamin D and exclusively breast fed infants are have increased risk of rickets. Vitamin D deficiency compromises length from birth itself and continues into childhood, finally compromising adult height.

VITAMIN D DEFICIENCY AND AUTOIMMUNITY

Autoimmune diseases like type 1 diabetes mellitus, inflammatory bowel disease, rheumatoid arthritis[32] and multiple sclerosis are linked to Vitamin D deficiency as VDR are present on monocytes, macrophages, dendritic cells, WBCs, CD4+ and CD8+ T cells and thus affect immune response in our body. Vitamin D inhibits cytokine production and T cell proliferation. [54]

Epidemiological data show correlation between Vitamin D deficiency and seasonal variation in the onset of these autoimmune disorders.[55] Vitamin D has been found effective in improving and preventing Multiple Sclerosis by increasing TGF β levels.[31]

VITAMIN D DEFICIENCY AND TUBERCULOSIS:

Cod liver oil and high doses of Vitamin D was initially used to treat tuberculosis in the 1770s and continued till the 19th century, before the advent of ATT, on the basis that Vitamin D would cause calcification of tuberculosis lesions.[33]Low serum Vitamin D is an independent risk factor for TB in South Asians.[34]Vitamin D increases cathelicidin in the macrophages which promotes killing of the intracellular mycobacteria

VITAMIN D DEFICIENCY AND MALIGNANCY

People living at higher latitudes are found to be at high risk for varieties of malignancies such as Hodgkin's lymphoma, colon, pancreatic, prostate, ovarian, breast and other cancers due to low Vitamin D levels.

Vitamin D regulates the cell cycle and induces apoptosis and cell differentiation. It inhibits tumor growth, angiogenesis and metastasis. Some studies have demonstrated 30-50% reduction in the risk of malignancy after vitamin D supplementation.[40]

DIAGNOSIS OF VITAMN D DEFICIENCY

25(OH)D is the main circulating form of Vitamin D and it is the most sensitive marker to assess Vitamin D status in the general population. This is because 25(OH)D can be easily measured and it has a long half life of around 2 to 3 weeks. Moreover, serum 25(OH)D levels correlate well with clinical disease states.[65]

Serum calcium is usually found to be normal in people with Vitamin D deficiency. 1,25-dihydroxyVitamin D is a poor indicator of deficiency states because it has a short half life of 15 hours and is very easily affected by parathormone, calcium and phosphorous.[60] Also the levels of $1,25(OH)_2D$ fall only when Vitamin D deficiency is severe. It is misleading because its values may be normal or even raised.

METHODS TO ASSESS 25(OH)D LEVELS

- **Ligand-Binding Assays**
- Radioimmunoassay
- Competitive protein-binding assays
- Chemiluminescence assay
- **High-performance liquid chromatography (HPLC)**
- **Liquid chromatography-tandem mass spectrometry (LC-MS/MS)**

- Accurate and precise and considered the “Gold standard” method.

TARGET LEVELS OF 25(OH) VITAMIN D

Serum 25(OH)D Concentrations and Health		
nmol/L	**ng/mL**	**Health status**
<37.5	<15	Deficiency
37.5–75	15-30	Insufficiency
≥75	≥30	Sufficiency
>187.5	>75	Toxicity

1 nmol/L = 0.4 ng/mL

TREATMENT OF VITAMIN D DEFICIENCY

Dosing [67]

As per the Institute of Medicine (IOM), Vitamin D supplementation is based on the level of deficiency and treatment should be individualized.

- 25(OH)D < 20 ng/mL (50 nmol/L) → 50,000 IU of Vitamin D2 or D3 orally once a week for 6 to 8 weeks, followed by 800 to 1000 IU of Vitamin D3 daily.
- 25(OH)D 20 to 30 ng/mL (50 to 75 nmol/L) → 800 to 1000 IU of Vitamin D3 daily for 3 months.

- In infants and children whose 25(OH)D is <20 ng/mL (50 nmol/L) → 1000 to 5000 IU of Vitamin D2 daily for 2 – 3 months.
- 1000 mg of calcium daily for premenopausal women and men and 1200 mg daily for postmenopausal women should also be supplemented along with Vitamin D.

Blood levels of 25(OH)D must be monitored three months after beginning treatment and dose adjustments may be made subsequently.

To maintain sufficient Vitamin D levels, 50,000 IU of Vitamin D2 two times a month or 1000-2000 IU of Vitamin D3 is given daily.[60]

PREVENTION OF VITAMIN D DEFICIENCY

People with Vitamin D deficiency have no obvious symptoms until it is so severe that they develop osteomalacia. These patients are usually misdiagnosed as fibromyalgia as there is a general lack of awareness regarding the dangers of Vitamin D deficiency and the health benefits associated with Vitamin D.

Although, there is adequate sunshine in India, high temperatures during daytime and humid climate in many areas are hindrance for adequate sun exposure. Hence, food fortification programs and public health campaigns that emphasize the consequences of Vitamin D deficiency on health are required.

Vitamin D deficiency and its complications can be prevented by adequate Vitamin D supplementation, sun exposure, fortification of foods and public awareness campaigns. Vitamin D supplementation must be advised to the general public and the dosing depends on the skin color, degree of sun exposure, diet and underlying medical conditions.

Recommended Dietary Allowances (RDAs) for Vitamin D [67]

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

(40 IU = 1 mcg)

It is currently recommended to take 1-1.5 g of calcium and 2000 IU of Vitamin D daily in order to prevent Vitamin D deficiency and its consequences in the Indian population.

VITAMIN D - DRUG INTERACTIONS [69]

Increase metabolism of Vitamin D and decrease serum levels:

Phenytoin, Fosphenytoin, Phenobarbital, Carbamazepine, Rifampin, Theophylline, Cimetidine, Non-nucleoside reverse transcriptase inhibitors

Decrease the intestinal absorption of Vitamin D:

Cholestyramine, Colestipol, Orlistat, Mineral oil and fat substitutes

Others:

Ketoconazole inhibits 1α hydroxylase enzyme and reduces serum Vitamin D levels. Hypercalcemia caused by Vitamin D toxicity can precipitate cardiac arrhythmias in patients on digoxin. Corticosteroids reduce calcium absorption and impair Vitamin D metabolism. Statins and thiazide diuretics increase serum Vitamin D levels.

HYPERVITAMINOSIS D

Vitamin D intoxication is extremely rare. It can result from over treating Vitamin D deficiency without monitoring serum levels or from poisoning.

Doses more than 10,000 IU /day can cause acute hypercalcemia and hyperphosphatemia where serum levels of 25(OH)D are >150 ng/ml (375 nmol/L).[71]

Caution should be exercised while treating patients of chronic granulomatous disorders like sarcoidosis and tuberculosis because macrophages produce 1,25(OH)D can precipitate hypercalcemia and hyperphosphatemia.[70] Primary hyperparathyroidism and lymphoma also increase the risk of hypercalcemia in response to Vitamin D.

TOLERABLE UPPER INTAKE LEVEL FOR VITAMIN D [70]

As per the Institute of Medicine (IOM),

Infants: 0 - 6 months – 1000 IU/day

6 - 12 months – 1500 IU/ day

Children: 1-3 years – 2500 IU/day

4 - 8 years – 3000IU/day

Adults: > 9 years – 4000 IU/day

As per the European Food and Safety Authority (EFSA),

0 - 10 years – 1000 IU/day

> 11 years - 2000 IU/day

CLINICAL FEATURES OF HYPERVITAMINOSIS D

- Headache, Lethargy, Dehydration
- Nausea, Vomiting, Abdominal Pain
- Constipation, loss of appetite

- Failure to Thrive (In Children)
- Polyuria, Polydipsia
- Renal stones
- Increased risk of pancreatic cancer, vascular calcification and death has been associated with serum levels of 25(OH)D > 60 ng/ml (150 nmol/L)
- Increased 1α hydroxylase activity led to premature aging in mice[72].

MANAGEMENT OF HYPERVITAMINOSIS D

Rapid treatment with intravenous fluids, steroids and calcium restricted diet. Some may require bisphophonates to control hypercalcemia.[72]

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTING : Government Royapettah Hospital, Chennai

COLLABORATIVE DEPARTMENT : Department of Cardiology, GRH

STUDY DESIGN : Observational Case Control Study

PERIOD OF STUDY : April 2012 to September 2012

SAMPLE SIZE : 100 cases (50 cases ; 50 controls)

INCLUSION CRITERIA:

1. Patients with acute ST Elevation Myocardial Infarction admitted in the Intensive Coronary Care Unit at GRH were selected as cases
2. Patients without Diabetes / Hypertension / Coronary Artery Disease who attended the medical OPD were selected as controls
3. Patient's age > 18 years

EXCLUSION CRITERIA:

1. Age < 18yrs
2. Diabetes
3. Hypertension

4. Prior History of Cardiovascular disease
5. Prior History of Cerebrovascular or Peripheral Vascular disease
6. Renal disease
7. Hepatic disease
8. Prior history of vitamin D supplementation
9. Patients on drugs that affect vitamin D metabolism

   (Anti Epileptics, Steroids, Rifampin)
10. History of Tuberculosis
11. Pregnancy and Lactation

Cases and Controls were selected after considering the above inclusion and exclusion criteria

ETHICAL CLEARANCE: Obtained

INFORMED CONSENT:

Both the cases and controls study groups were informed about the nature of the study. Members who were willing to participate in this study were included after getting their written informed consent.

METHODOLOGY:

Patients admitted with acute ST Elevation Myocardial Infarction in the Intensive Coronary Care Unit of Government Royapettah Hospital were chosen as cases. A total of 50 cases who satisfied the inclusion and exclusion criteria above were included in the study over a period of 6 months. 50 age and sex matched subjects were kept as controls.

A data collection form was prepared to note the Name, Age, Sex, Occupation, Address, Complaints, Past Medical History, Smoking, Alcoholism, Drug Intake and other relevant history. General Examination with examination of the Vital Signs, Cardiac,Respiratory, Abdomen and Central Nervous System was done. Each patient's clinical profile was noted. The ECG and ECHO reports of the patients were recorded.

LABORATORY INVESTIGATIONS:

Blood samples were drawn at the time of admission to measure the serum levels of 25(OH) Vitamin D, Random blood sugar and lipid profile. Renal function and hepatic function was assessed by measuring the urea, creatinine and total protein, serum bilirubin, serum albumin levels respectively.

Serum levels of 25(OH) Vitamin D were measured using Chemi Luminescence ImmunoAssay technique.

STATISTICAL ANALYSIS:

Data was entered in Microsoft Excel spreadsheet and analyzed. Data analysis was done with the use of standard SPSS (Statistics Products Services Solutions) 16.0 software package. Descriptive statistics were used to calculate the frequency, mean and standard deviation. Student 't' values was applied for significance. Significance was considered if the 'p' value was below 0.05.

CONFLICT OF INTEREST:

There was no conflict of interest

FINANCIAL SUPPORT:

Nil

DEFINITIONS USED IN THE STUDY

I. ACUTE ST ELEVATION MYOCARDIAL INFARCTION :

- New ST elevation [4] at the J point in at least 2 contiguous leads of
  - ≥ 2 mm in men or
  - ≥ 1.5 mm in women in leads V2–V3 and/or
  - ≥ 1 mm in other contiguous chest leads or limb leads
- New onset LBBB

II. SERUM 25(OH)D CONCENTRATIONS AND HEALTH STATUS :[21]

- **Vitamin D sufficiency → > 30 ng/ml**
- **Vitamin D insufficiency → 15.1 – 29.9 ng/ml**
- **Vitamin D deficiency → < 15 ng/ml**

Vitamin D deficiency is further classified as

- <5 ng/ml - severe Hypovitaminosis D
- 5-10 ng/ml - moderate Hypovitaminosis D
- 10-15 ng/ml - mild Hypovitaminosis D

III. BODY MASS INDEX :

It is estimated by using the formula: BMI = Weight (kg)/ Height^2(m)

A BMI of

- < 18.5 → underweight
- 18.5 - 24.9 →normal
- 25.0 - 29.9 → overweight
- 30 → obese

Obesity:

- Class I (BMI 30 to 39.9)
- Class II (BMI 40 to 49.9)
- Class III (BMI >50)

CLINICAL CLASSIFICATION OF OBESITY[81]
Mortality and coronary heart disease risk

Class of Obesity	**Body mass index (kg/m2)**	**Class**
0	20–25	Not obese
1	25–30	Mild risk
2	30–35	Moderate risk
3	35–40	High risk
4	> 40	Very high risk

IV. **NORMAL VALUES**:

- Serum albumin – 3.5 – 5.0 mg/dl
- Serum calcium – 8.7 – 10.2 mg/dl
- Serum triglycerides – 30 – 200 mg/dl
- Serum cholesterol – < 200 mg/dl → normal

  200 – 239 mg/dl → borderline high

  240 mg/dl → high

RESULTS

OBSERVATIONS AND RESULTS

STUDY POPULATION CHARACTERISTICS

A total of 100 subjects were included in this study out of which 50 were cases (Acute Myocardial Infarction) and 50 were controls. Both men and women between age of 25 to 80 years were included in the study.

TABLE 1 :

GROUP

	Frequency	Percent	Valid Percent	Cumulative Percent
Case	50	50.0	50.0	50.0
Control	50	50.0	50.0	100.0
Total	100	100.0	100.0	

FIGURE 1 :

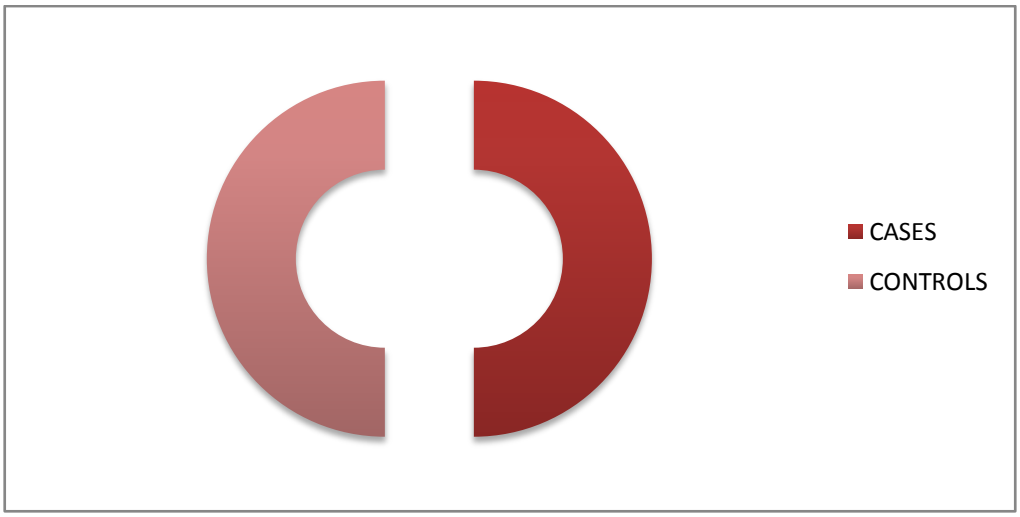
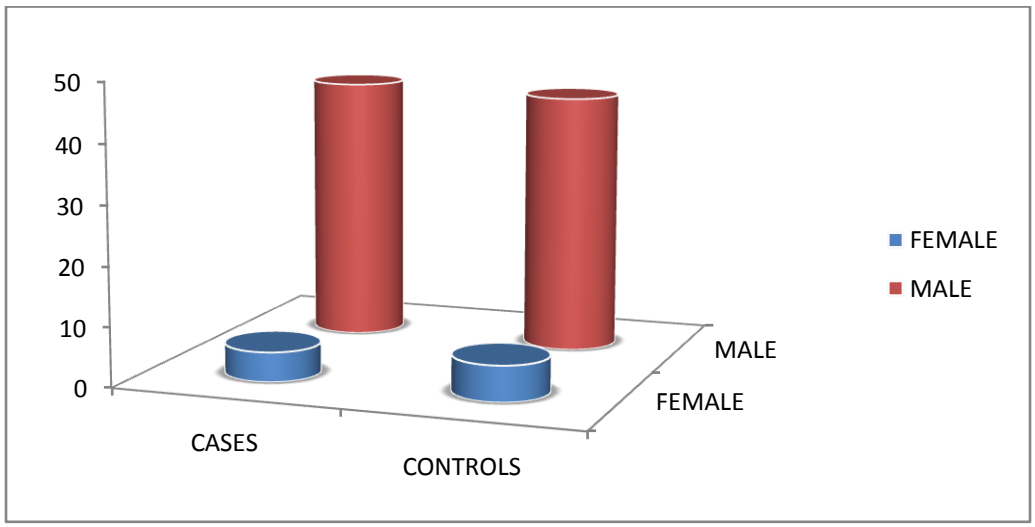


TABLE 2 : GENDER WISE DISTRIBUTION OF PATIENTS

			Sex		
			Male	Female	Total
GROUP	Case	Count	45	5	50
		% within GROUP	90.0%	10.0%	100.0%
	Control	Count	44	6	50
		% within GROUP	88.0%	12.0%	100.0%
Total		Count	89	11	100
		% within GROUP	89.0%	11.0%	100.0%

p value - 1.000 (not significant)

FIGURE 2 : GENDER WISE DISTRIBUTION OF PATIENTS



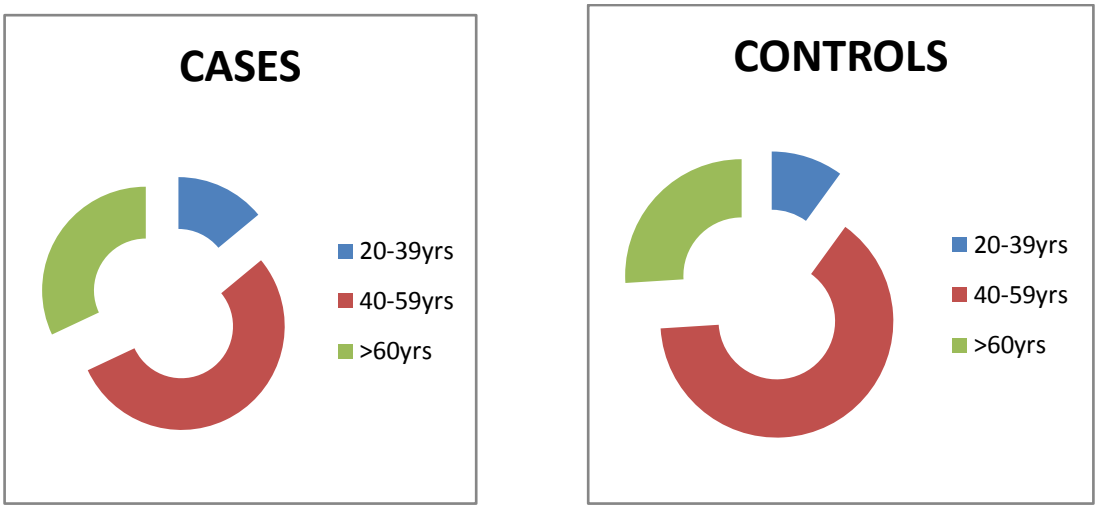
Among the 50 cases studied, there were 45 (90%) males and 5 (10%) females. Among the 50 controls, there were 44 (88%) males and 6 (12%) females. The sex composition of the case and control group did not differ significantly.

TABLE 3 : AGE WISE DISTRIBUTION OF PATIENTS

			AGE			
			20-39yrs	40-59yrs	>60yrs	Total
GROUP	Case	Count	7	27	16	50
		% within GROUP	14.0%	54.0%	32.0%	100.0%
	Control	Count	5	32	13	50
		% within GROUP	10.0%	64.0%	26.0%	100.0%
Total		Count	12	59	29	100
		% within GROUP	12.0%	59.0%	29.0%	100.0%

p value – 0.586 (not significant)

FIGURE 3 : AGE WISE DISTRIBUTION OF PATIENTS



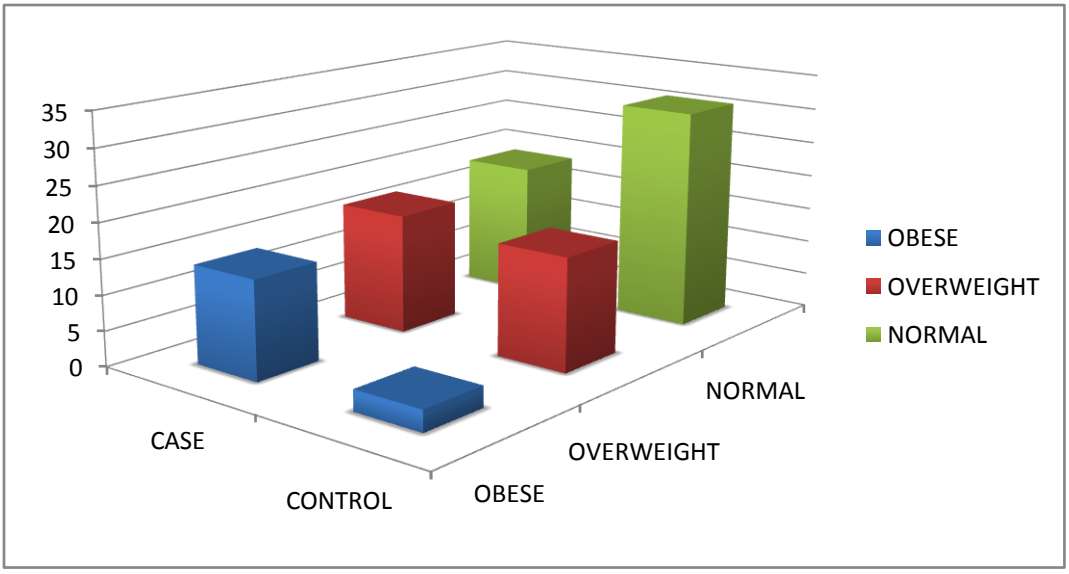
The mean age in the case and control groups were 51.72 ± 12.99 and 51.8 ± 10.63 years respectively. The study population was stratified into 3 groups according to their age. There was no significant difference in the age distribution between the cases and controls in each of the three age groups.

TABLE 4 : CASES AND CONTROLS WITH RESPECT TO BMI

			BODY MASS INDEX (kg/m²)			
			Normal	Over weight	Obese	Total
GROUP	Case	Count	19	17	14	50
		% within GROUP	38.0%	34.0%	28.0%	100.0%
	Control	Count	31	16	3	50
		% within GROUP	62.0%	32.0%	6.0%	100.0%
Total		Count	50	33	17	100
		% within GROUP	50.0%	33.0%	17.0%	100.0%

p value – 0.007 (significant)

FIGURE 4 : CASES AND CONTROLS WITH RESPECT TO BMI



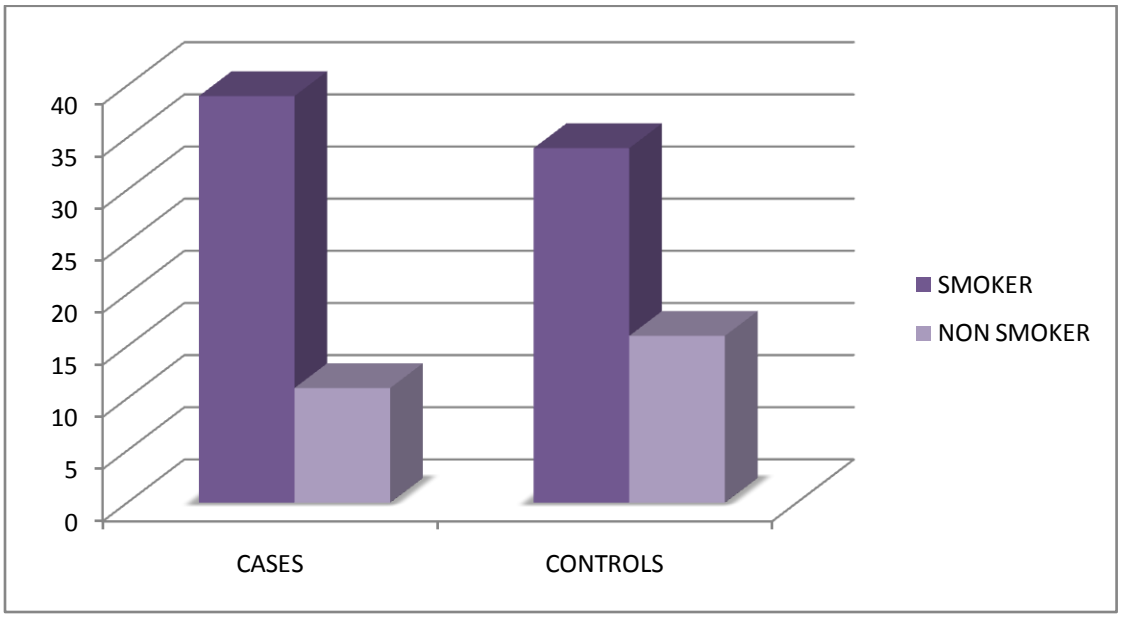
The mean and standard deviation for the cases and controls were 27.14 ± 3.88 and 24.5 ± 2.84 kg/m^2 respectively. The Body Mass Index of the study group was significantly higher than that of the control group.

TABLE 5 : CASES AND CONTROLS WITH RESPECT TO SMOKING

			Smoker		
			Yes	No	Total
GROUP	Case	Count	39	11	50
		% within GROUP	78.0%	22.0%	100.0%
	Control	Count	34	16	50
		% within GROUP	68.0%	32.0%	100.0%
Total		Count	73	27	100
		% within GROUP	73.0%	27.0%	100.0%

p value – 0.368 (not significant)

FIGURE 5 : CASES AND CONTROLS WITH RESPECT TO SMOKING



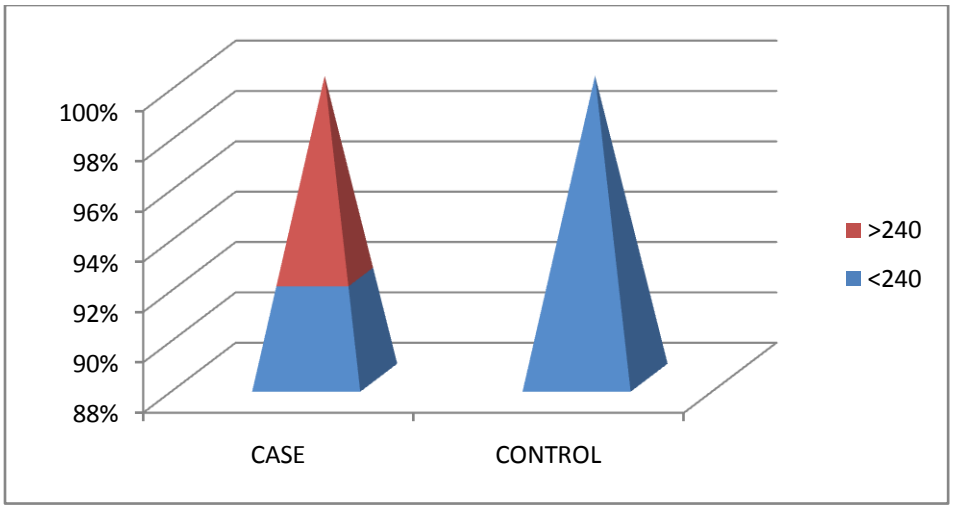
There was no significant difference between the number of smokers and non smokers among the cases and the controls. Hence, we could exclude smoking as a confounding factor for cardiovascular risk.

TABLE 6 : SERUM CHOLESTEROL IN STUDY GROUP

			TOTAL CHOLESTEROL		
			<240mg%	>240mg%	Total
GROUP	Case	Count	46	4	50
		% within GROUP	92.0%	8.0%	100.0%
	Control	Count	50	0	50
		% within GROUP	100.0%	0%	100.0%
Total		Count	96	4	100
		% within GROUP	96.0%	4.0%	100.0%

p value – 0.126 (not significant)

FIGURE 6 : SERUM CHOLESTEROL IN STUDY GROUP



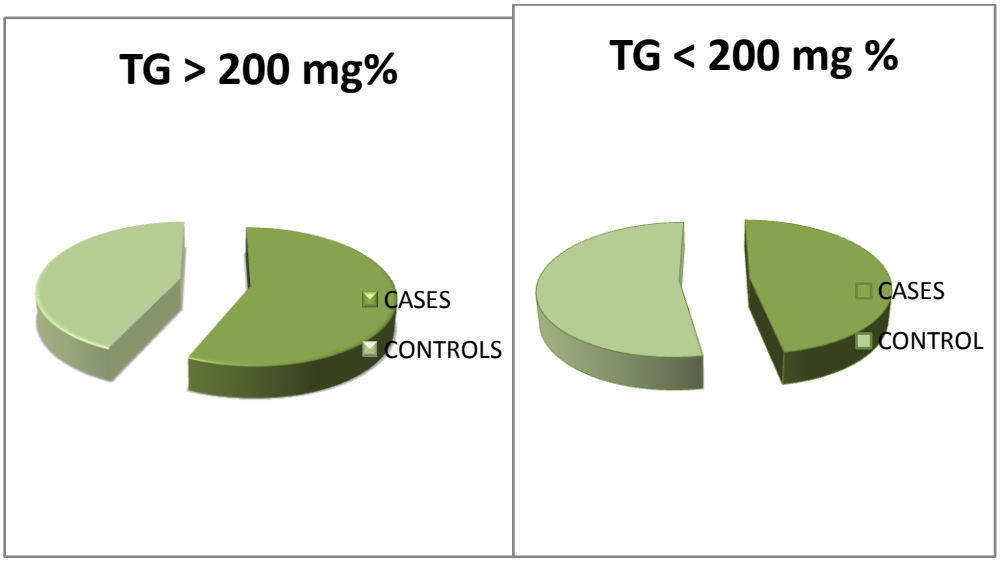
The mean serum cholesterol level in the cases was 209.02 ± 31.95 mg/dl and in the controls was 182.38 ± 20.33 mg/dl. The difference between the two groups was not statistically significant.

TABLE 7 : SERUM TRIGLCERIDES IN STUDY GROUP

			TRIGLYCERIDES(mg%)		
			<200	>200	Total
GROUP	Case	Count	33	17	50
		% within GROUP	66.0%	34.0%	100.0%
	Control	Count	37	13	50
		% within GROUP	74.0%	26.0%	100.0%
Total		Count	70	30	100
		% within GROUP	70.0%	30.0%	100.0%

p value – 0.147 (not significant)

FIGURE 7 : SERUM TRIGLCERIDES IN STUDY GROUP



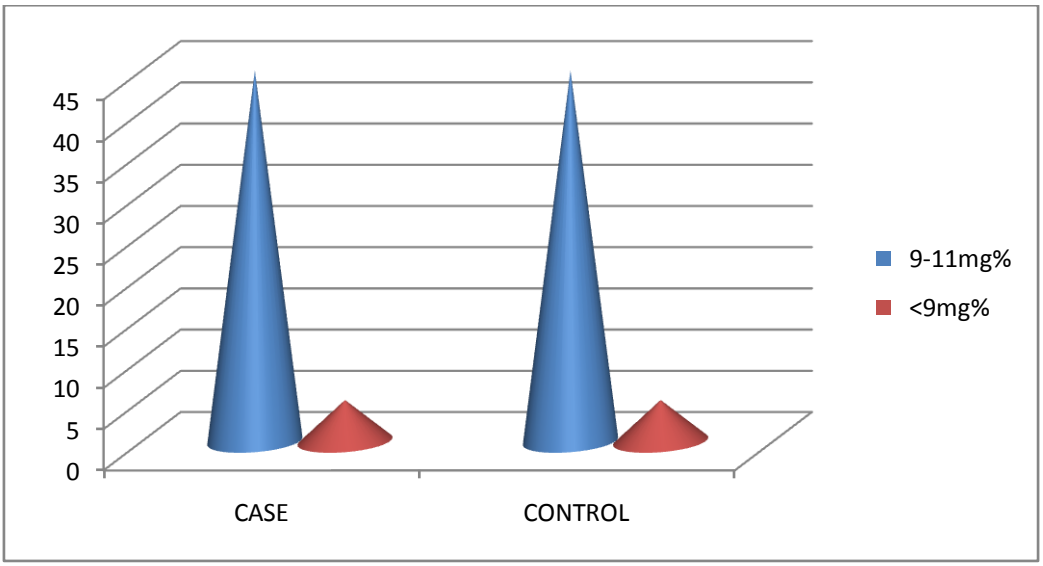
The mean serum triglyceride level in the cases was 170.94 ± 48.77 mg/dl and in the controls was 122.74 ± 23.57 mg/dl. The difference between the two groups was not statistically significant.

TABLE 8 : SERUM CALCIUM IN STUDY GROUP

			CALCIUM		
			9–11 mg%	< 9 mg%	Total
GROUP	Case	Count	45	5	50
		% within GROUP	90.0%	10.0%	100.0%
	Control	Count	45	5	50
		% within GROUP	90.0%	10.0%	100.0%
Total		Count	90	10	100
		% within GROUP	90.0%	10.0%	100.0%

p value - 1.000 (not significant)

FIGURE 8 : SERUM CALCIUM IN STUDY GROUP



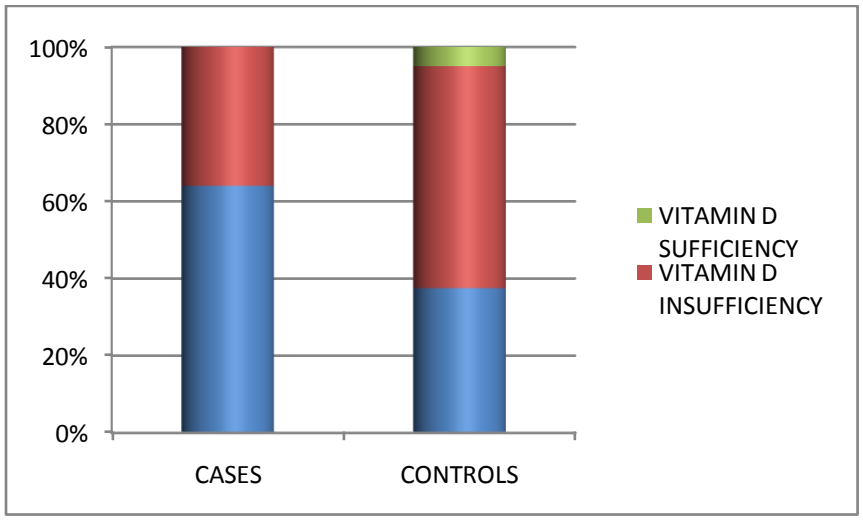
The mean serum calcium in the cases was 8.92 ± 0.74 mg/dl and in the controls was 9.09 ± 0.62 mg/dl. The difference between the cases and controls was not statistically significant

TABLE 9 : VITAMIN D STATUS IN THE STUDY POPULATION

			25(OH) VITAMIN D (ng/ml)			
			Deficiency	Insufficiency	Normal	Total
GROUP	Case	Count	32	18	0	50
		% within GROUP	64.0%	36.0%	0%	100.0%
	Control	Count	13	25	12	50
		% within GROUP	26.0%	50.0%	24.0%	100.0%
Total		Count	45	43	12	100
		% within GROUP	45.0%	43.0%	12.0%	100.0%

p value - 0.001 (significant)

FIGURE 9: VITAMIN D STATUS IN CASES AND CONTROL



Cases:

None of the cases had normal vitamin D levels

64% had Vitamin D deficiency

36% had Vitamin D insufficiency

Controls:

Only 24% had normal vitamin D levels

26% had Vitamin D deficiency

50% had Vitamin D insufficiency

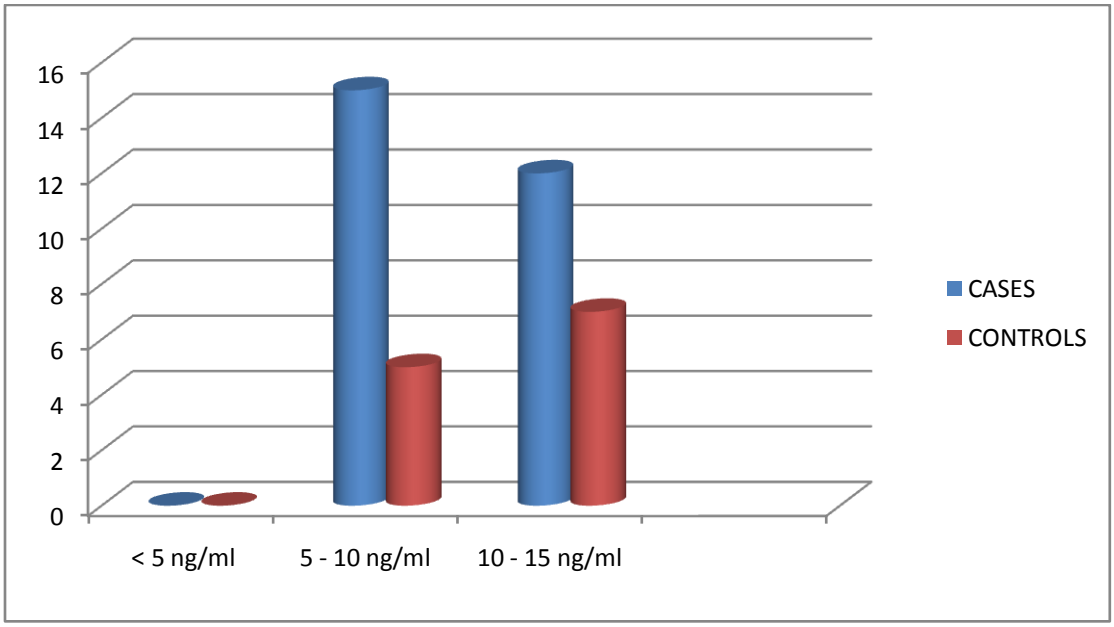
The mean serum 25(OH) Vitamin D in the cases was 13.49 ± 5.35 ng/ml and the mean serum 25(OH) Vitamin D in the controls was 23.43± 12.52 ng/ml.

The p value was 0.001 and this difference between the two groups was statistically significant showing significant Hypovitaminosis D among the cases.

TABLE 9.1: SEVERITY OF VITAMIN D DEFICIENCY IN CASES AND CONTROLS

			VITAMIN D DEFICIENCY < 15 ng/ml			Total
			< 5 ng/ml	5 – 10 ng/ml	10 – 15 ng/ml	
GROUP	Case	Count	0	16	16	32
		% within GROUP	0%	36%	36%	72%
	Control	Count	0	5	8	13
		% within GROUP	0%	11%	18%	29%
Total		Count	0	21	24	45
		% within GROUP	0%	47%	53%	100.0%

FIGURE 9.1: SEVERITY OF VITAMIN D DEFICIENCY IN CASES AND CONTROLS



Vitamin D deficiency

Cases:

Severe Vitamin D deficiency → 0%

Moderate Vitamin D deficiency → 36%

Mild Vitamin D deficiency → 36%

Controls:

Severe Vitamin D deficiency → 0%

Moderate Vitamin D deficiency → 11%

Mild Vitamin D deficiency → 18%

The patients who had vitamin D deficiency were further divided into three groups based on severity. None of them had severe deficiency.

Moderate deficiency was present in 36% of cases but only in 11% of controls.

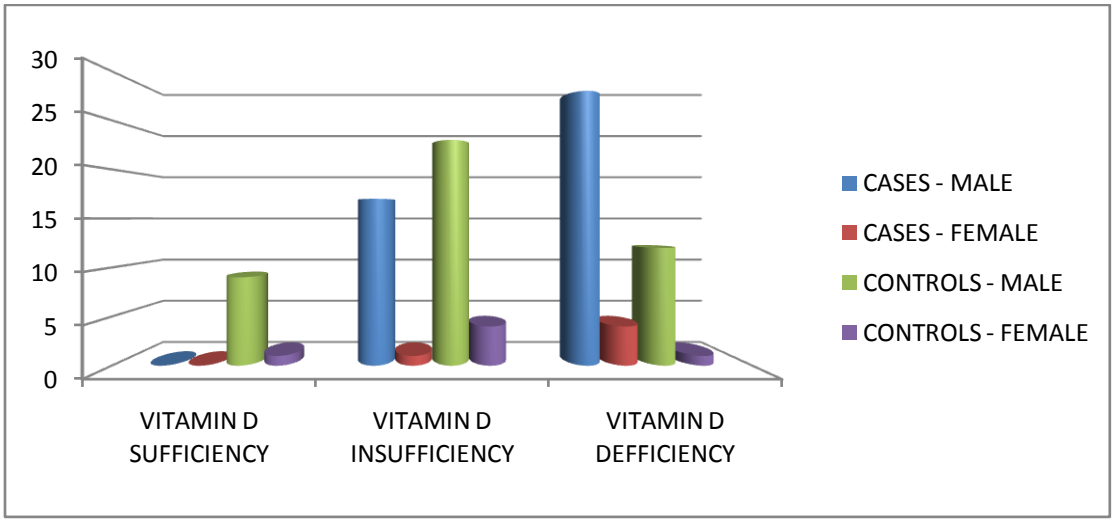
Mild deficiency was present in 36% of cases and in 18% of controls

TABLE 10: GENDER WISE DISTRIBUTION OF VITAMIN D

	Sex	N	Mean	Std. Deviation	P-value
VIT. D (ng/ml)	Male	89	18.6980	10.99856	0.536
	Female	11	16.5482	9.28151	

p value - 0.586 (not significant)

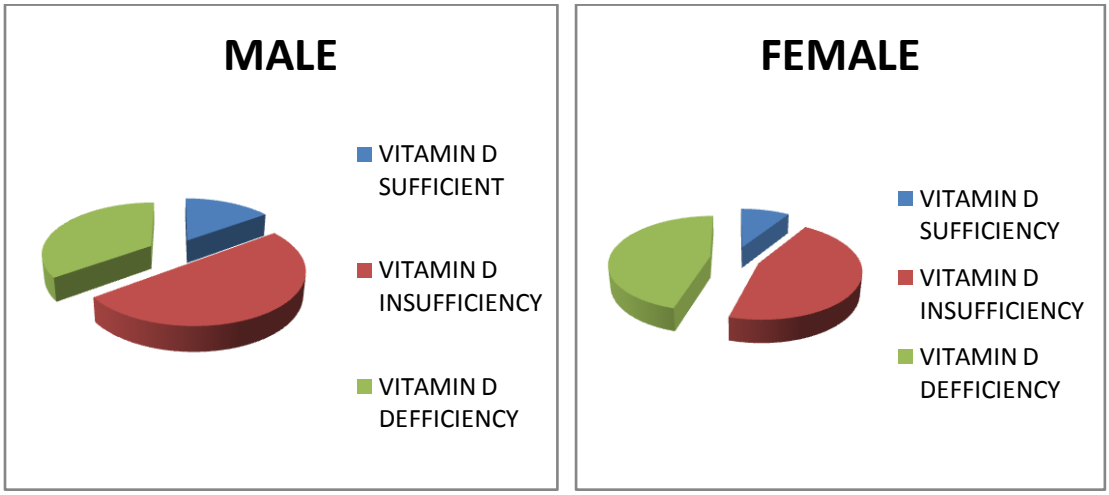
FIGURE 10 : GENDER WISE DISTRIBUTION OF VITAMIN D LEVELS IN CASES AND CONTROLS



Among the cases, vitamin D deficiency was present in 28 males and 4 females whereas vitamin D insufficiency was seen in 17 males and 1 female.

In the controls group, sufficient vitamin D levels were seen in 9 men and 1 woman. Vitamin D insufficiency was present in 23 men and 4 women. 12 men and 1 woman had Vitamin D deficiency.

FIGURE 10.1 : VITAMIN D STATUS IN MALES AND FEMALES



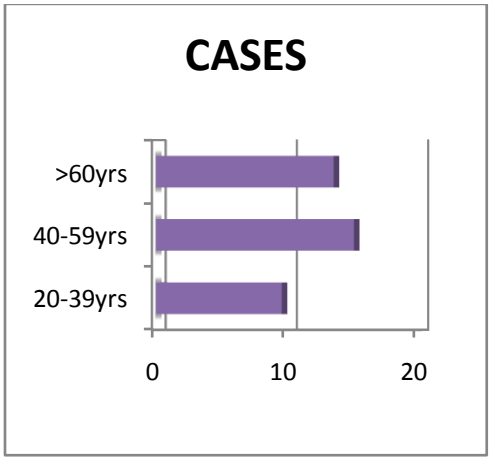
The total population included 89 males and 11 females. The mean Vitamin D level among males was 18.69 ng/ml and among females was 16.54 ng/ml.

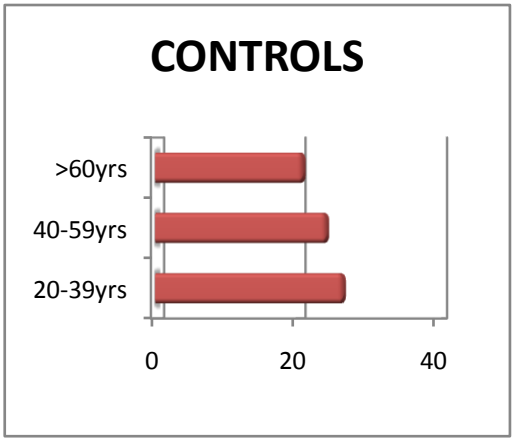
The p value was 0.586 and was not significant indicating that there was no significant difference between the gender distribution of vitamin D levels.

TABLE 11 : VITAMIN D STATUS IN EACH AGE GROUP

AGE GROUP	MEAN 25(OH) VITAMIN D (ng/ml)	
	CASES	CONTROLS
20-39yrs	9.58	26.52
40-59yrs	15.08	24.15
>60yrs	13.54	20.83

FIGURE 11 : AGE WISE DISTRIBUTION OF VITAMIN D LEVELS





The cases and controls were divided into 3 age groups and their vitamin D status was assessed.

Among the cases, mean serum 25(OH)vitamin D in the age group 20-39yrs was 9.58ng/ml as compared to a mean value of 26.52ng/ml which showed a significant degree of vitamin D deficiency in young MI patients.

As for the patients in the age group 40-59yrs, the mean vitamin D levels in the cases was 15.08 and that of the controls was 24.15ng/ml.

In the patients > 60yrs age, mean of 13.54ng/ml was found in the cases and 20.83ng/ml in the controls.

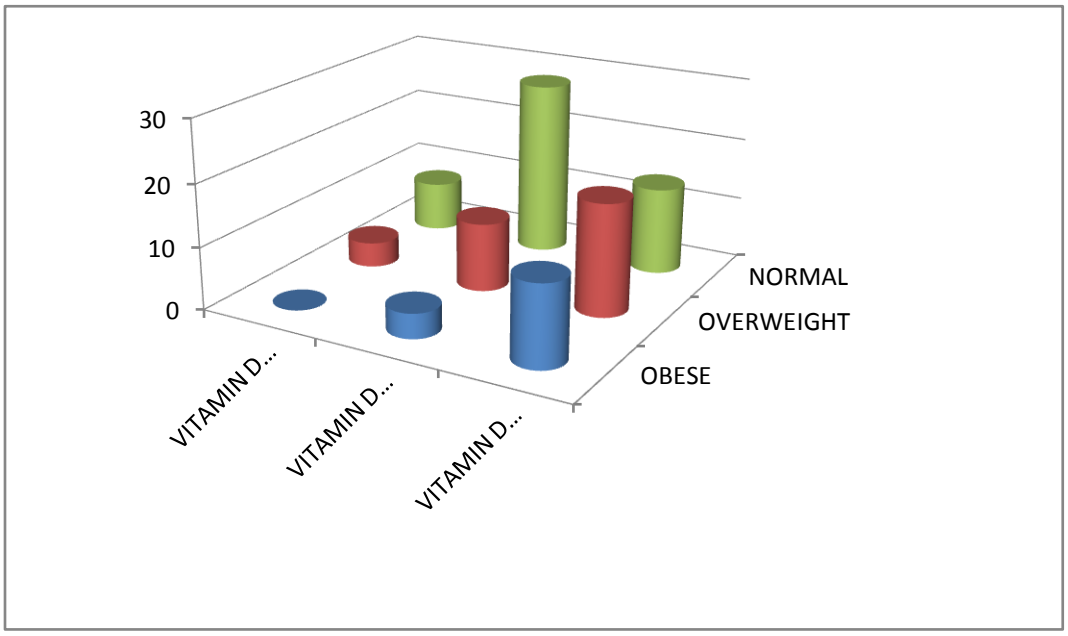
This denotes significant degree of Vitamin D deficiency in all the 3 age groups in the patients with Myocardial Infarction. The level of deficiency was more significant in the patients < 40yrs who presented with acute myocardial infarction.

TABLE 12: CORRELATION OF VITAMIN D STATUS & BMI

			BODY MASS INDEX			
			Normal	Over weight	Obese	Total
25(OH) Vitamin D (ng/ml)	Deficiency	Count	14	18	13	45
		% within VIT.D_GP	31.1%	40.0%	28.9%	100.0%
	Insufficiency	Count	28	11	4	43
		% within VIT.D_GP	65.1%	25.6%	9.3%	100.0%
	Sufficiency	Count	8	4	0	12
		% within VIT.D_GP	66.7%	33.3%	0%	100.0%
Total		Count	50	33	17	100
		% within VIT.D_GP	50.0%	33.0%	17.0%	100.0%

p value - 0.007 (significant)

FIGURE 12 : VITAMIN D STATUS AND BODY MASS INDEX



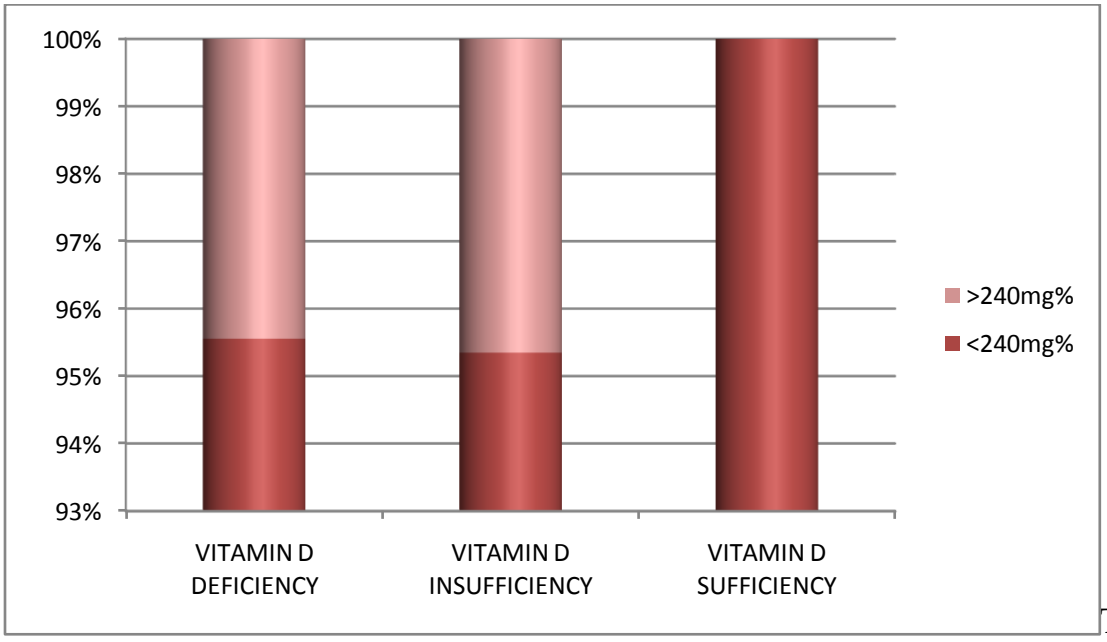
The Vitamin D levels were significantly lower in those with higher BMI in the study group.

TABLE 13: CORRELATION OF VITAMIN D & TOTAL CHOLESTEROL

			TOTAL CHOLESTEROL		
			<240	>240	Total
25(OH) Vitamin D (ng/ml)	Deficiency	Count	43	2	45
		% within VIT.D_GP	95.6%	4.4%	100.0%
	Insufficiency	Count	41	2	43
		% within VIT.D_GP	95.3%	4.7%	100.0%
	Sufficiency	Count	12	0	12
		% within VIT.D_GP	100.0%	0%	100.0%
Total		Count	96	4	100
		% within VIT.D_GP	96.0%	4.0%	100.0%

p value - 0.752 (not significant)

FIGURE 13 : VITAMIN D & TOTAL CHOLESTEROL



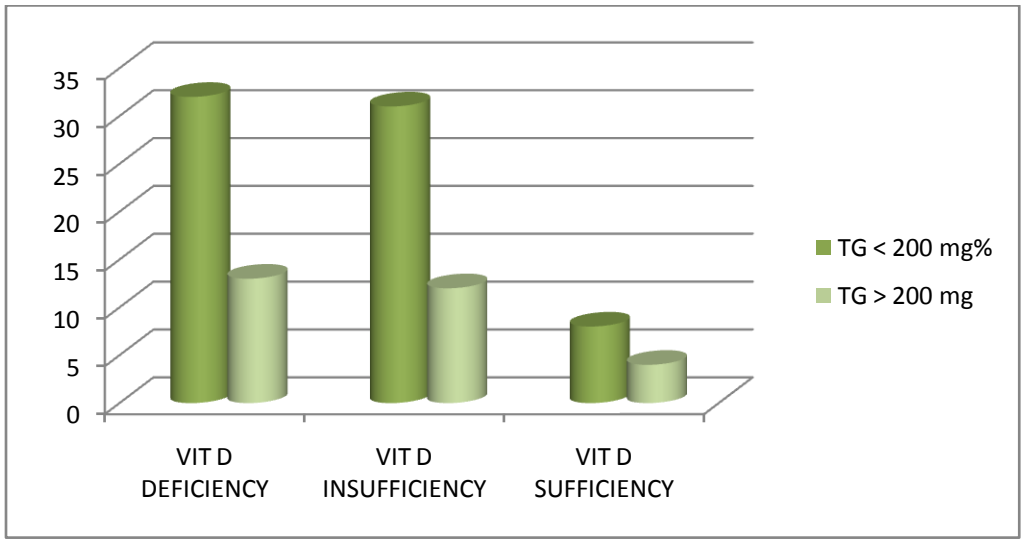
There was no significant correlation between Serum 25(OH) vitamin D and Total cholesterol levels in the cases and controls.

TABLE 14 : CORRELATION OF VITAMIN D & TGL

			TRIGLCERIDE		
			<200	>200	Total
25(OH) Vitamin D (ng/ml)	Deficiency	Count	32	13	45
		% within VIT.D_GP	71.1%	29.9%	100.0%
	Insufficiency	Count	31	12	43
		% within VIT.D_GP	72.1%	27.9%	100.0%
	Sufficiency	Count	8	4	12
		% within VIT.D_GP	66.6%	33.3%	100.0%
Total		Count	71	29	100
		% within VIT.D_GP	71.0%	29.0%	100.0%

p value - 0.400 (not significant)

FIGURE 14 : VITAMIN D AND TRIGLYCERIDES



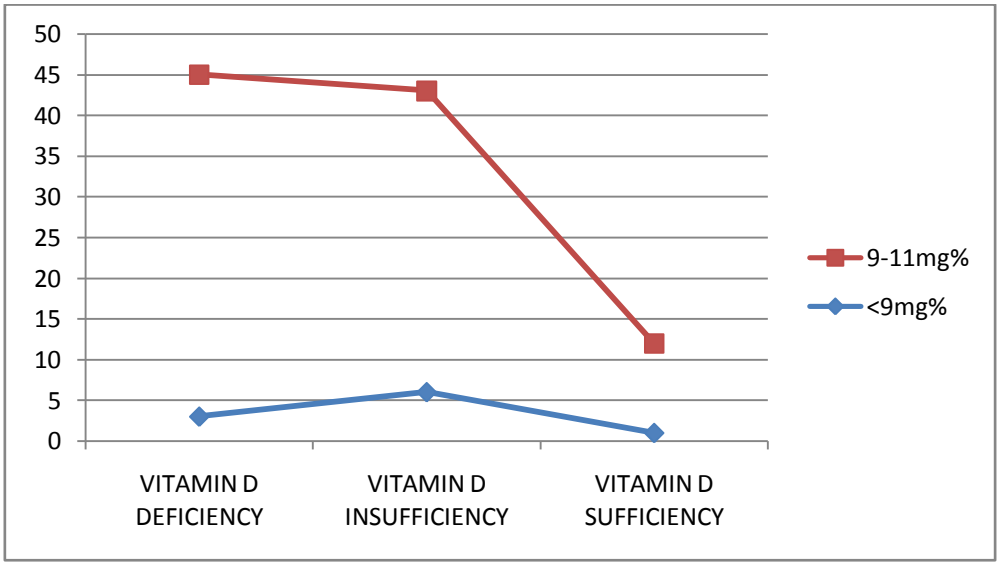
There was no significant correlation between Serum 25(OH) vitamin D and triglyceride levels in the cases and controls.

TABLE 15 : CORRELATION OF VITAMIN D & SERUM CALCIUM

			CALCIUM		
			9–11 mg%	< 9 mg%	Total
25(OH) Vitamin D (ng/ml)	Deficiency	Count	42	3	45
		% within VIT.D_GP	93.3%	6.7%	100.0%
	Insufficiency	Count	37	6	43
		% within VIT.D_GP	86.0%	14.0%	100.0%
	Normal	Count	11	1	12
		% within VIT.D_GP	91.7%	8.3%	100.0%
Total		Count	90	10	100
		% within VIT.D_GP	90.0%	10.0%	100.0%

p value - 0.512 (not significant)

FIGURE 15 : CORRELATION OF VITAMIN D & SERUM CALCIUM



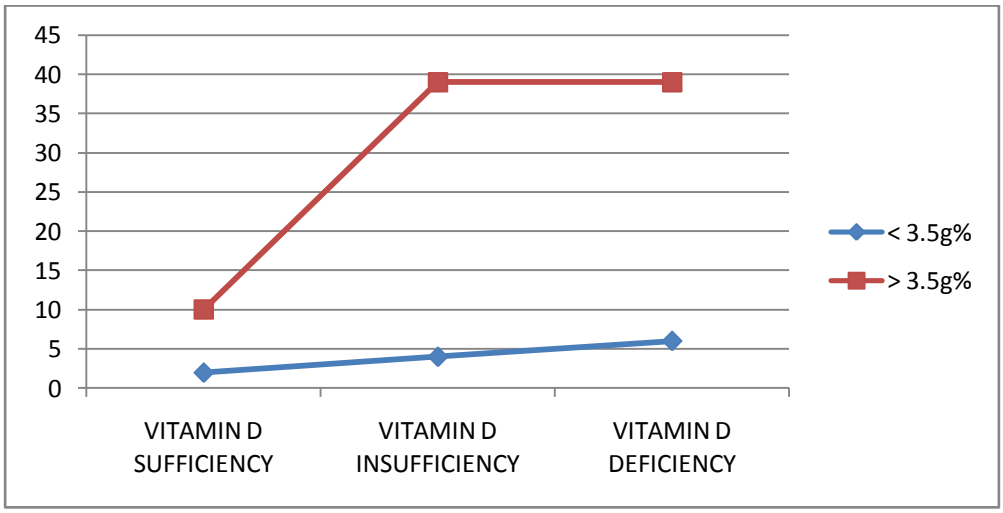
There was no significant correlation between Serum 25(OH) vitamin D and Serum Calcium levels in the cases and controls.

TABLE 16 : CORRELATION OF VITAMIN D AND SERUM ALBUMIN

			SERUM ALBUMIN		
			<3.5 g%	>3.5g%	Total
25(OH) Vitamin D	Deficiency	Count	6	39	45
		% within VIT.D_GP	13.3%	86.7%	100.0%
	Insufficiency	Count	4	39	43
		% within VIT.D_GP	9.3%	90.7%	100.0%
	Sufficiency	Count	2	10	12
		% within VIT.D_GP	16.7%	83.3%	100.0%
Total		Count	12	88	100
		% within VIT.D_GP	12.0%	88.0%	100.0%

p value - 0.734 (not significant)

FIGURE 16 : VITAMIN D AND SERUM ALBUMIN



There was no significant correlation between Serum 25(OH) Vitamin D and Serum Albumin levels in the cases and controls. Hence Vitamin D levels were not biased by low serum albumin levels.

T-Test

Statistical analysis was done by using the SPSS software. Student t test was used to derive statistical significance on comparing the following variables between the cases and controls. p value < 0.05 was considered significant.

	GROUP	N	Mean	Std. Deviation	P-value
Age (years)	Case	50	51.72	12.998	0.973
	Control	50	51.80	10.633	
BMI (kg/m^2)	Case	50	27.1370	3.87449	0.000
	Control	50	24.5016	2.83610	

T-Test

	GROUP	N	Mean	Std. Deviation	P-value
T.Chol. (mg/dl)	Case	50	209.02	31.952	0.126
	Control	50	182.38	20.329	
TGL (mg/dl)	Case	50	170.94	48.772	0.147
	Control	50	122.74	23.576	

T - Test

	GROUP	N	Mean	Std. Deviation	P-value
VIT. D (ng/ml)	Case	50	13.4894	5.34646	0.001
	Control	50	23.4336	12.51863	
Calcium (mg/dl)	Case	50	8.9178	0.74067	0.206
	Control	50	9.0916	0.62002	

Among the study population of 50 cases and 50 controls, significant p value was observed between BMI > 25 kg/m^2 and Hypovitaminosis D.

DISCUSSION

DISCUSSION

In our study of 100 patients we included 50 cases of acute Myocardial Infarction and 50 age and sex matched controls. We had selected our cases on the basis that they had no previous history of Diabetes, Hypertension, Dyslipidemia or prior Cardiovascular disease because we wanted to study the association of low vitamin D levels as an independent risk factor for the occurrence of first cardiovascular event in a patient.

We found a statistically significant correlation of Hypovitaminosis D in the patients with Acute Coronary Syndrome. All the patients who were admitted with acute MI had subnormal Vitamin D levels. 64% of the cases were deficient in Vitamin D (<15ng/ml) and 36% of the cases had insufficient levels (15-30ng/ml). In the control group, 26% had deficient levels and 50% had insufficient levels whereas only 24% of the control group had normal 25(OH) Vitamin D levels. The mean Vitamin D level among the cases was 13.5ng/ml and that among the controls was 24.3ng/ml and this was indicative of a statistically significant difference.

In the CACTI study by Young et al,[87] the association of Vitamin D deficiency with prevalent Coronary Artery Calcification was independent of known CAD risk factors, including confounders such as BMI and mediators such

as lipids. This adds proof to the fact that Vitamin D is related to CAD through unique biologic mechanisms.

It was observed in the Framingham heart study[88] that those patients whose Vitamin D levels were <15ng/ml had a 60% greater incidence of cardiac events than those with higher levels. Though there are many meta analyses that have reported both positive and neutral correlations, some Indian studies have even reported that high levels of vitamin D may attribute to ischemic events. Shanker et al[84] found that low vitamin D levels were associated with increased risk for CAD, in contrary to which, Rajasree et al reported a paradoxical increase in coronary heart disease with 25(OH)D levels >89 ng/mL compared to those with lower levels.[83] Sanjeev kumar Syal et al[85] observed a high prevalence of hypovitaminosis D in Indian patients with angiographically documented CAD. They demonstrated that patients with lower levels of Vitamin D had higher prevalence of severe (double- and triple-vessel CAD) and diffuse disease on coronary angiography, independent of established CV risk factors. In their study, endothelial dysfunction as assessed by brachial artery FMD was also more frequently observed in those with 25(OH)D levels.[85]

On assessing the overall Vitamin D status in our study population of 100 subjects, we found that only 12% had normal 25(OH)D levels. The remaining 88% had Hypovitaminosis D out of which 45% were deficient and 43% were

insufficient in Vitamin D. The high rates of vitamin D deficiency in our study group is reflective of the high prevalence of Hypovitaminosis D in the Indian population as demonstrated in a study by Harinarayan et al which showed that 50-90% of the people living in India are deficient in Vitamin D.[62]

The mean Vitamin D level in the control group was found to be 24.3ng/ml. This is similar to the NHANES 2005-2006 survey that showed a mean Vitamin D level of 24ng/ml among apparently healthy subjects.

In our study, we also analyzed the association of Vitamin D with other parameters such as Age, Gender, Body Mass Index, Total cholesterol and Triglyceride levels, Serum albumin and Serum calcium.

We did not find any significant association between the **gender distribution** of serum Vitamin D levels among the cases or controls. The mean serum Vitamin D level among the male subjects was 18.69ng/ml and among the female subjects was 16.54ng/ml indicating no specific correlation between gender and Vitamin D levels.

The study participants were divided into three **age groups** in both the cases and controls. The mean Vitamin D level in the cases was lower than the controls in each age group. There was significant decrease in Vitamin D levels in the young

CAD patients < 40yrs. Their mean Vitamin D level was only 9.58ng/ml when compared to the control group < 40yrs whose mean Vitamin D level was 26.52ng/ml suggestive of a significant role of Hypovitaminosis D as an independent risk factor for Myocardial Infarction in the absence of other conventional risk factors.

In our study, we found low Vitamin D levels in those with higher **BMI**. Body Mass Index > 25kg/m² was seen in approximately 70% of our patients with Vitamin D deficiency. This is in concurrence with many studies that link Vitamin D deficiency to high BMI, Obesity and the Metabolic Syndrome.

We did not find any association between **Dyslipidemia** and Hypovitaminosis D. There was no significant association between the calcium levels in the cases and controls nor was there any significant association between low Vitamin D levels and hypocalcemia. Also, serum albumin levels did not correlate with the Vitamin D status.

High mortality rates associated with CAD in people living far away from the equator was studied by Fleck et al[73] and Rostand et al.[76] Grimes et al[74] showed that mortality was inversely proportional to the amount of hours exposed to sunlight. He also proposed Vitamin D as a protective factor by regulating serum cholesterol levels and by inhibiting Chlamydia pneumonia. Douglas et al[75] reported a strong

seasonal variation with higher mortality rates in winter when Vitamin D levels are lowest. Many large prospective studies such as The Framingham Offspring Study, The Health Professionals Follow up Study, The Third National Health and Nutrition Examination Survey (NHANES III) have proved a positive association between low Vitamin D levels and the risk of adverse cardiac events.[77] Hence, many studies suggest that poor Vitamin D status is associated with poor cardiovascular outcomes.

But, the 2011 IOM report concluded that the evidence that vitamin D prevents cardiovascular disease was not consistent.[79] Many reports argue that the 25(OH)D acts as a acute phase reactant and its levels reduce significantly during disease processes, similar to other vitamins. Moreover, there isn't substantial evidence to state that a single hormone can be a harbinger of such severe and diverse disease processes.

In spite of these controversies, there are multiple studies worldwide reporting positive correlation between low vitamin D levels and adverse cardiac events. Various studies have also claimed that Vitamin D supplementation has reduced the incidence of cardiovascular disease and its complications with a significant decrease in all cause mortality.[80]

Hence, to conclude, our study showed a positive correlation of low Serum 25(OH) Vitamin D < 15ng/ml as a risk factor for Coronary Heart Disease. There was also a positive correlation of Hypovitaminosis D with high Body Mass Index > 25 kg/m^2. There was no significance in the age and gender distribution of Vitamin D levels. Serum calcium did not correlate with the occurrence of CAD or with the severity of Vitamin D deficiency.

SUMMARY

Various epidemiologic data and observational studies show that serum vitamin D concentrations are lower in patients with coronary heart disease compared with healthy controls. However, Hypovitaminosis D is also associated with other cardiovascular risk factors like hypertension, diabetes, obesity, metabolic syndrome and dyslipidemia.

The present study was proposed to assess the 25(OH)Vitamin D status in patients with acute Myocardial Infarction and to find its association with age, gender, BMI, dyslipidemia and serum calcium. Patients were selected carefully and evaluated after getting ethical clearance and informed consent. The study included 50 cases of Acute Myocardial Infarction and 50 healthy age and sex matched controls.

Our analysis revealed that serum 25(OH)Vitamin D levels were significantly lower in the cases of acute Myocardial Infarction when compared to the control population. Body Mass Index >25 kg/m^2 significantly correlated with hypovitaminosis D.

Large randomized controlled trials are needed to firmly establish the relevance of vitamin D status to cardiovascular health. In the meanwhile,

monitoring serum 25- hydroxyvitamin D levels and correction of vitamin D deficiency is indicated for optimization of general health".

LIMITATIONS OF THE STUDY

- The main limitation in our study was the small number of subjects that were included.
- Very few female patients were studied. Further studies need to be done with a larger study population including more women.
- 25(OH) Vitamin D estimation was not performed by the gold standard Liquid Chromatography Tandem Mass Spectrometry method. We used the Chemiluminescence assay for the quantitative determination of the 25(OH) Vitamin D levels in our patients. The concentration of vitamin D in each specimen may vary due to differences in methods and reagent specificity.
- The Parathormone levels were not measured and hence its role as a confounding factor could not be analyzed.
- The cause for hypovitaminosis D in the study subjects was not evaluated.
- The patients were not followed up after Vitamin D supplementation and hence we could not assess the prognosis.
- The etiology for MI in the young patients was not studied and so we could not rule out other confounding factors

IMPLICATIONS FOR FUTURE

- Routine estimation of serum vitamin D levels need be done in those with CAD, diabetes, hypertension and other risk factors because early detection and treatment of deficiency states has proven beneficial effects on mortality and morbidity.
- Diabetic and hypertensive patients with low Vitamin D levels should be carefully monitored for CAD and other vascular events.
- Obese individuals and those with dyslipidemia should also have routine estimations of serum Vitamin D.
- India is a developing country with high prevalence of CAD in both urban and rural populations where poverty and illiteracy dominate. It is necessary to implement public health awareness programs and food fortification programs to overcome this deficit.
- Fortification of foods such as milk and dairy products with Vitamin D has already been initiated in many developed countries and such food fortification programs are the need of the hour in our country. This is a very efficient method to reduce the incidence of Vitamin D deficiency especially in those on a purely vegetarian diet.

CONCLUSION

CONCLUSION

- Vitamin D deficiency is associated with a wide variety of diseases, each of which poses a great burden on the community. The discovery of the causal association of Vitamin D deficiency in cardiovascular diseases is indeed an important breakthrough.
- In our study, Serum Vitamin D levels were significantly lower in patients with acute Myocardial Infarction.
- Our results add to the growing body of evidence suggesting that low Vitamin D levels may be an independent and potentially modifiable cardiovascular risk factor.
- These findings may have potentially broad public health implications, given the high prevalence of Vitamin D deficiency in our country and the contribution of lifestyle and geography to Vitamin D status.
- Vitamin D deficiency is a risk factor that can be easily measured and corrected. The treatment is safe and cost effective. Hence, general awareness needs to created on the early detection and management of this risk factor and guidelines need to be implemented.

- Simple preventive measures like adequate sun exposure and food fortification can show a significant reduction in adverse cardiovascular events and other disease states associated with Vitamin D deficiency.
- Large scale prospective randomized control trials are needed to further analyze the role of Vitamin D deficiency in coronary artery disease and to study the effects of Vitamin D supplementation on the prognosis and prevention of Coronary Artery Diseases.

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ANNEXURES

ANNEXURES

DATA COLLECTION FORM

- NAME :
- AGE :
- SEX :
- OCCUPATION :
- ADDRESS :

HISTORY

- CHEST PAIN , PALPITATIONS , BREATHLESSNESS , GIDDINESS , SYNCOPE , FATIGUE - DURATION, ONSET , PROGRESSION

PAST HISTORY

- DIABETES MELLITUS , SYSTEMIC HYPERTENSION, CARDIOVASCULAR DISEASE , CEREBROVASCULAR DISEASE , PERIPHERAL VASCULAR DISEASE

PERSONAL HISTORY

- ALCOHOL - AMOUNT, FREQUENCY, DURATION
- SMOKING - BEEDI/CIGARETTE, NUMBER/DAY, DURATION

DRUG HISTORY

- VITAMIN D SUPPLEMENTATION
- ANTI DIABETIC , ANTI HYPERTENSIVE MEDICATIONS , CARDIAC DRUGS
- DRUGS AFFECTING VITAMIN D METABOLISM

EXAMINATION

- GENERAL EXAMINATION:
  - PALLOR , ICTERUS , CYANOSIS , CLUBBING , PEDAL EDEMA ,
    LYMPHADENOPATHY
- HEIGHT , WEIGHT , BODY MASS INDEX
- VITAL SIGNS :
  - PULSE RATE
  - BLOOD PRESSURE
  - RESPIRATORY RATE
  - TEMPERATURE

- SYSTEMIC EXAMINATION :
  - CARDIOVASCULAR SYSTEM
  - RESPIRATORY SYSTEM
  - ABDOMEN
  - CENTRAL NERVOUS SYSTEM

INVESTIGATIONS

- COMPLETE BLOOD COUNT
- BLOOD SUGAR
- RENAL FUNCTION TESTS – UREA , CREATININE
- LIPID PROFILE
- SERUM ALBUMIN
- SERUM BILIRUBIN
- ECG
- X-RAY CHEST
- ECHO

- SERUM 25(OH) VITAMIN D levels

ABBREVIATIONS

25(OH)D	–	25 Hydroxy Vitamin D
$1,25(OH)_2D$	–	1,25 DiHydroxy Vitamin D
Alb	–	Albumin
Apo	-	Apolipoprotein
ATT	–	Anti Tuberculosis Treatment
AWMI	–	Anterior Wall Myocardial Infarction
BMD	–	Bone Mineral Density
BMI	–	Body Mass Index
CABG	–	Coronary Artery Bypass Grafting
CAD	–	Coronary Artery Disease
cAMP	–	cyclic adenosine monophosphate
CD	–	Cluster of Differentiation
CHD	–	Coronary Heart Disease
CVD	–	Cardiovascular Disease
DBP	–	Diastolic Blood Pressure
ECG	–	Electrocardiograph
FGF	–	Fibroblast Growth Factor
IL	-	Interleukin
IOM	–	Institute of Medicine
IU	–	International Units
IW/PWMI	–	Inferior Wall / Posterior Wall Myocardial Infarction
LBBB	–	Left Bundle Branch Block
MI	–	Myocardial Infarction

MED	–	Minimal Erythema Dose
MMP	–	Matrix Metalloproteinase
NCD	–	Non Communicable Disease
NHANES	-	The National Health and Nutritional Examination Surveys
PAR	-	Population Attributable Risk
PCI	–	Percutaneous Coronary Intervention
PTH	–	Parathyroid Hormone
RVMI	–	Right Ventricular Myocardial Infarction
S.Alb.	–	Serum Albumin
SBP	–	Systolic Blood Pressure
TB	–	Tuberculosis
T.Chol.	–	Total Cholesterol
TGF	–	Transforming Growth Factor
TGL	–	Triglycerides
TH2	–	Type 2 Helper T
TNF	–	Tumor Necrosis Factor
UVB	–	Ultraviolet B
VDD	–	Vitamin D Deficiency
VDR	–	Vitamin D Receptor
WBC	–	White Blood Cells

PARTICIPANT CONSENT FORM

Participant's name: Address:

TITLE OF THE PROJECT: A STUDY ON SERUM VITAMIN D LEVELS IN ACUTE CORONARY SYNDROME.

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant: _____

Date: _____

MASTER CHART

CASES

No.	Name	Age/Sex	STEMI	Smoker	BMI	SBP	DBP	RBS	S.Alb.	T.Chol.	TGL	VIT.D	Calcium
1	Jeyakumar	26/M	AWMI	+	31.24	130	80	120	3.5	190	60	10.09	8.53
2	Selvaraj	74/M	IW/RVMI	----	26.67	100	70	109	3.8	192	109	27.39	8.94
3	Suresh	27/M	AWMI	+	21.34	116	74	113	4.2	200	165	8.26	9.17
4	Arumugam	57/M	AWMI	+	24.91	130	80	97	3.5	173	135	19.32	8.9
5	Sahul Hameed	46/M	ALMI	+	24.77	124	74	70	3	165	110	11.88	9.76
6	Deenadayalan	60/M	AWMI	+	30.52	120	86	85	3.5	173	135	7.28	8.2
7	Dorairaj	58/M	AWMI	+	24.69	110	70	78	3.8	151	96	18.2	9.4
8	Ravi	53/M	AWMI	+	28.85	116	70	100	3.6	192	115	11.08	8.5
9	Palani	43/M	IWMI	----	21.26	108	70	112	3.8	162	160	28.32	10.9
10	Chelladurai	33/M	IWMI	+	23.05	120	80	90	3.5	245	154	8.94	9.2
11	Sambanthan	59/M	AWMI	+	29.43	120	80	92	3.5	220	120	14.86	10.03
12	Sriramulu	70/M	IW/PWMI	+	29.52	118	76	78	4	275	110	21.71	9.6
13	Mary	60/F	AWMI	----	29.3	140	80	85	3.5	290	174	14.1	8.43
14	ArivudaiNambi	43/M	IWMI	+	30.78	136	86	96	3.3	285	127	10.35	8.29
15	Ismail	42/M	AWMI	+	31.56	120	84	92	4.2	210	87	7.91	8.61
16	Mary	65/F	AWMI	----	32.89	136	76	72	3.5	245	210	12.21	9.45
17	Palani	60/M	AWMI	+	27.67	120	80	86	3	215	198	9.68	8.4
18	Swaminathan	62/M	IW/PWMI	----	29.9	118	60	111	3.5	219	201	24.39	10.55
19	Subramani	80/M	AWMI	----	20.05	100	80	89	2.8	195	150	14.08	9.16
20	Babu	42/M	AWMI	+	34.5	120	80	101	3.5	180	135	15.96	9.2
21	Rajkumar	50/M	AWMI	+	31.87	114	76	117	3.8	172	135	7.93	8.19
22	Jeganathan	40/M	AWMI	+	30.08	120	80	77	3.5	264	208	15.77	9.14
23	Chandran	65/M	AWMI	----	23.34	120	86	80	4.5	192	163	16.2	8.76
24	Iqbal Basha	50/M	AWMI	+	27.56	116	70	79	3.3	166	140	18.12	8.8
25	Kathirvel	50/M	AWMI	+	27.81	140	80	106	3.5	197	158	10.92	8.2
26	Sekar	67/M	IW/PWMI	+	24.52	90	70	76	4.2	210	183	7.6	7.9
27	Lakshmi	70/F	AWMI	----	29.9	100	70	92	3.5	188	148	9.23	8.9
28	Paramasivam	53/M	AWMI	+	28.03	120	80	98	3.8	187	145	13.87	8.44
29	Palani	62/M	IW/RVMI	+	21.89	110	70	124	4.5	193	200	12.11	9.2
30	Muthukumar	49/M	AWMI	+	32.15	130	86	110	3.5	239	136	6.57	8.83
31	Velu	30/M	AWMI	+	27.82	110	80	90	5.5	234	128	10.97	7.81
32	Sekar	45/M	IWMI	+	27.8	100	76	78	3.5	239	136	7.19	9.2
33	Dhanavel	67/M	AWMI	+	25.92	120	86	96	3.2	198	109	13.15	8.65
34	Koti	56/M	AWMI	+	30.05	116	70	109	4.2	171	139	9.38	9.76
35	Md. Saif	50/M	AWMI	+	22.87	124	80	110	3.8	226	246	20.6	8.22
36	Bala	40/M	IW/PWMI	+	20.14	110	70	74	3.5	206	236	10.3	9.78
37	Perumal	65/M	AWMI	+	22.43	120	80	85	4.2	221	236	15.76	8.68
38	Mala	60/F	AWMI	----	24.78	110	70	93	3.5	192	158	15.1	8.3
39	Sahira Banu	55/F	AWMI	+	25.5	100	60	102	3.6	187	140	9.79	9.27
40	Kali	62/M	IWMI	+	23.73	90	60	98	3.8	210	225	7.62	10.17
41	Babu	42/M	AWMI	+	24.19	128	70	78	3.5	185	106	11.23	8.2
42	Md. Talip	55/M	AWMI	+	20.95	126	70	108	3.5	210	124	16.17	8.9
43	Basha	59/M	AWMI	----	24.91	110	80	110	4.5	220	145	20.14	9.13
44	Vincent	49/M	AWMI	+	23.5	120	76	78	3.5	232	228	18.94	8.34
45	Murugan	32/M	AWMI	+	28.73	130	70	90	5.5	242	187	10.03	7.46
46	Srikanth	29/M	ALMI	----	32.3	128	70	65	4.2	238	204	9.56	8.2
47	Dhansekar	58/M	AWMI	+	23.17	116	80	92	3.5	230	224	21.09	10.19
48	Munusamy	45/M	AWMI	----	25.67	100	60	84	3.8	239	198	15.43	9.76
49	Hariharan	42/M	IWMI	+	29.78	90	70	78	5.5	199	149	8.47	7.79
50	Pratap	29/M	AWMI	+	26.56	110	70	89	3.5	185	160	9.22	8.5

CONTROLS

No.	Name	Age/Sex	Smoker	BMI	SBP	DBP	RBS	S.Alb.	T.Chol.	TGL	VIT.D	Calcium
1	Nataraj	67/M	----	25.09	110	80	89	3.8	153	105	16.47	10.06
2	Ravikumar	40/M	+	23.07	120	80	92	3.5	158	111	20.02	9.22
3	Jayaraman	40/M	+	23.45	120	80	95	3.5	162	93	30.8	8.5
4	Ganesh	35/M	+	24.15	128	76	78	4.2	152	103	23.29	9.78
5	Sivaraman	46/M	+	26.89	130	80	72	3.5	210	144	13.41	8.34
6	Govindsamy	52/M	+	22.51	110	76	80	3	170	110	69.23	8.92
7	Kandamani	60/F	----	22.92	100	70	102	3.5	161	101	15.17	9.72
8	Mani	65/M	----	23.34	100	60	116	4.2	184	138	25.26	8.16
9	Pachiannan	55/M	+	19.87	130	80	91	3.5	165	96	27.38	9.87
10	Moorthy	42/M	+	21.34	120	80	105	5.5	169	119	9.18	9.42
11	Chandran	35/M	----	24.22	118	70	72	2.8	176	112	20.7	8.28
12	Sardar	55/M	+	20.08	120	80	90	3.5	163	105	19.77	8.16
13	Abdul	60/M	+	30.87	118	76	97	3.2	156	99	15.2	8.9
14	Bhaskar	52/M	----	25.56	120	70	80	3.5	197	117	33.06	8.12
15	Ellappan	74/M	----	27.8	100	70	69	3.3	175	98	35.43	10.22
16	Kumar	52/M	+	29.49	110	70	76	3.5	168	92	10.03	9.56
17	Pandian	55/M	+	30.21	130	76	85	3.8	173	93	13.23	9.78
18	Sivakumar	52/M	+	27.68	126	70	120	3.5	200	120	9.83	8.34
19	Mani	52/M	----	26.22	120	80	75	3.5	179	120	13.19	9.42
20	Kanniappan	48/M	+	21.34	130	70	97	5.2	182	103	18.66	8.72
21	Muthusamy	75/M	----	23.8	110	70	86	3.5	164	108	23.37	8.36
22	Mariappan	60/M	+	24.49	100	60	92	3.5	180	223	11.5	9.7
23	Gangaiyan	70/M	----	21.37	100	70	107	5.5	186	235	19.66	9.45
24	Vasu	40/M	+	26.67	120	80	88	3.5	192	135	20.17	8.62
25	Manohar	48/M	+	27.93	120	70	106	3.5	188	251	43.62	8.4
26	Srinivas	46/M	----	22.92	110	70	99	3.8	198	142	10.15	8.62
27	Meena	51/F	----	24.56	110	76	113	3.5	186	213	16.06	9.27
28	Subramani	58/M	----	19.87	120	80	85	3.2	179	139	10.79	10.08
29	Meera	52/F	----	23.47	130	86	82	3.5	191	246	8.22	9.1
30	James	52/M	+	21.9	130	80	94	4.5	177	222	51.7	8.8
31	Vanaraj	60/M	+	23.5	118	70	126	3.5	170	124	8.56	8.3
32	Kamaraj	34/M	+	22.89	120	70	100	2.8	204	154	29.33	8.72
33	Pitchai	70/M	+	21.16	126	80	80	3.5	181	240	36.78	8.92

34	Manickam	55/M	+	20.86	130	80	67	3.5	218	170	28.14	9.17
35	Surendar	42/M	+	25.54	100	80	84	4.2	173	230	28.5	10.22
36	Sarada	62/F	+	22.68	120	70	102	3.5	152	105	18.78	8.67
37	Ponraj	48/M	+	22.71	110	70	90	5.2	168	115	34.89	9.82
38	Raman	45/M	+	23.34	110	78	68	3.5	158	96	26.73	8.92
39	Latha	50/F	+	26.12	120	80	82	5.2	210	282	41.7	8.64
40	Ganesh	55/M	+	23.53	120	76	105	3.5	187	123	35.6	9.72
41	Dilli Babu	60/M	+	28.12	126	76	67	4.8	220	274	12.8	8.47
42	Chinnasamy	62/M	+	30.09	110	70	120	3.5	194	150	20.93	9.22
43	Kolandaivel	51/M	+	25.2	100	60	130	4.2	185	110	23.45	9.13
44	Kalyan	48/M	----	24.76	120	80	116	3.5	192	178	39.88	8.7
45	Vijaykumar	34/M	+	23.45	120	78	72	3.8	189	262	42.56	8.9
46	Noor	40/F	----	24.9	130	80	99	4.5	228	159	21.67	9.61
47	Sampath	56/M	+	26.57	126	70	106	3.5	230	128	8.93	8.6
48	Shankar	30/M	+	28.85	110	86	110	5.5	226	235	16.72	10.32
49	Jayavendan	59/M	+	20.43	108	70	80	3.5	172	140	19.87	9.43
50	Rajesh	40/M	----	27.3	110	70	92	3.5	168	259	21.31	9.21

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,CHENNAI-10
Ref.No.1463/MEI(Ethics)/2012 Dt: 03.04.2012
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College , Chennai reviewed and discussed the application for approval entitled "Vitamin D Deficiency in Acute Myocardial Infraction"- For Dissertation Purpose submitted by Dr.Sandhya Sundarajan, MD(GM), PG STUDENT, KILPAUK MEDICAL COLLEGE, CHENNAI-600010.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information / informed consent and asks to be provided a copy of the final report.

14/12/12

CHAIRMAN,
Ethical Committee
Govt. Kilpauk Medical College,
Chennai